



*e*LITERATURE
REVIEW

*e*Infections Review

The Johns Hopkins University School of Medicine

*e*Infections Review™ Volume 1 Monograph

CONTENTS

CME Information	<i>i</i>
Program Description	1
Summaries/Articles	
Upper Respiratory Tract Infections; 1:1	3
Common Tick-Borne Infections in the United States; 1:2	6
Community-Acquired Methicillin-Resistant <i>Staphylococcus aureus</i> (CA-MRSA) Skin and Soft-Tissue Infections; 1:3.....	9
Illness in the Returned Traveler; 1:4	13
Diagnosis and Management of <i>Clostridium difficile</i> Infections; 1:5	15
Clinical Topics in Sexually Transmitted Infections; 1:6.....	16
Update on Adult Immunizations; 1:7	20
Community-Acquired Pneumonia; 1:8	22
Update on New Antimicrobials; 1:9	25
Infectious Diarrhea in Adults; 1:10	29
Infectious Mononucleosis; 1:11	31
Challenges in the Management of Urinary Tract Infections; 1:12	35

IMPORTANT CME INFORMATION

GOAL

To provide primary care physicians, internists, and infectious disease specialists with up-to-date information on the diagnosis and treatment of patients with infectious diseases.

LEARNING OBJECTIVES

At the conclusion of this activity, the participants should be better able to:

- Identify current key topics related to the diagnosis and treatment of infectious disease conditions
- Discuss how the information presented may impact current clinical paradigms
- Evaluate how the information presented may be best incorporated into current clinical practice

STATEMENT OF RESPONSIBILITY

The Johns Hopkins University School of Medicine takes full responsibility for the content, quality, and scientific integrity of this CME activity.

Supported by an educational grant from ViroPharma Incorporated.

ACCREDITATION STATEMENT

The Johns Hopkins University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 4 *AMA PRA Category 1 Credit(s)*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

METHOD OF PARTICIPATION

After reviewing the monograph, please go to <http://www.hopkinscme.edu/ofp/einfectionsmonograph.htm> to view instructions on how to take a post test. There are four post-tests for this monograph; each post test offers a maximum of 1 *AMA PRA Category 1 Credit*[™]. Each post test, in sequence, contains questions from three topics. A passing grade on the post test and a completed evaluation are required to receive CME credit.

There are no prerequisites or fees associated with this activity.

Release date: February 9, 2010.

Expiration date: February 8, 2012.

eInfections Review[™] monthly issues originally released June 2007 through May 2008

Estimated time to complete activity: 4 hours.

INTENDED AUDIENCE

This activity has been developed for primary care physicians, internists, and infectious disease specialists.

INTERNET CME POLICY

The Office of Continuing Medical Education (CME) at The Johns Hopkins University School of Medicine is committed to protecting the privacy of their members and customers. The Johns Hopkins University maintains its Internet site as an information resource and service for physicians, other health professionals, and the public.

Continuing Medical Education at The Johns Hopkins University School of Medicine will keep your personal and credit information confidential when you participate in a CE Internet-based

program. Your information will never be given to anyone outside these institutions. CE collects only the information necessary to provide you with the service you request.

DISCLAIMER STATEMENT

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only. Use of The Johns Hopkins University School of Medicine name implies review of educational format, design, and approach. Please review the complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings, and adverse effects before administering pharmacologic therapy to patients.

Full Disclosure Policy Affecting CME Activities:

As a provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of The Johns Hopkins University School of Medicine to require the disclosure of the existence of any relevant financial interest or any other relationship a faculty member or a provider has with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The presenting faculty reported the following.”

IMPORTANT CME INFORMATION

PROGRAM DIRECTORS

John G. Bartlett, MD

Professor of Medicine
Department of Medicine
The Johns Hopkins University
School of Medicine
Baltimore, Maryland

Disclosure†: HIV Advisory Board for GlaxoSmithKline, Abbott, Bristol-Myers Squibb, Pfizer, and Tibotec; Policy Board for Johnson & Johnson

Disclosure‡: *Consultant:* Salient

Paul G. Auwaerter, MD

Associate Professor of Medicine
Clinical Director, Division of Infectious Diseases
The Johns Hopkins University
School of Medicine
Baltimore, Maryland

Disclosure†: *Consultant:* Novartis, Pfizer, Ortho-McNeil, Schering-Plough, and Genzyme

Speakers' Bureau: Schering-Plough
Stock: Johnson & Johnson

Disclosure‡: *Consultant:* Adamas, LifeCell, Schering-Plough and Wyeth
Stock: Johnson & Johnson, Merck & Co., and Pfizer Inc

Sara E. Cosgrove, MD, MS

Associate Professor of Medicine
Division of Infectious Diseases
Director
Antibiotic Management Program
Associate Hospital Epidemiologist
The Johns Hopkins University
School of Medicine
Baltimore, Maryland

Disclosure†: *Grants/Research Support:* Merck & Co.

Advisory Boards: Ortho-McNeil, Cadence Pharmaceuticals, Theravance/Astellas

Disclosure†: *Grants/Research Support:* AdvanDx, Astellas, and Cubist
Consultant: Astellas/Theravance, Forest, and Merck & Co.

FACULTY

Khalil Ghanem, MD

Assistant Professor of Medicine
Associate Fellowship Program Director
Division of Infectious Diseases
The Johns Hopkins University
School of Medicine
Baltimore, Maryland

Disclosure†: *Speakers' Bureau:* Merck & Co.

Disclosure‡: Dr. Ghanem has no relevant financial relationships to disclose

Noreen A. Hynes, MD, MPH, DTM&H

Assistant Professor (part time) of Medicine
Division of Infectious Diseases
The Johns Hopkins University
School of Medicine
Assistant Professor of International Health
Section of Epidemiology and Disease Control
Bloomberg School of Public Health
The Johns Hopkins University
Baltimore, Maryland

Disclosure†‡: Dr. Hynes has no relevant financial relationships to disclose

Beth D. Kirkpatrick, MD

Associate Professor of Medicine
Unit of Infectious Diseases
The University of Vermont
College of Medicine
Burlington, Vermont

Disclosure†‡: *Grant/Research (principal investigator):* ACE BioSciences

Robin McKenzie, MD

Assistant Professor of Medicine
The Johns Hopkins University
School of Medicine
Baltimore, Maryland

Disclosure†‡: Dr. McKenzie has no relevant financial relationships to disclose

Tom Talbot, MD, MPH

Assistant Professor of Medicine and Preventive Medicine
Chief Hospital Epidemiologist
Vanderbilt University
School of Medicine
Nashville, Tennessee

Disclosure†: *Grant/Research (principal investigator):* Sanofi-Pasteur

Disclosure‡: *Grant/Research (principal investigator):* Sanofi-Pasteur
Consultant: Joint Commission Resources

Unlabeled/Unapproved Uses of Drugs/Devices

Dr. Bartlett: metronidazole

Dr. Cosgrove: retapamulin

Dr. Ghanem: nucleic acid amplification tests for *C. trachomatis* for rectal specimens

Dr. Hynes: use of multivalent vaginal suppositories for the prevention of recurrent urinary tract infections

The following faculty have indicated that they will not reference any unlabeled or unapproved uses of drugs or products in this publication: Dr. Auwaerter, Dr. Kirkpatrick, Dr. McKenzie, and Dr. Talbot

†Volume 1; ‡Volume 2

STATEMENT OF NEED

The treatment of infectious diseases is an increasingly complex and rapidly changing discipline with new pathogens emerging at an alarming rate. It is vital that practitioners remain vigilant in their professional development, to insure optimal patient care, and understand all aspects of a disease state. Studies modeling an “average” practice found that family physicians spent 4.6 hours per day treating acute problems (infectious disease diagnosis and management) and/or follow-up care, and would need to spend an additional 7.4 hours working per day providing all the preventive services recommended by the US Preventive Services Task Force.

Attempting to close the knowledge/practice gaps in the diagnosis and treatment of infectious diseases including MRSA, CAP, Hepatitis C and others, eInfections Review is based on the stated needs/knowledge gaps of our current subscribers. The introduction of new therapies, more resilient infectious disease strains/pathogens and other management challenges require physicians to close knowledge gaps across a range of issues. In addition, Volume 2 will continue to close practice gaps by encouraging learners to stay abreast of new infectious diseases guidelines and recommendations, as well as, new evidence-based diagnosis and treatment options.

PROGRAM DESCRIPTION

The Johns Hopkins University School of Medicine *eInfections Review*[™] is a unique, e-mail-delivered literature review program in which leading experts and educators in various infectious disease-related fields cull the current literature, provide concise peer-reviewed synopses of relevant publications, and offer commentary and clinical recommendations on the utility of the data. Directed toward primary care physicians (PCPs)—general practitioners, family practitioners, and internists—as well as infectious disease specialists, each monthly newsletter is a 4000-word mini-course on a specific infectious disease topic, accredited by the Johns Hopkins University School of Medicine for 1.0 *AMA PRA Category 1 Credits*[™]. In addition, these newsletters are supplemented with bimonthly podcasts (clinically focused audio interviews with issue authors), each accredited by the Johns Hopkins University School of Medicine for 0.5 *AMA PRA Category 1 Credits*[™].

Three infectious disease experts from the Johns Hopkins University School of Medicine served as the Program Directors of *eInfections Review*[™], Volume 1.

John G. Bartlett, MD – Professor of Medicine in the Division of Infectious Diseases at the Johns Hopkins University School of Medicine and former Chief of the Division. Dr. Bartlett is a member of the Institute of Medicine, a Master of the American College of Physicians, past president of the Infectious Diseases Society of America (IDSA), and a recipient of the Kass Award from the IDSA. He has authored more than 500 articles and reviews in peer-reviewed journals, more than 280 book chapters, and 67 editions of 18 books. He has also served on the editorial boards of 19 medical journals.

Paul G. Auwaerter, MD – Associate Professor of Medicine in the Divisions of Infectious Diseases and General Internal Medicine at the Johns Hopkins University School of Medicine, and Clinical Director of the Division of Infectious Diseases. Dr. Auwaerter

is a Fellow of the American College of Physicians, and a member of the IDSA, the American Society of Tropical Medicine and Hygiene, and the American Society of Microbiology. He is the author of 26 original manuscripts, 24 textbook chapters, 1 book, and 79 electronic media publications.

Sara E. Cosgrove, MD, MS – Assistant Professor of Medicine in the Division of Infectious Diseases at the Johns Hopkins University School of Medicine, as well as Director of the Antibiotic Management Program and an Associate Hospital Epidemiologist at the Johns Hopkins Hospital. Her research has investigated the epidemiology and outcomes of antimicrobial resistance in the hospital setting, and she has developed tools and programs to encourage the safe and rational use of antimicrobial agents. Dr. Cosgrove is the author of 43 current PubMed citations.

The Program Directors were solely responsible for determining the content of each newsletter and podcast. For some topics, they chose to author the article reviews and commentary themselves; for others, they recruited leaders in specific subspecialties as Guest Authors. All materials were peer-reviewed by the Program Directors, as well as by the Johns Hopkins University School of Medicine Continuing Medical Education faculty, in order to ensure both scientific accuracy and lack of commercial bias. An outside staff performed minor editing for clarity and brevity, as necessary.

This *eInfections Monograph* summarizes each individual issue of *eInfections Review*[™] Volume 1. The original authors and the Program Directors have reviewed and approved these summaries, and, where appropriate, have provided updates to the original material. Subscribers may access the newsletters and podcasts at <http://www.hopkinscme.net/ofp/eInfectionsReview/newsletters.html>.

Volume 2 of *eInfections Review* began publication in January 2010. Current subscribers will be notified by e-mail. New subscribers may register to receive the newsletters and podcasts, at no charge, at <http://www.hopkinscme.net/ofp/eInfectionsReview/index.html>.

— **Robert M. Busker, Managing Editor**

The Johns Hopkins University School of Medicine
eLiterature Review Series

Upper Respiratory Tract Infections

Cosgrove SE, Auwaerter PG, and Bartlett JG.
June 2007; Volume 1, Number 1

LEARNING OBJECTIVE

Describe the proper use of antibiotic agents in treating upper respiratory infections

Reporting on **acute sinusitis**, Dr. Sara E. Cosgrove of the Johns Hopkins University School of Medicine noted that the condition accounts for 21% of all antibiotic prescriptions in adults, despite current guidelines that recommend antibiotics only if physicians suspect a bacterial pathogen and only after patients have failed supportive measures after 7 to 10 days.¹ Recent prospective, randomized, double-blind, placebo-controlled trials support the belief that the majority of cases of acute sinusitis do not require antibiotic therapy. One study, which compared amoxicillin with placebo, found no significant difference in improvement rates or patients' rating of illness severity,² whereas another study, which compared mometasone furoate nasal spray (MFNS) against amoxicillin against placebo, reported similar outcomes in the amoxicillin and placebo arms.³ However, the latter study did demonstrate a significant difference in major symptom scores in patients who received intranasal corticosteroids ($P < 0.001$ versus placebo and $P = 0.002$ versus amoxicillin). This finding suggests that such treatment may provide benefits similar to or better than antibiotics for the management of acute sinusitis without exposing patients to the risk for colonization or infection with resistant organisms, or putting them at risk for disease recurrence (a finding that was supported in a recent *Cochrane Review*).⁴

Dr. Paul G. Auwaerter of The Johns Hopkins University School of Medicine reported that **group A β -hemolytic streptococcus (GAS) pharyngitis** remains one of the most common illnesses that prompted office visits to primary care providers and pediatricians; streptococcal infection in children accounted for approximately 15% to 30% of all cases of pharyngitis.⁵ Although antibiotics

prescribed for GAS pharyngitis have been shown to reduce the incidence of uncommon suppurative complications, such as sinusitis and peritonsillar abscess, their use has been shown, at best, to shorten the duration of the routine symptoms of sore throat by 16 hours.⁶

Since viruses cause the majority of adult cases of pharyngitis, both the Infectious Diseases Society of America (IDSA)⁷ and the American College of Physicians – American Society of Internal Medicine (ACP-ASIM)⁸ recommend that clinicians neither test nor treat mild pharyngitis (as defined by the Centor scoring system of 0 or 1 point each for history of fever, lack of cough, enlarged/tender anterior cervical lymphadenopathy, and tonsillar exudates). For more severe pharyngitis, the IDSA recommends antibiotic therapy only for patients with positive rapid Group A streptococcal testing; the ACP-ASIM suggests empiric therapy for patients with Centor scores of 3 or 4. The differences in these guidelines became less meaningful in light of a 2006 report that found physician nonadherence (primarily to testing and antibiotics prescribed for patients at low risk for streptococcal pharyngitis) to either of these strategies in 66% of office visits.⁹ Another study found that the specificity for GAS-related pharyngitis using clinical criteria (Centor score of 3 or 4) was only 43.8%.¹⁰ Moreover, the unnecessary use of antibiotic prescriptions was deemed to be highest in the group diagnosed empirically (45.7%), compared with those treated based on the results of rapid testing (24.7%). These conclusions suggested that following the IDSA guidelines is associated with prescribing both lower doses and more appropriate antibiotics.¹⁰

According to Dr. John G. Bartlett of The Johns Hopkins University School of Medicine, **acute bronchitis** is another of the most common respiratory infections encountered in primary care. Because nearly all cases are due to a viral infection, the condition is highly associated with considerable overuse of antibiotics. A *Cochrane Review* of randomized, controlled trials of antibiotics for the treatment of acute bronchitis showed a reduction

in the duration of cough by an average of only 0.6 days — statistically significant, but a minor benefit compared to the risk associated with antibiotic side effects, cost, and increased resistance.¹¹ A 2006 analysis of the relationship between antibiotic prescribing for acute bronchitis with hospitalization for respiratory infections found that the number of patients with a diagnosis of acute bronchitis who received antibiotics ranged from a high of 73% in 1998 to a low of 53% in 2001. These data are consistent with those from multiple other studies, which have shown that 50% to 70% of all patients diagnosed with acute bronchitis receive an antibiotic, despite consistent recommendations against this practice.¹²

The major exception is influenza, which can be proven with the rapid influenza test (sensitivity of 70%) and, if identified early, can be treated with oseltamivir or zanamivir within 48 hours of symptom onset. The other treatable pathogen is *Bordetella pertussis*, which is relatively uncommon but should be considered in any patient with a paroxysmal cough that persists for weeks. The major condition to exclude in patients with acute bronchitis is community-acquired pneumonia; key indicators of abnormal vital signs or rales should lead the clinician to order a chest x-ray.¹³

The authors noted that the unifying concept in these three conditions is the fact that most are caused by viral infections that do not benefit from either antibacterial treatment or diagnostic testing. The notable exceptions are the rapid strep antigen test in patients with pharyngitis and the rapid influenza test in patients with typical flu symptoms during an influenza epidemic. Both tests are generally available for use in office practices and both can be utilized to render therapeutic decisions.

Prior to this publication, the authors added the following updated information:

Sinusitis. A double-blind, randomized, placebo-controlled factorial trial of 240 adults with acute sinusitis compared four treatment regimens: (1)

antibiotic (amoxicillin 500 mg orally 3 times daily for 7 days) plus nasal corticosteroid (budesonide 400 µg daily for 10 days); (2) placebo antibiotic plus nasal corticosteroid; (3) antibiotic plus placebo nasal corticosteroid; and (4) placebo antibiotic plus placebo nasal corticosteroid. With the primary endpoint defined as clinical cure at day 10, the authors found no differences in cure among the treatment groups,¹⁴ although a secondary analysis suggested that nasal corticosteroids may be more effective in patients with less severe symptoms at baseline.¹⁴

A meta-analysis of randomized trials used individual patient data to evaluate the use of antibiotics for the treatment of clinically diagnosed acute rhinosinusitis. Individual data from 2547 patients enrolled in nine clinical trials assessed the clinical utility of treating patients with signs and symptoms of acute sinusitis by determining the number needed to treat (NNT) with antibiotics to cure one additional patient. The NNT was 15 patients (95% CI, NNT[benefit] 7 to NNT[harm] 190).¹⁵ Thus, the authors concluded that, given the large number of patients who will receive unnecessary antibiotics and the minimal clinical effect, antibiotics are not justified in the treatment of acute rhinosinusitis, even in patients whose symptoms last longer than 7 to 10 days.¹⁵ An update to the 2001 *Cochrane Review* that assessed the benefit of antibiotics for the treatment of patients with acute maxillary sinusitis detected a “slight” statistical benefit of antibiotics over placebo in improving clinical symptoms (pooled risk ratio, 0.66; 95% CI, 0.44 to 0.98). However, the authors observed that 80% of the participants experienced symptom resolution within 2 weeks regardless of whether they received antibiotics.¹⁶

Although physicians can identify that patients with high fevers, severe facial pain or swelling, and/or systemic symptoms have a clear need antibiotics, these studies provide additional support for the theory that antibiotics do not modify the disease course significantly in most cases of clinically diagnosed acute sinusitis.

Pharyngitis. Recognizing that antibiotic prescriptions for outpatient respiratory tract conditions account for 60% of total antibiotic use, even though the vast majority of these infections are self-limiting, in 2008 the United Kingdom's National Institute for Health and Clinical Excellence issued a short set of guideline recommendations for practitioners.¹⁷ Regarding pharyngitis, the guidelines recommended no antibiotic prescribing and strongly advised delayed antibiotic use for most patients, who should be counseled that symptoms may last for up to one week. The guidelines recommended immediate antibiotic prescribing only for those with an acute sore throat or acute tonsillitis if they have Centor criteria of 3 or 4.

In addition, new guidelines for the prevention of rheumatic fever and the treatment of acute streptococcal pharyngitis have also been published.¹⁸ Important points include the following:

- Symptoms suggestive of streptococcal pharyngitis include sudden onset, pain on swallowing, fever (101° to 104°F), and headache.
- Microbiologic confirmation should be performed with throat culture or rapid antigen test.
- The rapid strep test is highly specific but not very sensitive, so a negative test does not exclude this diagnosis.
- The antistreptolysin O (ASLO) titer increases in 1 week and peaks at 3 to 6 weeks.
- The preferred antibiotics are intramuscular benzathine penicillin or oral penicillin V; alternatives for penicillin-allergic patients are oral cephalosporins, oral clindamycin, or an oral macrolide (eg, erythromycin or clarithromycin) or azalide (eg, azithromycin). Dosing with all antibiotics except azithromycin is for 10 days. Agents that should not be used are tetracycline, fluoroquinolones, and sulfonamides.

Acute bronchitis. An article summarizing acute bacterial exacerbations in chronic obstructive pulmonary disease reflected the authors' 20 years of experience with a cohort of patients in Buffalo, New York.¹⁹ Of particular note are the conclusions

that bacterial infection accounts for about 50% of exacerbations of chronic bronchitis; *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and rhinovirus were the major pathogens. The authors noted that moderate or severe cases are marked by two of the following three features: (1) increased dyspnea; (2) increased sputum purulence; or (3) increased sputum volume. Complicated cases may be encountered in patients over 65 years of age, as well as in those whose forced expiratory volume in one second (FEV1) is less than or equal to 50% of the predicted value, heart disease, or three or more exacerbations per year. Treatment recommendations for uncomplicated cases are azithromycin, clarithromycin, doxycycline, trimethoprim-sulfamethoxazole, or oral cephalosporin.¹⁹

References

1. Anon JB, Jacobs MR, Poole MD, et al; Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg*. 2004;130(suppl 1):S1-S45.
2. Merenstein D, Whittaker C, Chadwell T, Wegner B, D'Amico F. Are antibiotics beneficial for patients with sinusitis complaints? A randomized double-blind clinical trial. *J Fam Pract*. 2005;54(2):144-151.
3. Meltzer EO, Bachert C, Staudinger H. Treating acute rhinosinusitis: comparing efficacy and safety of mometasone furoate nasal spray, amoxicillin, and placebo. *J Allergy Clin Immunol*. 2005;116(6):1289-1295.
4. Zalmanovici A, Yaphe J. Steroids for acute sinusitis. *Cochrane Database Syst Rev*. 2007;(2):CD005149.
5. St. Sauver JL, Weaver AL, Orvidas LJ, Jacobson RM, Jacobsen SJ. Population-based prevalence of repeated group A β -hemolytic streptococcal pharyngitis episodes. *Mayo Clin Proc*. 2006;81(9):1172-1176.
6. Del Mar CB, Glasziou PP, Spinks AB. Antibiotics for sore throat. *Cochrane Database Syst Rev*. 2006;(4):CD000023.

7. Bisno AL, Gerber MA, Gwaltney JM Jr, Kaplan EL, Schwartz RH; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. *Infectious Diseases Society of America. Clin Infect Dis*. 2002;35(2):113-125.
8. Cooper RJ, Hoffman JR, Bartlett JG, et al; American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine; Centers for Disease Control. Principles of appropriate antibiotic use for acute pharyngitis in adults: background. *Ann Intern Med*. 2001;134(6):509-517.
9. Linder JA, Chan JC, Bates DW. Evaluation and treatment of pharyngitis in primary care practice: the difference between guidelines is largely academic. *Arch Intern Med*. 2006;166(13):1374-1379.
10. McIsaac WJ, Kellner JD, Aufricht P, Vanjaka A, Low DE. Empirical validation of guidelines for the management of pharyngitis in children and adults. *JAMA*. 2004; 291(13):1587-1595.
11. Smucny J, Fahey T, Becker L, Glazier R. Antibiotics for acute bronchitis. *Cochrane Database Syst Rev*. 2000;(4):CD000245.
12. Mainous AG, Saxena S, Hueston WJ, Everett CJ, Majeed A. Ambulatory antibiotic prescribing for acute bronchitis and cough and hospital admissions for respiratory infections: time trends analysis. *J R Soc Med*. 2006;99(7):358-362.
13. Metlay JP, Kapoor WN. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. *JAMA*. 1997;278(17):1440-1445.
14. Williamson IG, Rumsby K, Bengt S, et al. Antibiotics and topical nasal steroids for treatment of acute maxillary sinusitis: a randomized controlled trial. *JAMA*. 2007; 298(21):2487-2496.
15. Young J, De Sutter A, Merenstein D, et al. Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data. *Lancet*. 2008;371(9616):908-914.
16. Ahovuo-Saloranta A, Borisenko OV, Kovanen N, et al. Antibiotics for acute maxillary sinusitis. *Cochrane Database Syst Rev*. 2008;(2):CD000243.
17. Tan T, Little P, Stokes T; Guideline Development Group. Antibiotic prescribing for self limiting respiratory tract infections in primary care: summary of NICE guidance. *BMJ*. 2008;337:a437.
18. Gerber MA, Baltimore RS, Eaton CB, et al; Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation*. 2009;119(11):1541-1551.
19. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359(22):2355-2365.

Common Tick-Borne Infections in the United States

Auwaerter PG. July 2007; Volume 1, Number 2

LEARNING OBJECTIVE

Identify new diagnostic procedures and therapeutic options for tick-borne diseases in the US

Dr. Paul G. Auwaerter of the Johns Hopkins University School of Medicine reported that Lyme disease, caused by *Borrelia burgdorferi* bacteria and transmitted by hard ticks belonging to several species of the genus *Ixodes*, has become the most commonly reported vector-borne disease in the United States, as well as a source of some controversy. Primary symptoms of early infection

include an ovoid, enlarging erythematous rash (erythema migrans; EM), which may be accompanied by such systemic symptoms as fever, headache, neck stiffness, arthralgia, myalgia, and fatigue. Other manifestations may include certain neurologic, arthritic, and cardiac disorders. More than 85% of recent reports come from temperate coastal and riparian environs in Northeast, Mid-Atlantic, and Upper Midwest states.

The controversy arises, Dr. Auwaerter notes, from a small group of physicians and other health care professionals who label themselves “Lyme literate.” They advocate that Lyme disease is responsible for a sizable proportion of patients with chronic subjective problems, such as fatigue, musculoskeletal complaints, and/or neurocognitive dysfunction, in the absence of any objective history of Lyme disease, such as EM or validated Lyme serologic testing. Moreover, this group also believes that persistent *B. burgdorferi* infection is responsible for these chronic symptoms and that long-term antibiotic administration is appropriate.

Recently, both the Infectious Diseases Society of America and the American Association of Neurology issued new guideline statements that present the best available evidence for the diagnosis and treatment of Lyme disease.^{1,2} The recommendations stress the importance of distinguishing two different sets of patients — those with evidence of active infection and objective symptoms of late Lyme disease (such as monoarthritis, radiculitis, or true encephalopathy), who require antibiotic treatment, and those who have only subjective symptoms and did not experience significant benefit from the additional administration of antibiotics when studied in prospective, randomized, placebo-controlled trials.³⁻⁵ Patients with objective symptoms should be termed “late Lyme disease,” whereas those with subjective, persistent complaints for more than 6 months after receiving appropriate antibiotic therapy should fall under the recently coined “post-Lyme disease syndrome.” The recommendations also include strong statements that Lyme disease is often misdiagnosed by many in the “Lyme literate” group.

Although EM is often considered to specifically indicate Lyme disease, some patients in southern regions of the United States present with such lesions after a tick bite yet do not have evidence of *B. burgdorferi* infection.⁶ These patients appear to have a milder illness than those with Lyme disease, and there appears to be a lack of well-documented reports reflecting persistent symptoms, such as fatigue and musculoskeletal pain, in contradistinction to the well-known minority of patients with Lyme disease who experience these symptoms even after appropriate antibiotic treatment. This non-*B. burgdorferi* EM illness should be referred to as STARI (Southern Tick-Associated Rash Illness) and not reported as Lyme disease to public health authorities.

Dr. Auwaerter notes that a good resource for the basics of common tick-borne diseases in the United States, such as endemic range of infections, photographs of tick vectors, diagnosis, and treatment, can be found at the Centers for Disease Control and Prevention website.⁷

In the podcast that originally accompanied this review, Dr. Auwaerter addressed common clinical situations, including tick removal, doxycycline prophylaxis versus the need for clinician awareness of local area tick burden, tick bite prevention in adults and children, differential diagnosis of Lyme disease, and patient selection for antibiotic therapy.

Prior to this publication, Dr. Auwaerter provided the following updated information: A critique of “chronic Lyme disease,” as used by many so-called “Lyme literate” physicians and other health care professionals, was authored by an ad hoc committee of physicians who severely questioned the legitimacy of the diagnosis in most patients, as well as the concept that the bacteria persist and require long-term combination and/or parenteral antibiotic therapy.⁸ The concept that parenteral antibiotics somehow equate with superior outcomes in patients with neuroborreliosis was challenged in a prospective, noninferiority trial from Norway that found that oral doxycycline provided similar results

to intravenous ceftriaxone when either agent was administered for 14 days.⁹ Whether this finding is applicable to North American *B. burgdorferi* infection is unclear; however, other studies have suggested that as few as 10 days of antibiotic therapy is sufficient and that longer courses of antibiotics do not appear to enhance the outcomes of patients with Lyme disease.¹⁰⁻¹² In patients with persistent, subjective symptoms following appropriate antibiotic therapy for *B. burgdorferi*, optimal approaches to their management are unfortunately unclear. Many clinicians borrow approaches from the treatment of patients with chronic fatigue syndrome and fibromyalgia, and extended antibiotic therapy does not appear to provide a benefit when studied in a prospective manner.

References

1. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* 2006;43(9):1089-1134.
2. Halperin JJ, Shapiro ED, Logigian E, et al; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: treatment of nervous system Lyme disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2007;69(1):91-102.
3. Klempner MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med.* 2001; 345(2):85-92.
4. Krupp LB, Hyman LG, Grimson R, et al. Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. *Neurology.* 2003;60(12):1923-1930.
5. Fallon BA, Keilp JG, Corbera KM, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. *Neurology.* 2008;70(13):992-1003.
6. Wormser GP, Masters E, Nowakowski J, et al. Prospective clinical evaluation of patients from Missouri and New York with erythema migrans-like skin lesions. *Clin Infect Dis.* 2005;41(7):958-965.
7. Centers for Disease Control and Prevention. Tickborne rickettsial diseases. Accessed August 2, 2009.
8. Feder HM Jr, Johnson BJ, O'Connell S, Shapiro ED, Steere AC, Wormser GP; Ad Hoc International Lyme Disease Group. A critical appraisal of "chronic Lyme disease." *N Engl J Med.* 2007;357(14):1422-1430.
9. Ljøstad U, Skogvoll E, Eikeland R, et al. Oral doxycycline versus intravenous ceftriaxone for European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blind, randomised trial. *Lancet Neurol.* 2008;7(8):690-695.
10. Wormser GP, Ramanathan R, Nowakowski J, et al. Duration of antibiotic therapy for early Lyme disease: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 2003;138(9):697-704.
11. Oksi J, Nikoskelainen J, Hiekkänen H, et al. Duration of antibiotic treatment in disseminated Lyme borreliosis: a double-blind, randomized, placebo-controlled, multicenter clinical study. *Eur J Clin Microbiol Infect Dis.* 2007;26(8):571-581.
12. Thorstrand C, Belfrage E, Bennet R, Malmberg P, Eriksson M. Successful treatment of neuroborreliosis with ten day regimens. *Pediatr Infect Dis J.* 2002; 21(12):1142-1145.

Community-Acquired Methicillin-Resistant *Staphylococcus aureus* (CA-MRSA) Skin and Soft-Tissue Infections

Cosgrove SE. August/September 2007;
Volume 1, Number 3

LEARNING OBJECTIVE

Discuss key issues regarding antibiotic therapy of skin and soft tissue infections caused by CA-MRSA

Reviewing current studies on community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA), Dr. Sara E. Cosgrove of the Johns Hopkins University School of Medicine noted that the pathogen has emerged as a frequent cause of skin and soft-tissue infections in adults and children, with rates of infection rising over the past 5 years to the point that most clinicians have had at least some experience treating the condition.¹ A 2006 study that examined the etiology of purulent skin and soft-tissue infections among patients presenting to 11 university-affiliated emergency departments across the United States found that 59% of all infections were caused by MRSA; the majority of those were caused by USA300 — the predominant CA-MRSA strain in the United States.²

Risk factors for CA-MRSA include a history of prior MRSA infection, reported spider bite, contact with another person with a similar infection, and use of any antibiotic in the past month. Prior use of antibiotics as a risk factor for CA-MRSA was also demonstrated in a large study (~3.2 million patients) in the United Kingdom, which found that exposure to any antimicrobial agent within the year, was an independent predictor of MRSA. This association was most striking in patients who received fluoroquinolones or macrolides.³ This association between antibiotic use and subsequent CA-MRSA colonization and infection provides an additional reason to limit antibiotics in the outpatient setting as much as possible.

Dr. Cosgrove noted that although incision and drainage remain the mainstay of management for CA-MRSA skin infections, the role of adjunctive antibiotics is unclear, and recent studies provide conflicting results. Three studies noted that receipt of an antibiotic that was inactive against CA-MRSA did not affect patient outcomes,^{2,4,5} whereas a fourth study found that receipt of inactive antibiotics was associated with treatment failure.⁶ In 2006, the Centers for Disease Control and Prevention (CDC) recommended that practitioners consider adjunctive antibiotic therapy in patients with (a) severe or rapidly progressive infections; (b) the presence of extensive associated cellulitis; (c) signs and symptoms of systemic illness; (d) diabetes or other conditions associated with immunosuppression; (e) advanced age; (f) location of the abscess in an area in which complete drainage is difficult; or (g) lack of response to incision and drainage alone.⁷ In addition, in 2007, the American Heart Association recommended that antibiotic therapy be administered prior to incision and drainage in patients with prosthetic heart valves or other conditions that place them at high risk for endocarditis.⁸

Clindamycin, tetracyclines, and trimethoprim-sulfamethoxazole are the agents most commonly used to treat CA-MRSA infections. However, Dr. Cosgrove cited a 2007 *Journal of Clinical Microbiology* report that noted decreased rates of susceptibility to clindamycin and tetracycline in an outpatient clinic in Boston.⁹ This finding underscores the importance of examining local susceptibility data when making decisions about antibiotic choice and also emphasizes the importance of judicious antibiotic use when managing these infections, in order to prevent increasing rates of resistance.

Recurrent infection and infection among multiple household members are frequently observed in patients with CA-MRSA skin and soft-tissue infections. A 2007 German study provided the first published evidence that an aggressive strategy of personal decolonization, as well as cleaning the

environment and personal items, could control an outbreak of *S. aureus* skin infections in the community setting.¹⁰ Formal recommendations for the management of recurrent CA-MRSA skin infections do not currently exist because of the paucity of available data. Most experts believe that systemic antibiotics should not be used for decolonization alone, and that if patients experience recurrence or if other household members develop symptoms despite these measures, then practitioners can consider decolonization with mupirocin to the nares (if nasal swabs grow MRSA), as well as antiseptic skin and throat washes, for the patient and all household members.

Prior to this publication, Dr. Cosgrove added the following update: In the past year, new information has emerged regarding the epidemiology of CA-MRSA colonization and infection.^{11,12}

A 2008 study examined data on nasal colonization with *S. aureus* collected between 2001 and 2004 from the National Health and Nutrition Examination Survey.¹² The authors observed that, although the prevalence of nasal colonization with *S. aureus* decreased overall from 32.4% in 2001 to 2002 to 28.6% in 2003 to 2004, the prevalence of nasal colonization with MRSA increased significantly, from 0.8% to 1.5%.¹² Of the 1.5% of individuals with MRSA, 19.7% of the cases were community-acquired strains.¹² Thus, whereas the overall rates of MRSA colonization are low, the increase indicates that additional monitoring of the rates over time will be essential. In addition, only assessing the nares for MRSA colonization may underestimate the degree of CA-MRSA colonization, given CA-MRSA's propensity to colonize other sites, such as the axilla and inguinal regions.

Another 2008 study described the emergence of a multidrug-resistant CA-MRSA USA300 strain reported predominantly among men who have sex with men in San Francisco.¹³ The strain carries a conjugative plasmid (pUSA03) that confers constitutive (as opposed to inducible) resistance to clindamycin, as well as resistance to tetracycline and mupirocin. The authors conducted a population-based survey of San Francisco residents who were

treated for culture-proven CA-MRSA infections at 9 of 10 medical centers serving the city and determined that the annual incidence of multidrug-resistant USA300 infection was 26 cases per 100,000 persons. This study highlights the importance of continued vigilance for determining local susceptibility patterns of CA-MRSA infections.

Additional data have emerged regarding the need for antibiotics in the management of CA-MRSA abscesses and the utility of intranasal mupirocin for the prevention of CA-MRSA infections. A 2007 randomized, double-blind trial of 166 adult outpatients compared cephalexin with placebo after surgical incision and drainage of uncomplicated skin abscesses, in order to define the role of antibiotics in the management of such infections.¹⁴ Approximately two-thirds of the lesions involved only subcutaneous tissue and one-third involved the fascia or muscle. Many patients had abscesses greater than 5 cm in diameter.¹⁴ *S. aureus* was isolated as the only pathogen in 69% of cephalexin-treated patients and 67% of placebo-treated patients; 87 of 99 (88%) of the isolates tested for susceptibility were MRSA, and 93% of the MRSA strains isolated produced Panton-Valentine leucocidin (PVL). In total, 69 of 82 (84.1%) of the patients who received cephalexin and 76 of 84 (90.5%) of those who treated with placebo experienced a clinical cure.¹⁴

Despite the fact that the majority of patients had CA-MRSA that physicians would not expect to treat with either cephalexin or placebo, true clinical failures with worsening abscess or inadequate healing occurred in only 8% of the patients.¹⁴ The results of this study suggest that antibiotics are not beneficial in the majority of patients with CA-MRSA skin abscesses, provided that health care providers perform a complete incision and drainage. A useful follow-up study would involve comparing an agent expected to be active against CA-MRSA with placebo in the same population.

A cluster randomized, double-blind, placebo-controlled 2007 trial of mupirocin versus placebo for decolonization of MRSA-colonized soldiers

demonstrated that intranasal mupirocin therapy does not decrease subsequent CA-MRSA infection in treated individuals or their close contacts.¹⁵ Soldiers underwent nasal cultures for CA-MRSA on the first day of training, and those with positive CA-MRSA cultures were offered treatment with study drug (either mupirocin or placebo). All participants were followed prospectively for the development of skin and soft-tissue infections for 16 weeks and had repeat nasal swabs. Seven training groups (1669 soldiers) were randomized to the placebo arm and 7 training groups (1778 soldiers) to the mupirocin arm. Researchers detected no benefit with the use of intranasal mupirocin for the prevention of CA-MRSA infections in subjects colonized with CA-MRSA (7.7% infection rate in the placebo arm versus 10.6% infection rate in the mupirocin arm) or their contacts, despite the fact that mupirocin was associated with decolonization of the nares in 87.9% of the patients. The authors noted that the infection rate in the placebo group was significantly lower than that observed in a previous study by the same group, in which 38% of the soldiers colonized with CA-MRSA went on to develop infection,¹⁶ and they hypothesized that all study participants may have become more aware of the importance of good hygiene. Nevertheless, this study suggests that mupirocin therapy alone is unlikely to be beneficial in preventing CA-MRSA infections in patients colonized with CA-MRSA.

References

1. Crum NF, Lee RU, Thornton SA, et al. Fifteen-year study of the changing epidemiology of methicillin-resistant *Staphylococcus aureus*. *Am J Med.* 2006;119(11):943-951.
2. Moran GJ, Krishnadasan A, Gorwitz RJ, et al.; EMERGENCY ID Net Study Group. Methicillin-resistant *S. aureus* infections among patients in the emergency department. *N Engl J Med.* 2006;355(7):666-674.
3. Schneider-Lindner V, Delaney JA, Dial S, Dascal A, Suissa S. Antimicrobial drugs and community-acquired methicillin-resistant *Staphylococcus aureus*, United Kingdom. *Emerg Infect Dis.* 2007;13(7):994-1000.
4. Miller LG, Quan C, Shay A, Mostafaie K, Bharadwa K, Tan N, et al. A prospective investigation of outcomes after hospital discharge for endemic, community-acquired methicillin-resistant and -susceptible *Staphylococcus aureus* skin infection. *Clin Infect Dis.* 2007;44(4):483-492.
5. Fridkin SK, Hageman JC, Morrison M, et al; Active Bacterial Core Surveillance Program of the Emerging Infections Program Network. Methicillin-resistant *Staphylococcus aureus* disease in three communities. *N Engl J Med.* 2005;352(14):1436-1444.
6. Ruhe JJ, Smith N, Bradsher RW, Menon A. Community-onset methicillin-resistant *Staphylococcus aureus* skin and soft-tissue infections: impact of antimicrobial therapy on outcome. *Clin Infect Dis.* 2007;44(6):777-784.
7. Gorwitz RJ, Jernigan DB, Powers JH, Jernigan JA; Participants in the Centers for Disease Control and Prevention-Convended Experts' Meeting on Management of MRSA in the Community. Strategies for clinical management of MRSA in the community: summary of an experts' meeting convened by the Centers for Disease Control and Prevention. March 2006. Accessed July 20, 2009.
8. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis. Guidelines from the American Heart Association. American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation.* 2007;116(15):1736-1754.

-
9. Han LL, McDougal LK, Gorwitz RJ, et al. High frequencies of clindamycin and tetracycline resistance in methicillin-resistant *Staphylococcus aureus* pulsed-field type USA300 isolates collected at a Boston ambulatory health center. *J Clin Microbiol.* 2007;45(4):1350-1352.
 10. Wiese-Posselt M, Heuck D, Draeger A, et al. Successful termination of a furunculosis outbreak due to lukS-lukF-positive, methicillin-susceptible *Staphylococcus aureus* in a German village by stringent decolonization, 2002-2005. *Clin Infect Dis.* 2007;44(11): e88-e95.
 11. Gorwitz RJ, Fridkin SK, Workowski KA. More challenges in the prevention and management of community-associated, methicillin-resistant *Staphylococcus aureus* skin disease. *Ann Intern Med.* 2008;148(4):310-312.
 12. Gorwitz RJ, Kruszon-Moran D, McAllister SK, et al. Changes in the prevalence of nasal colonization with *Staphylococcus aureus* in the United States, 2001-2004. *J Infect Dis.* 2008;197(9):1226-1234.
 13. Diep BA, Chambers HF, Graber CJ, et al. Emergence of multidrug-resistant, community-associated, methicillin-resistant *Staphylococcus aureus* clone USA300 in men who have sex with men. *Ann Intern Med.* 2008;148(4):249-257.
 14. Rajendran PM, Young D, Maurer T, et al. Randomized, double-blind, placebo-controlled trial of cephalexin for treatment of uncomplicated skin abscesses in a population at risk for community-acquired methicillin-resistant *Staphylococcus aureus* infection. *Antimicrob Agents Chemother.* 2007;51(11):4044-4048.
 15. Ellis MW, Griffith ME, Dooley DP, et al. Targeted intranasal mupirocin to prevent colonization and infection by community-associated methicillin-resistant *Staphylococcus aureus* strains in soldiers: a cluster randomized controlled trial. *Antimicrob Agents Chemother.* 2007;51(10):3591-3598.
 16. Ellis MW, Hospenthal DR, Dooley DP, Gray PJ, Murray CK. Natural history of community-acquired methicillin-resistant *Staphylococcus aureus* colonization and infection in soldiers. *Clin Infect Dis.* 2004;39(7):971-979.

>> PROCEED TO POST-TEST

<http://www.hopkinscme.edu/ofp/einfectionsmonograph.htm>

Illness in the Returned Traveler

McKenzie R. October 2007; Volume 1, Number 4

LEARNING OBJECTIVE

Describe the difficulties in diagnosing illnesses in travelers returning from different regions of the world

Dr. Robin McKenzie of the Johns Hopkins University School of Medicine noted that, in addition to the presenting symptoms, three other factors are especially important in helping clinicians diagnose illness in a returned traveler: (1) the region visited; (2) the timing of symptom onset; and (3) pre-travel preparation (vaccination and malaria prophylaxis).

The region visited. Knowing which illnesses are common in specific regions will assist in diagnosing illness in a returned traveler. An excellent reference is the database that the GeoSentinel Surveillance Network maintains. Currently, this network, affiliated with the International Society of Travel Medicine and the Centers for Disease Control and Prevention, comprises 41 travel and tropical medicine clinics on six continents.¹ A report published in *The New England Journal of Medicine* in 2006 compared the frequency of illnesses by region of exposure in 17,000 travelers seen at GeoSentinel clinics from 1996 to 2004.² Overall, malaria was the most common cause of systemic febrile illness. Since malaria can be fatal if not promptly treated, this diagnosis must be considered first in any febrile traveler returning from an endemic area, especially Africa. The second most common systemic febrile illness in Africa was African tick-bite fever, a rickettsial infection transmitted by ticks that may attach to hikers, often in the bush of southern Africa. Manifestations include fever and rash, including one or several eschars at the site of a tick bite. As with many rickettsial infections, doxycycline is effective treatment.

Although dengue is uncommon among travelers to Africa, visitors frequently acquired it after trips to Asia, Central and South America, and the Caribbean. In addition, clinicians diagnosed mononucleosis and enteric fever (typhoid and paratyphoid fever) in returned, febrile travelers. Enteric fever was much more common after travel to the Indian subcontinent than to any other region. Another illness that travelers may acquire in India is Chikungunya fever. In 2005 to 2006, this little-known illness erupted on several islands in the Indian Ocean, including Reunion, where about one-third of the island's 770,000 people were afflicted. This mosquito-borne viral illness causes fever, rash, and arthritis, which can be debilitating.³

The timing of symptom onset. Knowing the incubation period of an illness may also be helpful. For example, dengue and rickettsial illnesses generally develop within one week (maximum, two weeks) after infection by mosquitoes (dengue) or ticks, fleas, or mites (rickettsia). Malaria caused by *Plasmodium falciparum* has no latent liver phase and thus generally presents within several weeks or 1 month of travel. *P. vivax* and *P. ovale*, on the other hand, may remain dormant in the liver and may cause fever months or even years after travel.⁴ Two-thirds of *P. falciparum* malaria infections present within two weeks of travel, but half of *P. vivax* cases present more than six weeks after travel.

Pre-travel preparation. Determining the vaccination/prophylaxis status of a patient can also provide significant information. Typhoid fever, hepatitis A, and influenza are the most common vaccine-preventable diseases. An analysis of the GeoSentinel database revealed that, compared with other groups of travelers, those who visited friends and relatives (VFRs) were less likely to have received pre-travel medical advice and were more likely to have vaccine-preventable causes of fever.⁵ A 2007 study found that more than half of the malaria cases in US civilians occurred in VFRs, and only 20% of these VFRs had received recommended prophylaxis.⁶ Prophylaxis with the commonly used antimalarial drugs, however, does not prevent or

eradicate hypnozoites (latent liver forms) of *P. vivax* or *P. ovale*. Malaria prophylaxis may, in fact, delay the presentation of vivax or ovale malaria, rendering the diagnosis more difficult.⁴

Prior to this publication, Dr. McKenzie provided the following updated information: An article by GeoSentinel focused on dengue, emphasizing its prevalence by region and by season of the year.⁷ A mosquito-borne viral infection, dengue causes fever, rash, headache, myalgias, arthralgias, and occasionally internal or external bleeding and shock. This report analyzed 522 cases of dengue diagnosed from 1997 to 2006 by serology, viral RNA, antigen, or viral isolation in travelers who became ill within two weeks of return from an endemic area. Among such travelers, 12 (2%) had dengue hemorrhagic fever or dengue shock syndrome. In total, 68% of the cases of dengue emerged after travel to Asia, 15% after travel to Latin America, 9% after travel to the Caribbean, and only 5% after travel to Africa.⁷ Large numbers of cases occurred among travelers to Thailand (154), India (66), Indonesia (38), and Brazil (22).⁷ Marked increases in cases, reflecting epidemics in the local populations, occurred in Southeast Asia in 1998 and 2002, South Central Asia (which includes India) in 2003, and South Central Asia and Indonesia in 2005. Although dengue occurs year-round in endemic areas, the disease has seasonal peaks in many regions. These annual peaks were in June and September in Southeast Asia, October in South Central Asia, August and October in the Caribbean, and March in South America.⁷ Knowing the seasonal peaks and recognizing epidemics in specific regions will help clinicians diagnose dengue in travelers who become ill within one to two weeks of their return.

Chikungunya fever has continued to spread from several islands in the Indian Ocean to the mainland of India and down to Sri Lanka, Malaysia, Indonesia, and Singapore, including popular travel destinations. A recent report describes three tests to diagnose Chikungunya fever.⁸ Using 720 samples from 680 patients returning to Europe from the Indian Ocean region, the authors confirmed

Chikungunya infection in 22% of the patients.⁸ For these confirmed cases, reverse transcription–polymerase chain reaction (PCR) was positive in all samples obtained with four days of symptom onset, but viremia and PCR positivity decreased after this time. Immunofluorescent immunoglobulin (Ig)M and IgG were positive in all patients by Day 5. During the first few days of illness, patients had very high viral loads — some more than 10⁹ copies/mL plasma.⁸ This illness should be considered in travelers with fever and arthralgias or arthritis returning from India and other nearby Asian countries.

References

1. GeoSentinel. The Global Surveillance Network of the ISTM (International Society of Travel Medicine) and the CDC (Centers for Disease Control and Prevention). Accessed August 3, 2009.
2. Freedman DO, Weld LH, Kozarsky PE, et al. Spectrum of disease and relation to place of exposure among ill returned travelers. *N Engl J Med*. 2006;354(2):119-130.
3. Simon F, Parola P, Grandadam M, et al. Chikungunya infection: an emerging rheumatism among travelers returned from Indian Ocean islands. Report of 47 cases. *Medicine* (Baltimore). 2007;86(3):123-137.
4. Bottieau E, Clerinx J, Van den Enden E, et al. Imported non-Plasmodium falciparum malaria: a five-year prospective study in a European referral center. *Am J Trop Med Hyg*. 2006;75(1):133-138.
5. Wilson ME, Weld LH, Boggild A. Fever in returned travelers: results from the GeoSentinel Surveillance Network. *Clin Infect Dis*. 2007;44(12):1560-1568.
6. Thwing J, Skarbinski J, Newman RD, et al.; Centers for Disease Control and Prevention. Malaria surveillance – United States, 2005. *MMWR Surveill Summ*. 2007;56(6):23-40.
7. Schwartz E, Weld LH, Wilder-Smith A, et al.; GeoSentinel Surveillance Network. Seasonality, annual trends, and characteristics of dengue among ill returned travelers, 1997-2006. *Emerg Infect Dis*. 2008;14(7):1081-1088.

8. Panning M, Grywna K, van Esbroeck M, Emmerich P, Drosten C. Chikungunya fever in travelers returning to Europe from the Indian Ocean region, 2006. *Emerg Infect Dis*. 2008;14(3):416-422.

Diagnosis and Management of *Clostridium difficile* Infections

Bartlett JG. November 2007; Volume 1, Number 5

LEARNING OBJECTIVE

Describe the contemporary standards for diagnosing and managing *C. difficile*-associated diarrhea

Although *Clostridium difficile* is the most common bacterial cause of diarrhea, there appears to be a current epidemic of a new and problematic strain, which is designated NAP1. Dr. John G. Bartlett of the Johns Hopkins University School of Medicine provided the background and reviewed current research on this new “hypervirulent strain,” which emerged with multiple near-simultaneous outbreaks in hospitals in the United States, Canada, and several countries in Europe. Dr. Bartlett noted that NAP1 presents more frequently and with greater severity than the historic strain of *C. difficile*, with an attributable mortality of 6% to 17%; additionally, NAP1 is more refractory to therapy and patients with the strain are more prone to relapse.¹⁻³

Previously, the risk factors for *C. difficile* had been identified as antibiotic exposure, elderly age, and hospitalization or residence in a chronic care facility. The most important observation regarding this new strain is the high frequency of fluoroquinolones as inducing agents, the presumed explanation for which was that the majority of NAP1 strains are highly resistant to this antibiotic, whereas the historic strains were almost uniformly sensitive to it.⁴

The diagnostic testing for *C. difficile* had been the “gold standard” cytotoxin assay; however, more than 95% of laboratories in the United States use enzyme

immunoassays (EIAs), which are relatively easy to perform and provide rapid results. Extensive studies have shown reduced sensitivity with the use of this assay, reported as 60% to 95%.⁴ Further, in a 2006 report from the Johns Hopkins University Hospital, the sensitivity of this assay was only 40%, necessitating a shift to an alternative diagnostic testing strategy.^{5,6} Currently, experts recommend that physicians exercise caution when depending on the EIA and encourage their laboratories to use alternative testing systems.

Researchers have identified two major treatment issues. First, they are evaluating the benefits of oral vancomycin and metronidazole for the treatment of acute *C. difficile* infections. These two agents have usually been considered equivalent, despite the fact that vancomycin exhibits superior pharmacokinetic properties. A 2007 prospective, randomized, double-blind trial conducted to determine the relative merits of metronidazole versus vancomycin found that individuals with severe *C. difficile* disease had a higher cure rate with vancomycin (97% vs 76%; $P=.02$).⁷ For patients with mild *C. difficile* disease, the response rates with vancomycin and metronidazole were 98% and 90%, respectively (not statistically significant).⁷ A second treatment problem is relapse. The previously reported rate of relapse was relatively consistent between both agents, although the NAP1 strain may actually have higher rates. Clinicians have access to multiple methods for patient management, although human stool transplants are almost uniformly effective.

In the podcast that originally accompanied this review, Dr. Bartlett presented case studies of both mild and severe *C. difficile* infections, discussing the following: (1) differentiating between mild and severe cases; (2) treatment protocols; (3) balancing the treatment of community-acquired pneumonia with the development of *C. difficile* infection; and (4) therapeutic options for recurrent relapse, including stool transplant, probiotics, and the recommendation for surgery (colectomy) in 0.5% of cases.

Prior to this publication, Dr. Bartlett added the following updated information: Clinicians should become familiar with probiotics, since patients have become very aware of these dietary supplements from the Internet and have ready access to them in health food stores. A recent review⁸ of published reports on *Saccharomyces boulardii* showed this agent's efficacy in preventing relapses in the largest trial reported,⁹ but a meta-analysis by the Cochrane Library in 2009 concluded that this and other probiotics showed no evidence of efficacy for the treatment of *C. difficile* infections and inadequate data on their use for preventing relapse. With respect to *Lactobacillus* preparations, the data were considered inadequate to reach any conclusion.¹⁰

References

1. McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant of *Clostridium difficile*. *N Engl J Med*. 2005;353(23):2433-2441.
2. McDonald LC, Coignard B, Dubberke E, Song X, Horan T, Kuty PK; Ad Hoc *Clostridium difficile* Surveillance Working Group. Recommendations for surveillance of *Clostridium difficile*-associated disease. *Infect Control Hosp Epidemiol*. 2007;28(2):140-145.
3. Pépin J, Valiquette L, Cossette B. Mortality attributable to nosocomial *Clostridium difficile*-associated disease during an epidemic caused by a hypervirulent strain in Quebec. *CMAJ*. 2005;173(9):1037-1042.
4. Blossom DB, McDonald LC. The challenges posed by reemerging *Clostridium difficile* infection. *Clin Infect Dis*. 2007;45(2):222-227.
5. Ticehurst JR, Aird DZ, Dam LM, Borek AP, Hargrove JT, Carroll KC. Effective detection of toxigenic *Clostridium difficile* by a two-step algorithm including tests for antigen and cytotoxin. *J Clin Microbiol*. 2006;44(3):1145-1149.
6. Musher DM, Manhas A, Jain P, et al. Detection of *Clostridium difficile* toxin: comparison of enzyme immunoassay results with results obtained by cytotoxicity assay. *J Clin Microbiol*. 2007;45(8):2737-2739.
7. Zar FA, Bakkanagari K, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clin Infect Dis*. 2007;45(3):302-307.
8. Parkes GC, Sanderson JD, Whelan K. The mechanisms and efficacy of probiotics in prevention of *Clostridium difficile*-associated diarrhoea. *Lancet Infect Dis*. 2009;9(4):237-244.
9. McFarland LV, Surawicz CM, Greenberg RN, et al. A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for *Clostridium difficile* disease. *JAMA*. 1994;271(24):1913-1918.
10. Pillai A, Nelson R. Probiotics for treatment of *Clostridium difficile*-associated colitis in adults. *Cochrane Database Syst Rev*. 2008;(1):CD004611.

Clinical Topics in Sexually Transmitted Infections

Ghanem K. December 2007; Volume 1, Number 6

LEARNING OBJECTIVE

Describe the clinical characteristics and management of common sexually transmitted infections

Dr. Khalil Ghanem of the Johns Hopkins University School of Medicine reviewed reports on major advances in treating sexually transmitted infections (STIs) since the Centers for Disease Control and Prevention (CDC) last updated its STI guidelines in 2006.

Human papillomavirus (HPV) is the most prevalent STI worldwide. In 2006, the US Food and Drug Administration (FDA) approved a quadrivalent HPV vaccine (HPV types 6, 11, 16, and 18) for use in women 9 to 26 years of age for the prevention of genital warts and anogenital cancers caused by these four HPV types. Dr. Ghanem noted that two large, multicenter, randomized, controlled trials^{1,2} found

this vaccine to be highly effective at preventing cervical, vaginal, and vulvar high-grade lesions associated with HPV types 16 and 18, as well as low-grade lesions and warts caused by all four HPV types. Although at publication date, no serious side effects had been definitively linked to the vaccine, clinicians should note that this agent has no therapeutic benefits — that is, a woman infected with HPV-16 prior to vaccination will have the same risk for developing HPV-16–related dysplasia as will an unvaccinated woman. (A vaccinated woman will, however, be protected from infection with HPV types 6, 11, and 18 if she was not previously exposed to these strains.)

Dr. Ghanem reported that ongoing studies are evaluating the efficacy of the vaccine in mid-adult women (up to 45 years of age), in HIV-infected women, and in men. In addition, a bivalent vaccine (containing only HPV types 16 and 18) has demonstrated similar efficacy and is currently undergoing FDA review for licensure.

Treatment of the approximately 350,000 patients with **gonorrhea** reported annually in the United States has been hindered by the causative pathogen's ability to develop drug resistance. In 2005, more than 30% of gonorrhea infections were treated with fluoroquinolones. However, a retrospective, 15-year review of *Neisseria gonorrhoeae* antimicrobial resistance trends found that ciprofloxacin resistance increased from 0% in 1990 to 4.1% in 2003 and that by 2006, approximately 13% of all collected isolates were resistant to fluoroquinolones.³ Based on these data, the CDC issued an update to the 2006 Sexually Transmitted Disease Treatment Guidelines, no longer recommending the use of fluoroquinolones for the treatment of gonorrhea (and such related conditions as pelvic inflammatory disease).⁴ The only remaining recommended first-line treatment options are the cephalosporins — intramuscular ceftriaxone and oral cefixime — with alternate agents including ceftizoxime, cefoxitin plus probenecid, and cefotaxime. Studies have shown that a single 2 gram oral dose of azithromycin, although not widely recommended by the CDC

because of fears of increasing resistance and gastrointestinal intolerance, is effective and may be considered in penicillin-allergic patients.

Lymphogranuloma venereum (LGV) is an STI caused by *Chlamydia trachomatis* serovars L1 through L3. Endemic in tropical regions, the infection usually presents as a urogenital syndrome consisting of primary ulcers, followed by painful lymphadenopathy (also known as buboes). A 2007 report on a recent UK outbreak, however, found that the majority of cases were associated with HIV-infected men who had sex with men presenting with proctitis. Symptoms included rectal discharge, pain, bleeding, tenesmus, and constipation.⁵ Diagnosis of LGV is based on clinical suspicion and the exclusion of other etiologies of proctitis, along with *C. trachomatis* testing (if available). In the absence of specific LGV diagnostic testing, it is appropriate to treat a patient presenting with the typical syndrome for LGV with the CDC-recommended regimen of oral doxycycline 100 milligrams twice daily for 21 days.

Herpes simplex virus type 2 (HSV-2) infects about 25% of the US population, but the question of who is infected and how to test for the virus has become controversial. No formal recommendations have been issued, despite attempts by different groups to create a consensus statement.⁶ Regarding how to test, Dr. Ghanem reviewed a 2005 finding that, among laboratories that used crude antigen-based tests, more than half erroneously detected HSV-2 antibodies in samples known to be positive only for HSV-1.⁷ The authors of the study noted that this poor performance is likely due to the cross-reactivity of HSV-1 and HSV-2 antigens when non-glycoprotein G-based tests are used.

More recently, glycoprotein G-based tests have been shown to be more specific in differentiating HSV-1 from HSV-2 antibodies. The following tests are commercially available — (1) HerpeSelect[®] HSV-1 ELISA (enzyme-linked immunosorbent assay) and HerpeSelect[®] HSV-2 ELISA (Focus Technologies; Cyprus, CA); (2) HerpeSelect[®]

Immunoblot 1 and 2 (Focus Technologies; Cyprus, CA); (3) biokit HSV-2 Rapid Test™ (Biokit USA; Lexington, MA); and (4) SureVue HSV-2 Rapid Test™ (Fisher HealthCare; Houston, TX)—but many clinicians are unaware of their existence, and many laboratories continue to perform crude antigen-based tests despite their limitations. Although the current recommendation is that clinicians only use glycoprotein G-based tests for the serodiagnosis of HSV-1 and HSV-2, a 2007 study found that, in low prevalence settings, the number of false-positive tests increased.⁸ Clinicians are thus reminded that the interpretation of any serologic test for HSV depends on the type of test that they use; they should take into account the pretest probability of infection.

Prior to this publication, Dr. Ghanem added the following updated information: In addition to the prevention of cervical cancer, the FDA has approved the use of the quadrivalent vaccine for the prevention of vaginal and vulvar cancers caused by HPV-16 and HPV-18. Postmarketing vasovagal syncope has been reported among some women receiving the quadrivalent vaccine. The recommendation therefore is to vaccinate while the patient is seated and to observe the patient for about 15 minutes after injection if a vasovagal response is of concern. To date, no other serious side effects have been causally linked to the quadrivalent vaccine.

Preliminary efficacy results with the quadrivalent HPV vaccine in 3800 women aged 24 to 45 years were presented at the 24th International Papillomavirus Conference and Clinical Workshop in Beijing, China, in November 2007. The vaccine was more than 90% efficacious at preventing genital warts, persistent infections, and dysplasia caused by HPV types 6, 11, 16, and 18. However, the vaccine is still not approved for use in women more than 26 years of age. The question of cost-effectiveness of the quadrivalent vaccine for women more than 21 years of age has also been raised; the authors found that the cost-effectiveness would depend on the duration of vaccine immunity (ie, lack of future

need for booster vaccination) and recommended achieving high coverage in preadolescent girls to maximize cost-effectiveness.⁹ In response to that publication, the CDC issued a statement supporting the continued use of the vaccine in women up to 26 years of age.¹⁰ Data on the efficacy of the quadrivalent vaccine for the prevention of genital warts in men are expected in the near future.

References

1. Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med.* 2007;356(19):1915-1927
2. Joura EA, Leodolter S, Hernandez-Avila M, et al. Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials. *Lancet.* 2007;369(9574):1693-1702.
3. Wang SA, Harvey AB, Conner SM, et al. Antimicrobial resistance for *Neisseria gonorrhoeae* in the United States, 1988 to 2003: the spread of fluoroquinolone resistance. *Ann Intern Med.* 2007; 147(2):81-88.
4. Centers for Disease Control and Prevention. Update to CDC's Sexually Transmitted Diseases Treatment Guidelines, 2006: Fluoroquinolones no longer recommended for treatment of gonococcal infections. *MMWR Morb Mortal Wkly Rep.* 2007;56(14):332-336.
5. Ward H, Martin I, Macdonald N, et al. Lymphogranuloma venereum in the United Kingdom. *Clin Infect Dis.* 2007; 44(1):26-32.
6. Guerry SL, Bauer HM, Klausner JD, et al. Recommendations for the selective use of herpes simplex virus type 2 serological tests. *Clin Infect Dis.* 2005;40(1):38-45.
7. Morrow RA, Brown ZA. Common use of inaccurate antibody assays to identify infection status with herpes simplex virus type 2. *Am J Obstet Gynecol.* 2005; 193(2):361-362.

-
8. Mark HD, Nanda JP, Roberts J, Rompalo A, Melendez JH, Zenilman J. Performance of focus ELISA tests for HSV-1 and HSV-2 antibodies among university students with no history of genital herpes. *Sex Transm Dis*. 2007;34(9):681-685.
 9. Kim JJ, Goldie SJ. Health and economic implications of HPV vaccination in the United States. *N Engl J Med*. 2008;359(8):821-832
 10. Centers for Disease Control and Prevention. Press release. CDC's Advisory Committee recommends human papillomavirus virus vaccination. Accessed August 2, 2009.

>> PROCEED TO POST-TEST

<http://www.hopkinscme.edu/ofp/einfectionsmonograph.htm>

Update on Adult Immunizations

Talbot T; January 2008; Volume 1, Number 7

LEARNING OBJECTIVE

Evaluate the current immunization recommendations for integration into clinical practice

Over the past few years, new vaccines targeted against infectious diseases that can cause substantial morbidity in adults have been licensed for the adolescent and adult population, including vaccines against pertussis, human papillomavirus, and varicella. Dr. Tom Talbot of the Vanderbilt University School of Medicine reviewed recent investigations into these vaccines and discussed new recommendations on the immunization of adults from the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP).

Shingles. Reactivation of varicella zoster virus, whose primary infection results in chickenpox, causes up to 1 million cases of herpes zoster (shingles) in the United States annually, and the risk increases with advanced age.¹ The Shingles Prevention Study, a randomized, double-blind, placebo-controlled trial of 38,546 adults 60 years of age and older, found that vaccination with the zoster vaccine reduced the burden of illness due to herpes zoster by 61.1%, the incidence of postherpetic neuralgia by 66.5%, and the incidence of herpes zoster by 51.3%.² These results led the ACIP to recommend that all adults 60 years of age and older receive the zoster vaccine, regardless of a prior history of shingles.³

Pertussis. The incidence of infection due to *Bordetella pertussis* (ie, pertussis, or “whooping cough”) has escalated in recent years, and practitioners have noted an increasing proportion of cases in adolescents and adults because of waning protection from pediatric vaccination.⁴ The Adult Pertussis Trial (APERT) examined the safety and efficacy of an acellular pertussis vaccine, which

contained a lower concentration of pertussis antigen than that found in the pediatric vaccine, in this population. A total of 2,781 subjects between 15 and 65 years of age were enrolled in this double-blind, multicenter, randomized trial and were followed for 2.5 years. Of the 2,672 cough illnesses reported, only 1 episode in the vaccine arm met the primary case definition for pertussis (defined as a cough illness with confirmatory positive culture or polymerase chain reaction [PCR] for *B. pertussis*, or a predefined rise in antibody titers), yielding an overall vaccine efficacy of 92%.⁵

Prompted by the results of the APERT investigation, the ACIP released recommendations regarding a newly licensed “Tdap” vaccine (which includes tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis antigens) for use in adults. Specifically, the ACIP recommended that all adults 19 to 64 years of age should receive Tdap in place of the tetanus diphtheria (Td) booster if the last dose of Td was 10 or more years ago (or as indicated for wound care). Further, people who have close contact with infants less than 1 year of age should receive Tdap if at least 2 years have passed since they received the Td booster. Finally, to protect themselves and reduce transmission of pertussis to their patients, all health care workers with direct patient contact should receive a dose of Tdap if it has been at least 2 years since they received Td.⁴

Hepatitis A. The long-established method of postexposure prophylaxis (PEP) for the hepatitis A virus (HAV) has been the use of immune globulin, despite concerns over its cost, the need for a large volume of administration, limited access and availability, its inability to provide long-term immunity, and the potential to transmit blood-borne pathogens. Dr. Talbot reviewed a randomized, double-blind, noninferiority trial that compared hepatitis A vaccine with weight-based immune globulin administered to 4,524 healthy individuals between 2 and 40 years of age within 14 days of exposure to index cases of HAV infection. Symptomatic HAV infection was noted in 4.4% of contacts who received hepatitis A vaccination,

whereas 3.3% of contacts who received immune globulin developed HAV infection (relative risk for infection: 1.35), which met the predetermined criterion for noninferiority.⁶

Based on these findings, in mid-2007, the ACIP revised its recommendations for treating people recently exposed to HAV: (1) In healthy people 1 to 40 years of age, the group recommends single-antigen hepatitis A vaccine (not the combined hepatitis A and B vaccine, because of the reduced amount of HAV antigen in the combined vaccine) for PEP; (2) Clinicians should prefer immune globulin for healthy adults more than 40 years of age, but such contacts may be vaccinated if immune globulin is unavailable; (3) For infants under 1 year of age, immunocompromised patients, and those with chronic liver disease, immune globulin remains the preferred method of PEP; (4) For international travelers who plan to visit to areas of high or intermediate HAV endemicity, clinicians may administer the vaccine alone to healthy adults under 40 years of age prior to such travel.⁷

In the podcast that originally accompanied this review, Dr. Talbot (1) contrasted the success in pediatric outcomes due to expanded vaccination access with the slow development and adoption of adult vaccination programs; (2) reinforced the importance of Tdap, influenza, and other vaccinations for health care workers; and (3) discussed the need for the rapid development of multiyear and pandemic influenza vaccines, as well as a vaccine targeted at resistant *Staphylococcus*, for all populations.

Prior to this publication, Dr. Talbot added the following updated information:

Zoster (shingles) vaccination. In May 2008, the ACIP released formal recommendations regarding zoster immunization in adults 60 years of age and older,⁸ further clarifying whether to vaccinate older adults with a past history of zoster. The guidelines specifically note that such persons should be vaccinated, as recurrent episodes of zoster can occur soon after prior episodes, even in immunocompetent

persons. They also recommend that patients discontinue the use of any varicella-active antiviral medications (eg, acyclovir) for at least 14 days prior to vaccination, because of potential interference of vaccine replication.

The use of Tdap in pregnant and postpartum

women. Also in May 2008, the ACIP released new recommendations regarding the use of Tdap vaccine in pregnant women — a population in whom the safety and efficacy of Tdap have not been demonstrated.⁹ Regarding this patient population, (1) data do not suggest an increased risk for pertussis infection in pregnant women; (2) no causal relationship has been shown between maternal pertussis infection and fetal morbidity or adverse outcomes of pregnancy; and (3) the ability of transplacental antibodies associated with Tdap to protect infants against pertussis is unknown. However, neonates and infants under 1 year of age are at risk for severe pertussis, often requiring hospitalization, and the risk for death from pertussis is highest among infants in the first 6 months of life. For these reasons, the ACIP recommends that women without a history of Tdap vaccination (including those who are breastfeeding) should receive Tdap in the immediate postpartum period prior to discharge from the hospital or birthing center, in order to reduce the risk of introducing pertussis into the home and exposing the at-risk infant. Tdap may be administered to postpartum mothers if they have received adult tetanus toxoid and reduced diphtheria toxoid (ie, Td) vaccine at least two years prior (ie, there is no need to wait 10 years following the last Td immunization to receive Tdap in this setting). The ACIP also maintained its earlier recommendation that pregnant women with an indication for tetanus immunization receive Td if they cannot defer immunization until after delivery.

References

1. Kimberlin DW, Whitley RJ. Varicella-zoster vaccine for the prevention of herpes zoster. *N Engl J Med.* 2007; 356(13):1338-1343.

2. Oxman MN, Levin MJ, Johnson GR, et al.; Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352(22):2271-2284.
3. Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices. ACIP provisional recommendations for the use of zoster vaccine. Accessed November 15, 2007.
4. Kretsinger K, Broder KR, Cortese MM, et al. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for use of Tdap among health-care personnel. *MMWR Recomm Rep*. 2006;55(RR-17):1-37.
5. Ward JI, Cherry JD, Chang SJ, et al. Efficacy of an acellular pertussis vaccine among adolescents and adults. *N Engl J Med*. 2005;353(15):1555-1563.
6. Victor JC, Monto AS, Surdina TY, et al. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. *N Engl J Med*. 2007;357(17):1685-1694.
7. Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). Update: prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2007; 56(41):1080-1084.
8. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2008;57(RR-5):1-30; quiz CE2-4.
9. Murphy TV, Slade BA, Broder KR, et al. Prevention of pertussis, tetanus, and diphtheria among pregnant and postpartum women and their infants: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2008; 57(RR-4):1-51.

Community-Acquired Pneumonia

Bartlett JG. February 2008; Volume 1, Number 8

LEARNING OBJECTIVE

Discuss the current recommendations regarding diagnostic testing and antibiotic selection in the management of pneumonia

Community-acquired pneumonia (CAP) is the sixth most common cause of death in the United States and the major cause of death due to an infectious disease. In 2007, the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) released joint guidelines based on an enormous (>30,000 patients) database from Medicare addressing nearly all facets of CAP. Dr. John G. Bartlett of the Johns Hopkins University School of Medicine summarized these guidelines and reviewed some of the practical issues involved in the clinical management of patients with CAP.

In his analysis of the joint IDSA/ATS guidelines,¹ Dr. Bartlett noted the following key points:

- **Testing.** Routine diagnostic testing should include a history, physical examination, imaging (generally a chest x-ray), and pulse oximetry. With respect to microbiology, routine blood cultures are now recognized as “optional,” except in patients who require hospitalization in the intensive care unit (ICU). Dr. Bartlett noted that, despite advances in molecular diagnostics, the quality of standard microbiology with respiratory secretions has undergone a sharp decline. As a result, more than 80% of patients with CAP are treated empirically with no microbiology results for guidance.

-
- **Antibiotic selection.** Antibiotic selection is largely empiric, based on site of care and severity of illness; the joint guidelines provide specific recommendations for outpatients, patients hospitalized in the general medical service, and patients hospitalized in the ICU. The rationale for these selections is based largely on in vitro activity against the major pulmonary pathogens and excellent performance in clinical trials. Recommendations are also provided for pathogen-specific treatment for infections involving methicillin-resistant *Staphylococcus aureus* (MRSA; USA 300 strain) using vancomycin or linezolid.
 - **Prevention.** Among the most important findings regarding prevention of CAP are smoking cessation, appropriate use of influenza vaccine, and the use of the protein-conjugated pneumococcal vaccine in children.² IDSA/ATS advocates pneumococcal vaccine polyvalent for patients at risk for pneumococcal infections, but that vaccine has demonstrated only a modest effect on the frequency of pneumonia or pneumococcal pneumonia; its major effect appears to be a 40% to 50% reduction in the frequency of pneumococcal bacteremia.^{3,4}
 - **The “4-hour” rule.** Previously, Medicare audits required that antibiotics be administered within 4 hours of registration in a hospital or emergency department; unintended consequences of this rule have included antibiotic abuse, with associated costs, toxicities, and resistance. Studies to define these “unintended consequences” have resulted in two important changes: (1) a new category called “diagnostic uncertainty” of the CAP diagnosis, which eliminates this 4-hour requirement from the audit because it indicates that there may be congestive heart failure, pulmonary embolism, or some other diagnosis that would result in antibiotic abuse⁵; and (2) elimination of this measure as a criterion in the “pay-for-performance” decision.⁵

Among the clinical management issues addressed by Dr. Bartlett were the following:

- **MRSA CAP.** A 2007 Centers for Disease Control and Prevention paper reported on CAP associated with influenza and MRSA superinfection in 10 patients who were previously healthy and generally young (median age: 18 years).⁶ Patients presented with severe pneumonia that was associated with pulmonary necrosis, severe pulmonary symptoms, and a mortality rate of 60%. The median duration of symptoms from onset to death was only 3.5 days. The infective agent was “community-acquired MRSA” (designated the USA 300 strain). Antibiotic treatments recommended by the IDSA/ATS guidelines for MRSA CAP are vancomycin or linezolid.
- **Duration of treatment.** Scientific evidence does not support the duration of antibiotic treatment for patients with CAP, and experts are increasingly concerned that prolonged antibiotic use contributes to resistance, cost, and toxicity. A 2006 study from the Netherlands directly addressed the issue of duration of treatment.⁷ Patients with mild or moderate-to-severe CAP were randomized to receive intravenous amoxicillin and were evaluated for response after three days. Those who showed substantial improvement after three days were randomized to either oral amoxicillin or placebo for five days. The results showed no difference with treatment for three days versus eight days, in terms of clinical cure, bacteriologic cure, and radiologic cure (evaluated at day 10 as well as at day 28).⁷ Dr. Bartlett noted that, although it is premature to say that three days should be a “standard course” of antibiotics for patients with CAP, these data show that the customary response—treating for one week, ten days, or two weeks in patients with mild or moderate CAP—is probably too long for most of them.

- **Pathogen-directed therapy versus empiric antibiotic treatment.** A 2005 study addressed the issue of pathogen-directed therapy versus empiric antibiotic treatment.⁸ Hospitalized patients with CAP were randomized for treatment based on microbiology results or empiric treatment. The former group underwent extensive diagnostic testing and received penicillin for pneumococcal pneumonia, erythromycin for atypical pathogens, and amoxicillin-clavulanate for most other bacteria. Those who received empiric therapy were treated with a β -lactam/ β -lactamase inhibitor plus erythromycin. The clinical outcome was essentially the same in the two groups in terms of mortality, rate of clinical failure, length of stay, duration of antibiotics, and time to defervescence.⁸ However, rates of adverse events (primarily GI intolerance) differed significantly: 60% in the empiric antibiotic treatment group versus 17% in the pathogen-directed therapy group (95% CI, -0.5 to -0.3; $P < .001$).⁸ Dr. Bartlett noted that most of the GI intolerance reactions were associated with the use of erythromycin—an effect that would be unlikely with the macrolides most often prescribed in the United States.

In the podcast that originally accompanied this review, Dr. Bartlett provided a clinical perspective on the information presented in the newsletter, discussing the need for a chest x-ray to differentiate between CAP and acute exacerbation of chronic bronchitis in order to avoid antibiotic abuse; the cost issues that have reduced microbiology use; the need for laboratory results for necrotizing pneumonia caused by MRSA; and additional background on Medicare's "4-hour rule" and the effect of the changes regarding "clinical uncertainty." He provided advice for clinicians when selecting antibiotics for patients with CAP, outlining the problems they may encounter obtaining cultures after administering antibiotics in recalcitrant patients with CAP.

Prior to this publication, Dr. Bartlett added the following updated information: The most surprising

recent development in the field has been the sudden resistance of influenza A (H1N1) to oseltamivir. This strain will account for about 50% of the influenza cases in the 2008-2009 season. This major development of resistance has been precipitous: less than 1% in the 2006–2007 season, 19% in the 2007–2008 season, and 99% in the 2008–2009 season.⁹ Particularly surprising is the fact that this resistant strain was variably distributed in the world and showed no relationship to usage rates of oseltamivir.⁹ The illness appeared similar to that caused by oseltamivir-sensitive strains,¹⁰ and the revised recommendations for treatment (with the assumption that most physicians would not know the strain involved) was to prescribe either zanamivir (active against all strains) or oseltamivir plus either amantadine or ramantadine.¹¹

Another recent development is the huge impact that Prevnar[®] Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM197 Protein; for pediatric use only; Wyeth Pharmaceuticals, Inc.) has had on invasive pneumococcal infections in the United States. Although reports have documented the anticipated positive impact on children who received the vaccine, pneumococcal illness in older adults has also decreased significantly (a result attributed to the "herd effect"). However, there is now slippage with some new serotypes (called "replacement strains" — that is, to replace those in the vaccine).¹² Of particular importance is strain 19A, which is not in the vaccine and is resistant to penicillin and macrolides. Note that, whereas this strain will be included in the next protein-conjugated vaccine, it is not expected until 2012.

References

1. Mandell LA, Wunderink RG, Anzueto A, et al.; [Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults.](#) *Clin Infect Dis.* 2007;44(suppl 2):S27-S72.

2. Kyaw MH, Lynfield R, Schaffner W, Craig AS, Hadler J, et al. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. *N Engl J Med.* 2006;354(14):1455-1463.
3. Butler JC, Breiman RF, Campbell JF, Lipman HB, Broome CV, Facklam RR. Pneumococcal polysaccharide vaccine efficacy: an evaluation of current recommendations. *JAMA.* 1993;270(15):1826-1831.
4. Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Engl J Med.* 1991;325(21):1453-1460.
5. Metersky ML, Sweeney TA, Getzow MB, Siddiqui F, Nsa W, Bratzler DW. Antibiotic timing and diagnostic uncertainty in Medicare patients with pneumonia: is it reasonable to expect all patients to receive antibiotics within 4 hours? *Chest.* 2006;130(1):16-21.
6. Centers for Disease Control and Prevention (CDC). Severe methicillin-resistant *Staphylococcus aureus* community-acquired pneumonia associated with influenza — Louisiana and Georgia, December 2006-January 2007. *MMWR Morb Mortal Wkly Rep.* 2007;56(14):325-329.
7. el Moussaoui R, de Borgie CA, van den Broek P, et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community-acquired pneumonia: randomized, double blind study. *BMJ.* 2006;332(7554):1355.
8. van der Eerden MM, Vlasplolder F, de Graaff CS, et al. Comparison between pathogen directed antibiotic treatment and empirical broad spectrum antibiotic treatment in patients with community acquired pneumonia: a prospective randomised study. *Thorax.* 2005; 60(8):672-678.
9. Dharan NJ, Gubareva LV, Meyer JJ, et al.; Oseltamivir-Resistance Working Group. Infections with oseltamivir-resistant influenza A(H1N1) virus in the United States. *JAMA.* 2009;301(10):1034-1041.
10. Gooskens J, Jonges M, Claas EC, Meijer A, van den Broek PJ, Kroes AM. Morbidity and mortality associated with nosocomial transmission of oseltamivir-resistant influenza A(H1N1) virus. *JAMA.* 2009;301(10):1042-1046.
11. Weinstock DM, Zuccotti G. The evolution of influenza resistance and treatment. *JAMA.* 2009;301(10):1066-1069.
12. Richter SS, Heilmann KP, Dohrn CL, Riahi F, Beekmann SE, Doern GV. Changing epidemiology of antimicrobial-resistant *Streptococcus pneumoniae* in the United States, 2004-2005. *Clin Infect Dis.* 2009;48(3):e23-e33.

Update on New Antimicrobials

Cosgrove SE. March 2008; Volume 1, Number 9

LEARNING OBJECTIVE

Describe the indications, efficacy, and side effects of important new anti-infective agents

Although the past decade has witnessed disturbing increases in the rates of antimicrobial resistance in hospitals and community settings, the discovery, testing, and Food and Drug Administration (FDA) approval of novel antimicrobial agents has diminished dramatically during the same time period. Given these developments, appropriate use of currently available antimicrobial agents has become increasingly important. Dr. Sara E. Cosgrove of the Johns Hopkins University School of Medicine reviewed several new antimicrobial agents that have recently become available.

Daptomycin. A novel lipopeptide antibiotic with rapid bactericidal activity against Gram-positive organisms, particularly *Staphylococcus aureus*, daptomycin was initially FDA-approved for the treatment of skin and soft tissue infections. A 2006 open-label, randomized, controlled trial that compared daptomycin 6 mg/kg daily with standard therapy (initial low-dose gentamicin plus either an antistaphylococcal penicillin or vancomycin) in

adult patients with *S. aureus* bacteremia demonstrated that daptomycin is not inferior to standard therapy for the treatment of *S. aureus* bacteremia and right-sided endocarditis.¹ Although antistaphylococcal penicillins (eg, oxacillin and nafcillin) remain the antibiotics of first choice for the treatment of methicillin-susceptible *S. aureus* (MSSA) bacteremia and endocarditis, daptomycin is a reasonable alternative to vancomycin for patients with severe penicillin allergy or methicillin-resistant *S. aureus* (MRSA) bacteremia.

Tigecycline. A novel bacteriostatic glycylicycline antibiotic derived from tetracyclines, tigecycline has a broad spectrum of activity against most strains of staphylococci and streptococci (including MRSA and vancomycin-resistant enterococci [VRE]), anaerobes, and many Gram-negative organisms (with the exception of *Proteus* species and *Pseudomonas aeruginosa*). One 2005 report pooled data from two double-blind, randomized, controlled trials that compared tigecycline with parenteral imipenem-cilastatin for the treatment of patients with complicated intra-abdominal infections.² A second 2005 report pooled data from two double-blind, randomized, controlled trials that compared tigecycline with vancomycin plus aztreonam in hospitalized adults with complicated skin and skin structure infections that involved deep soft tissue (including infections associated with significant underlying disease, such as diabetes, peripheral vascular disease, or venous insufficiency).³ Both studies supported the efficacy of the agent. Tigecycline also was recently FDA-approved for the treatment of community-acquired pneumonia. Dr. Cosgrove noted that the major drawbacks of the agent include its cost relative to that of other therapeutic alternatives and the high incidence of nausea and vomiting associated with its use.

The Echinocandins. Caspofungin, micafungin, and anidulafungin, which make up a novel class of intravenous (IV) antifungal agents with excellent fungicidal activity against *Candida albicans* and most other *Candida* species, are FDA-approved for the treatment of candidemia. (There are no major

differences between the three agents.)⁴ A 2007 randomized, double-blind trial that compared anidulafungin with fluconazole for the treatment of invasive candidiasis demonstrated that anidulafungin is not inferior to fluconazole and is perhaps superior.⁵ Although fluconazole demonstrates efficacy for the treatment of candidemia — and is both relatively inexpensive and available in a highly bioavailable oral formulation — the results of this study have led most experts to now recommend that clinicians use echinocandins as first-line therapy for patients who have had prior exposure to fluconazole and in critically ill patients before they have identified the species of *Candida*.

Rifaximin. An oral, nonabsorbed derivative of rifamycin, rifaximin is FDA-approved for the treatment of noninvasive *Escherichia coli*-associated traveler's diarrhea. A 2005 randomized, double-blind, placebo-controlled trial of rifaximin versus placebo demonstrated that rifaximin provided 72% protection against traveler's diarrhea in adults.⁶ The advantage of rifaximin is that it is not absorbed, and thus individuals are not at risk for the toxicities associated with systemic antibiotic use. However, Dr. Cosgrove cautioned that researchers have not determined the agent's efficacy against such pathogens as *Shigella*, *Salmonella*, and *Campylobacter* species.

Retapamulin. A novel antibiotic available only in a topical formulation, retapamulin exhibits activity against staphylococci (including MRSA), as well as streptococci, and does not appear to have cross-resistance with other antibiotics, including mupirocin. The agent has been FDA-approved for the treatment of impetigo due to MSSA or *Streptococcus pyogenes*. To determine whether retapamulin can be used in place of systemic antimicrobial agents for the treatment of secondarily infected dermatitis, a 2006 randomized, double-blind, double-dummy, noninferiority trial compared topical retapamulin with oral cephalexin.⁷ The study found that treatment with retapamulin for five days was not inferior to treatment with oral cephalexin for ten days, and that patients preferred topical therapy.

Although retapamulin is not FDA-approved for the treatment of MRSA infections (only for MSSA infections), the agent exhibits in vitro activity against MRSA and would likely be adequate therapy for minor MRSA skin infections.

Prior to this publication, Dr. Cosgrove added the following updated information: Additional data regarding **doripenem**, a new carbapenem antibiotic with broad-spectrum activity against Gram-positive organisms (except MRSA and VRE) and Gram-negative organisms (including *Pseudomonas* and *Acinetobacter* species), have been published. Doripenem has a spectrum of activity that is quite similar to that of meropenem and is currently FDA-approved for the treatment of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis. The study supporting its use for complicated intra-abdominal infections compared doripenem 500 mg IV every 8 hours with meropenem 1 g IV every 8 hours in 476 patients. Doripenem was found to be noninferior to meropenem, with cure rates of 85.9% in the doripenem arm versus 85.3% in the meropenem arm. Both agents were well tolerated, and no patients reported seizures.⁸

Doripenem also has been evaluated for hospital-acquired pneumonia and ventilator-associated pneumonia (VAP). In the study evaluating VAP, 531 patients were randomized to receive either doripenem 500 mg every 8 hours infused over 4 hours or imipenem (doses were either 500 mg every 6 hours infused over 30 minutes or 1000 mg every 8 hours infused over 60 minutes, based on site preference).⁹ Doripenem was found to be noninferior to imipenem, with cure rates of 68.3% in the doripenem arm versus 64.8% in the imipenem arm. Clinical cure rates for VAP caused by *P. aeruginosa* were higher with doripenem (80%) than with imipenem (42.9%), although this difference was not statistically significant because of the small number of evaluable patients with *P. aeruginosa*. This finding is not surprising, given that, compared with imipenem, doripenem exhibits greater in vitro activity against *P. aeruginosa*.¹⁰ Researchers do not know whether there is any

clinical advantage against *P. aeruginosa* with doripenem compared with meropenem, which exhibits more potent Gram-negative activity than imipenem. One other notable feature of the study was the duration of infusion of doripenem of 4 hours, which can be difficult in the clinical intensive care unit setting, where it is not feasible to dedicate the lumen of an IV line for a long period of time.

Although doripenem is the only new antimicrobial agent with Gram-negative activity that has been released recently, it unfortunately does not offer enhanced activity against multidrug-resistant *Pseudomonas* and *Acinetobacter* species and other Gram-negative organisms with carbapenem resistance. A study by the Infectious Diseases Society of America, which reviewed the status of antimicrobial drug development in 2008, reported that there are currently no drugs in late-stage (phase 2 or greater clinical trials) development that have pure Gram-negative activity or activity against these highly resistant Gram-negative organisms.¹¹

References

1. Fowler VG Jr., Boucher HW, Corey GR, et al.; *S. aureus* Endocarditis and Bacteremia Study Group. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med*. 2006;355(7):653-665.
2. Babinchak T, Ellis-Grosse E, Dartois N, Rose GM, Loh E; Tigecycline 301 Study Group; Tigecycline 306 Study Group. The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infection: analysis of pooled clinical trial data. *Clin Infect Dis*. 2005;41(suppl 5):S354-S367.
3. Ellis-Grosse EJ, Babinchak T, Dartois N, Rose G, Loh E; Tigecycline 300 cSSSI Study Group; Tigecycline 305 cSSSI Study Group. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. *Clin Infect Dis*. 2005;41(suppl 5):S341-S353.

-
4. Sobel JD, Revankar SG. Echinocandins—first choice or first-line therapy for invasive candidiasis? *N Engl J Med.* 2007;356(24):2525-2526.
 5. Reboli AC, Rotstein C, Pappas PG, et al.; Anidulafungin Study Group. Anidulafungin versus fluconazole for invasive candidiasis. *N Engl J Med.* 2007;356(24):2472-2482.
 6. DuPont HL, Jiang Z, Okhuysen PC, et al. A randomized, double-blind, placebo-controlled trial of rifaximin to prevent travelers' diarrhea. *Ann Intern Med.* 2005; 142(10):805-812.
 7. Parish LC, Jorizzo JL, Breton JJ, et al.; SB275833/032 Study Team. Topical retapamulin ointment (1%, wt/wt) twice daily for 5 days versus oral cephalexin twice daily for 10 days in the treatment of secondarily infected dermatitis: results of a randomized controlled trial. *J Am Acad Dermatol.* 2006;55(6):1003-1013.
 8. Lucasti C, Jasovich A, Umeh O, Jiang J, Kaniga K, Friedland I. Efficacy and tolerability of IV doripenem versus meropenem in adults with complicated intra-abdominal infection: a phase III, prospective, multicenter, randomized, double-blind, noninferiority study. *Clin Ther.* 2008;30(5):868-883.
 9. Chastre J, Wunderink R, Prokocimer P, Lee M, Kaniga K, Friedland I. Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: a multicenter, randomized study. *Crit Care Med.* 2008;36(4):1089-1096.
 10. Jones RN, Sader HS, Fritsche TR. Comparative activity of doripenem and three other carbapenems tested against Gram-negative bacilli and various β -lactamase resistance mechanisms. *Diagn Microbiol Infect Dis.* 2005;52(1):71-74.
 11. Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: No ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;48(1):1-12.

>> PROCEED TO POST-TEST

<http://www.hopkinscme.edu/ofp/einfectionsmonograph.htm>

Infectious Diarrhea in Adults

Kirkpatrick BD. April 2008; Volume 1, Number 10

LEARNING OBJECTIVE

Discuss the current research identifying risk factors, treatment indications, and limitations for the prevention and management of infectious diarrhea

Cases of infectious diarrhea, especially from food- and water-borne sources, are common in all populations, particularly among travelers and immunocompromised individuals. Approximately 211 to 375 million cases occur in the United States each year,¹ and antibiotic resistance and the increasing importation of fresh fruits and vegetables contribute to new trends in the epidemiology of the disease. Dr. Beth D. Kirkpatrick of the University of Vermont, College of Medicine reviewed new data in four areas of this broad field.

Traveler's diarrhea. A 2006 randomized, double-blind, multicenter trial, compared the efficacy of the nonabsorbable antibiotic rifaximin with ciprofloxacin in patients with traveler's diarrhea.² A total of 399 adult subjects from travel health clinics in Peru, Guatemala, India, and Mexico were enrolled in the trial; all subjects had had acute diarrhea lasting more than 72 hours. This study demonstrated that rifaximin is well tolerated and effective in people who are infected with noninvasive pathogens (predominantly enterotoxigenic *Escherichia coli* [ETEC] and enteroaggregative *E. coli* [EAEC]). The benefits of this agent include its nonabsorbable nature, which may help clinicians avoid using fluoroquinolone to treat diarrhea caused by noninvasive pathogens. Conversely, as this trial demonstrated, the pitfalls associated with rifaximin use include its inferiority to ciprofloxacin for treating invasive pathogens. In this subset of patients, fewer achieved "clinical wellness" (68% with rifaximin versus 85.7% with ciprofloxacin), and more treatment failures (14.7%) occurred in the rifaximin arm.² Increases in the minimum inhibitory concentrations of rifaximin to

ETEC were also found in more than 50% of the ETEC isolates recovered post-therapy.²

Postinfectious irritable bowel syndrome (PI-IBS).

A 2006 meta-analysis of 188 articles and 8 trials was conducted to better estimate the risk for PI-IBS following episodes of acute gastroenteritis/diarrhea.³ The investigators reported an increased risk for IBS following gastrointestinal (GI) infection (median prevalence: 9.8%; odds ratio [OR]: 7.3, compared with control groups), thus reiterating the presence of PI-IBS as a distinct entity, rather than a subset of IBS. Overall, PI-IBS appears to affect both genders equally and is less likely to be associated with pre-existing psychiatric issues.⁴ Furthermore, the association between antecedent GI infection and PI-IBS appears to exist in all populations, including travelers and those diagnosed as part of an enteric disease outbreak.

Domestic outbreaks of ETEC. ETEC is considered the primary agent of traveler's diarrhea, responsible for 30% to 40% of all cases.⁵ A 2006 embedded cohort study investigated a large outbreak of acute diarrhea in Wisconsin in 1998, in ETEC infection spread from a single delicatessen. Guests became ill at 405 catered events, and an estimated 3,338 people reported ETEC diarrhea (median prevalence of illness: 20%).⁶ As one of the largest food-borne outbreaks ever reported in the United States, this study reiterates that food-borne infectious diarrhea due to ETEC occurs domestically as well as abroad and that clinicians should consider ETEC infection if routine cultures are negative. Dr. Kirkpatrick noted that, although other recent outbreaks of diarrhea have implicated tomatoes (*Shigella flexneri*), spinach (*E. coli* 0157:H7), and delicatessen food (ETEC),^{7,8} FoodNet data demonstrate that the overall incidence of *Campylobacter*, *E. coli* 0157:H7, *Salmonella*, and *Yersinia* infections decreased between 1996 and 2003.⁹ Following the discontinuation of fluoroquinolone use in poultry in the United States, experts anticipate that food-borne transmission of quinolone-resistant strains of enteric bacteria will also decrease.¹⁰

Bacterial diarrhea in HIV populations. Infectious diarrhea in immunocompromised people is associated with increased morbidity, and patients are infected with a more diverse range of pathogens than in immunocompetent individuals. A 2006 study analyzed the incidence and etiologies of diarrheal illnesses caused by bacteria in a large (44,778) cohort of HIV-infected individuals during 1992 to 2002 — a decade that spanned the pre-highly active retroviral therapy (HAART) and post-HAART era of HIV treatment.¹¹ Of the 9.6% cases with a confirmed bacterial origin, the most commonly identified pathogens were *Clostridium difficile* (54%), *Shigella* (14%), *Campylobacter* (13.8%), and *Salmonella* (7.4%). In the post-HAART era, all bacterial causes of diarrhea declined (OR, 0.3). Of particular note is the fact that, whereas 48% of the study population were men who have sex with men (MSM), 75% of the *Shigella* cases occurred in MSM. These data reconfirm that *Shigella* species are a sexually transmitted pathogen in HIV-infected MSM, as shown in recent outbreaks and case-control studies.^{12,13}

Prior to this publication, Dr. Kirkpatrick added the following updated information on two recently published articles. One paper described the phase 2 trial of a transcutaneous “patch” traveler’s diarrhea vaccine, which contained heat-labile (LT) enterotoxin — an important virulence component of most ETEC strains.¹⁴ Researchers analyzed a total of 170 travelers to Guatemala and Mexico who had received two LT patches prior to travel. The patch appeared to be safe, aside from local site rashes and pruritus. In addition, the patch was immunogenic; 92% and 82% of patch recipients seroconverted with LT immunoglobulin (Ig)G or IgA antibodies, respectively.¹⁴ Although this study was not powered to demonstrate efficacy, there was no significant difference in the rate of either diarrhea (of any cause) or LT-containing ETEC diarrhea between LT-patch and placebo recipients. However, the patch recipients had significantly lower rates of moderate-to-severe diarrhea ($P=.0070$), fewer loose stools ($P<.0001$), and shorter diarrheal episode duration ($P=.0006$).¹⁴ The formal efficacy evaluation of this novel strategy awaits a phase 3 field trial, but

a transcutaneous LT vaccine would certainly be a welcome approach to the treatment of traveler’s diarrhea.

The second article was a systematic review and meta-analysis of nine randomized, placebo-controlled studies to determine the effectiveness of adjunctive loperamide when used concurrently with antibiotics for the treatment of traveler’s diarrhea.¹⁵ Two primary efficacy outcomes were reviewed: (1) the proportion of people with clinical cure at 24, 48, or 72 hours; and (2) time to last unformed stool (TLUS). A variety of antibiotics and dosing durations (to a maximum of three days) were used in the chosen studies.¹⁵

The majority of participants in the reviewed studies were students or military personnel, with a mean age of 24 years.¹⁵ In these populations, use of loperamide and antibiotics as combination therapy was safe; however, all persons with dysenteric stool findings (blood or mucus in the stool) were excluded from the analysis. As anticipated, ETEC was the most frequently recovered pathogen (28% of patients), and “invasive pathogens” (*Salmonella*, *Shigella*, *Campylobacter*) were uncommon in most populations (14% of patients).¹⁵ Compared with antibiotic use alone, antibiotics administered concurrently with loperamide demonstrated an improved rate of clinical cure at 24 and 48 hours (OR, 2.58 and 2.15, respectively).¹⁵ Combination therapy was not beneficial at 72 hours. When evaluating TLUS, significant heterogeneity existed between the studies. Overall, adjunctive therapy led to a shorter TLUS by 2 to 23 hours ($P<.001$), with a pooled mean TLUS of 17 hours.¹⁵ For comparison, the literature has demonstrated a mean TLUS of 34 hours in patients with traveler’s diarrhea treated with loperamide alone.

This meta-analysis clarifies the additive benefits of loperamide administered concurrently with antibiotics and reiterates the safety of combination therapy for most cases of nondysenteric “ambulatory traveler’s diarrhea.” An analysis of loperamide use in patients, with diarrhea caused by invasive

pathogens, remains to be conducted. The importance of this information was reiterated by the finding that adjunctive loperamide had no benefit in one analyzed population in whom *Campylobacter* was the prevalent pathogen.¹⁵

References

1. Thielman NM, Guerrant RL. Clinical practice. Acute infectious diarrhea. *N Engl J Med*. 2004;350(1):38-47.
2. Taylor DN, Bourgeois AL, Ericsson CD, et al. A randomized, double-blind study of rifaximin compared with placebo and with ciprofloxacin in the treatment of travelers' diarrhea. *Am J Trop Med Hyg*. 2006;74(6):1060-1066.
3. Halvorson HA, Schlett CD, Riddle MS. Postinfectious irritable bowel syndrome—a meta-analysis. *Am J Gastroenterol*. 2006;101(8):1894-1899.
4. Spiller RC. Role of infection in irritable bowel syndrome. *J Gastroenterol*. 2007;42 (suppl 17):41-47.
5. Steffen R. Epidemiology of traveler's diarrhea. *Clin Infect Dis*. 2005;41(suppl 8):S536-S540.
6. Beatty ME, Adcock PM, Smith SW, et al. Epidemic diarrhea due to enterotoxigenic *Escherichia coli*. *Clin Infect Dis*. 2006; 42(3):329-334.
7. Reller ME, Nelson JM, Mølbak K, et al. A large, multiple-restaurant outbreak of infection with *Shigella flexneri* serotype 2a traced to tomatoes. *Clin Infect Dis*. 2006;42(2):163-169.
8. Centers for Disease Control and Prevention (CDC). Ongoing multistate outbreak of *Escherichia coli* serotype O157:H7 infections associated with consumption of fresh spinach—United States, September 2006. *MMWR Morb Mortal Wkly Rep*. 2006;55(38):1045-1046.
9. Centers for Disease Control and Prevention (CDC). Preliminary FoodNet data on the incidence of infection with pathogens transmitted commonly through food. *MMWR Morb Mortal Wkly Rep*. 2006;55(14):392-395.
10. Nelson JM, Chiller TM, Powers JH, Angulo FJ. Fluoroquinolone-resistant *Campylobacter* species and the withdrawal of fluoroquinolones from use in poultry: a public health success story. *Clin Infect Dis*. 2007;44(7):977-980.
11. Sanchez TH, Brooks JT, Sullivan PS, et al; Adult/Adolescent Spectrum of HIV Disease Study Group. Bacterial diarrhea in persons with HIV infection, United States, 1992-2002. *Clin Infect Dis*. 2005;41(11):1621-1627.
12. Morgan O, Crook P, Cheasty T, et al. *Shigella sonnei* outbreak among homosexual men, London. *Emerg Infect Dis*. 2006;12(9):1458-1460.
13. Aragón TJ, Vugia DJ, Shallow S, et al. Case-control study of shigellosis in San Francisco: the role of sexual transmission and HIV infection. *Clin Infect Dis*. 2007;44(3):327-334.
14. Frech SA, Duport HL, Bourgeois AL. Use of a patch containing heat-labile toxin from *Escherichia coli* against travellers' diarrhoea: a phase II, randomised double-blind, placebo-controlled field trial. *Lancet*. 2008;371(9629):2019-2025.
15. Riddle MS, Arnold S, Tribble DR. Effect of adjunctive loperamide in combination with antibiotics on treatment outcomes in traveler's diarrhea: a systematic review and meta-analysis. *Clin Infect Dis*. 2008;47(8):1007-1114.

Infectious Mononucleosis

Auwaerter PG; May 2008; Volume 1, Number 11

LEARNING OBJECTIVE

Describe how Epstein-Barr virus infection is acquired, diagnosed, and cautions regarding sequelae

Infectious mononucleosis (IM) has been described as a disease of the industrialized 20th century, whereby acute infection with Epstein-Barr virus (EBV) in susceptible adolescents and adults can yield the typical triad of fever, severe pharyngitis, and lymphadenopathy, often accompanied by

profound fatigue. Infection at younger ages is more typical in less industrialized societies and usually presents as a subclinical infection. Other features suggestive of IM include splenomegaly, elevations in liver transaminase levels, and increased percentages of both typical and atypical lymphocytes. Dr. Paul Auwaerter of the Johns Hopkins University School of Medicine reviewed the current literature to provide a “snapshot” of the ongoing research into this condition.

Transmission. IM is sometimes called the “kissing disease,” as the virus has been easily demonstrated in saliva samples from patients with the disease.¹ However, a number of studies have now concluded that EBV can also be found in both female and male genital secretions.^{2,3} A 2006 study to determine whether EBV can be transmitted through genital contact tested patients with IM and their close contacts. The investigators found EBV viral isolates to be identical in 41% of the IM/contact pairs, with those who engaged in sexual contact having a significantly higher rate (82%) of identical isolates than IM/non-sexual-contact pairs (17%; $P=.0012$).⁴ Although these results provide indirect support at best (because partners reporting sexual contact might still have acquired infection by oral means, the study did not account well for prior relationships, and the virus could also be acquired through other activities associated with sexual intercourse, such as deep kissing) overall, sexual activity appears to be a risk factor for the acquisition of both EBV and IM.

Prevention. The complications of IM — including prolonged and debilitating fatigue that can last months after acute infection,⁵ death or severe morbidity secondary to airway obstruction, splenic rupture, and neurologic sequelae,⁶ (along with epidemiologic studies that suggest an increased risk for the development of Hodgkin’s lymphoma⁷ and multiple sclerosis⁸) — have all enhanced interest in prevention strategies. A 2007 randomized, double-blind study sought to determine whether acute EBV infection or IM could be prevented through the immunization of naïve young adults using a recombinant gp350 vaccine.⁹ The authors

found that immunization yielded detectable antibody response in 98.7% of the subjects. By the end of the 18-month study period, the primary endpoint of preventing IM demonstrated an efficacy of 78% but did not halt asymptomatic acquisition of EBV. Adverse events did not differ between the vaccine and placebo groups.⁹

Management of symptoms. Although some clinicians have long used corticosteroids to help provide immediate relief from symptoms of IM,¹⁰ this practice remains controversial, since the two largest studies examining the role of glucocorticoids for the treatment of patients with IM failed to demonstrate significant improvement in pharyngeal symptoms or a faster return to work or school.^{11,12} A 2006 evidenced-based Cochrane review¹³ that examined corticosteroids versus placebo reported that only two trials found a benefit of 12 hours in the resolution of throat soreness; one trial suggested that fatigue was reduced at four weeks (although the benefit was confounded by combination with antiviral therapy), and two trials reported severe complications in the corticosteroid group (symptomatic ketoacidosis, peritonsillar infection). These data reaffirm that the use of corticosteroids for symptom control in patients with IM remains in the “art” rather than in the science of medicine.

Fatigue. Although fatigue is a common component of acute IM infection, fatigue that persists beyond one month affects a small minority of patients but can last for one year or more; female patients and those with preexisting affective disorders are at higher risk.¹⁴⁻¹⁶ The explanation for this persistent fatigue is unclear. One study, designed to test for a measurable cytokine response, failed to discriminate between a prolonged fatigue group and a recovery group when it evaluated a total of eight pro-inflammatory cytokines.¹⁷ Other research, seeking to identify genetic transcriptional changes, has implicated mitochondrial dysfunction, cell-cycle dysregulation, myogenic changes, and neuronal disturbance as potential factors.^{18,19} A 2006 study, analyzing genetic variants between subjects with significant fatigue at six months and control patients

with IM who recovered promptly, revealed a total of 35 genes with increased expression in the former group.²⁰ Whether these genes will hold the key to understanding IM-related fatigue remains uncertain.

Splenomegaly. Splenic rupture due to IM, whether occurring spontaneously or resulting from trauma,^{21,22} occurs mostly within 2 to 21 days of symptom onset; however, some people have reported occurrences taking place thereafter — 7 weeks postinfection was one of the latest in the medical literature.^{23,24} A common approach clinicians take is to recommend that athletes wait an average of four weeks postinfection before resuming contact sports; such a recommendation assumes that the spleen has returned to normal size. Since physical examination of the spleen is unreliable, some clinicians have thought that obtaining an ultrasound to document the absence of splenomegaly can offer some confidence that patients may safely resume activities.²⁵ A 2006 study tested the adequacy of this measurement by ultrasound evaluation of spleen size in a college-aged, athletic population (male and female) without evident illness.²⁶ The investigators found that 7% of this population met the criteria for splenomegaly, although a prior history of IM did not correlate with splenic enlargement.²⁶ Unfortunately, this information only makes deciding whether the athlete can return to play even more difficult, as ultrasonographic evidence of splenomegaly in an athlete may be a normal finding in some, rather than continued evidence of risk from EBV-driven processes.

Prior to this publication, Dr. Auwaerter added the following updated information. Other groups are examining a number of different vaccine strategies, including those that target both lytically and latently expressed proteins of EBV,²⁷ as well as a T-cell peptide epitope-based vaccine that is uniquely targeted to an individual human leukocyte antigen haplotype.²⁸ To date, no vaccine has proven to prevent infection, but at least two seem to correlate with asymptomatic acquisition of EBV.^{28,29} Given the craftiness of this

immunologically-oriented virus, EBV may prove to be as tricky as HIV in terms of generating either protective or important preventive responses — whether for the avoidance of initial infection or for decreasing the development of EBV-associated malignancies.

A prospective study of athletes evaluated with respect to splenic size over five years included a subset of 20 athletes who developed IM.³⁰ The subjects diagnosed with IM received weekly ultrasounds. On average, they had approximately a one-third increase in splenic size from baseline values, and they reached a peak size at day 12.3 (\pm 5.1 days). The latest that an individual reached peak splenic size was at 3.5 weeks; a linear regression model based on this study suggested a 1% decline in size per day once the athlete attained peak size.³⁰ All subjects exhibited resolution of splenic enlargement within four to six weeks of the onset of illness. This small study comports reasonably well with expert opinion recommendations that athletes should avoid heavy contact sports for at least three weeks and/or until the spleen has returned to normal size.³¹ However, whether spleen size is strongly correlated with risk for splenic rupture is not based on robust data.

References

1. Balfour HH Jr., Holman CJ, Hokanson KM, et al. [A prospective clinical study of Epstein-Barr virus and host interactions during acute infectious mononucleosis.](#) *J Infect Dis.* 2005;192(9):1505-1512.
2. Israele V, Shirley P, Sixbey JW. [Excretion of the Epstein-Barr virus from the genital tract of men.](#) *J Infect Dis.* 1991;163(6):1341-1343.
3. Sixbey JW, Lemon SM, Pagano JS. [A second site for Epstein-Barr virus shedding: the uterine cervix.](#) *Lancet.* 1986;2(8516):1122-1124.
4. Thomas R, Macsween KF, McAulay K, et al. [Evidence of shared Epstein-Barr viral isolates between sexual partners, and low level EBV in genital secretions.](#) *J Med Virol.* 2006;78(9):1204-1209.

5. White PD, Thomas JM, Kangro HO, et al. Predictions and associations of fatigue syndromes and mood disorders that occur after infectious mononucleosis. *Lancet*. 2001;358(9297):1946-1954.
6. Bailey RE. Diagnosis and treatment of infectious mononucleosis. *Am Fam Physician*. 1994;49(4):879-888.
7. Hjalgrim H, Askling J, Rostgaard K, et al. Characteristics of Hodgkin's lymphoma after infectious mononucleosis. *N Engl J Med*. 2003;349(14):1324-1332.
8. Thacker EL, Mirzaei F, Ascherio A. Infectious mononucleosis and risk for multiple sclerosis: a meta-analysis. *Ann Neurol*. 2006;59(3):499-503.
9. Sokal EM, Hoppenbrouwers K, Vandermeulen C, et al. Recombinant gp350 vaccine for infectious mononucleosis: a phase 2, randomized, double-blind, placebo-controlled trial to evaluate the safety, immunogenicity, and efficacy of an Epstein-Barr virus vaccine in healthy young adults. *J Infect Dis*. 2007;196(12):1749-1753.
10. Disney FA. Corticosteroids for infectious mononucleosis. *Pediatr Infect Dis J*. 1988;7(11):820-821.
11. Tynell E, Aurelius E, Brandell A, et al. Acyclovir and prednisolone treatment of acute infectious mononucleosis: a multicenter, double-blind, placebo-controlled study. *J Infect Dis*. 1996;174(2):324-331.
12. Collins M, Fleisher G, Kreisberg J, Fager S. Role of steroids in the treatment of infectious mononucleosis in the ambulatory college student. *J Am Coll Health*. 1984;33(3):101-105.
13. Candy B, Hotopf M. Steroids for symptom control in infectious mononucleosis. *Cochrane Database Syst Rev*. 2006;(3):CD004402.
14. Krilov LR, Fisher M, Friedman SB, Reitman D, Mandel FS. Course and outcome of chronic fatigue in children and adolescents. *Pediatrics*. 1998;102(2 pt 1):360-366.
15. Bennett BK, Hickie IB, Vollmer-Conna US, et al. The relationship between fatigue, psychological and immunological variables in acute infectious illness. *Aust N Z J Psychiatry*. 1998;32(2):180-186.
16. Petersen I, Thomas JM, Hamilton WT, White PD. Risk and predictors of fatigue after infectious mononucleosis in a large primary-care cohort. *QJM*. 2006;99(1):49-55.
17. Vollmer-Conna U, Cameron B, Hadzi-Pavlovic D, et al.; Dubbo Infective Outcomes Study Group. Postinfective fatigue syndrome is not associated with altered cytokine production. *Clin Infect Dis*. 2007;45(6):732-735.
18. Vernon SD, Nicholson A, Rajeevan M, et al. Correlation of psycho-neuroendocrine-immune (PNI) gene expression with symptoms of acute infectious mononucleosis. *Brain Res*. 2006;1068(1):1-6.
19. Vernon SD, Whistler T, Cameron B, Hickie IB, Reeves WC, Lloyd A. Preliminary evidence of mitochondrial dysfunction associated with post-infective fatigue after acute infection with Epstein Barr virus. *BMC Infect Dis*. 2006;6:15.
20. Cameron B, Galbraith S, Zhang Y, et al; Dubbo Infection Outcomes Study. Gene expression correlates of postinfective fatigue syndrome after infectious mononucleosis. *J Infect Dis*. 2007;196(1):56-66.
21. Safran D, Bloom GP. Spontaneous splenic rupture following infectious mononucleosis. *Am Surg*. 1990;56(10):601-605.
22. Rutkow IM. Rupture of the spleen in infectious mononucleosis: a critical review. *Arch Surg*. 1978;113(6):718-720.
23. Asgari MM, Begos DG. Spontaneous splenic rupture in infectious mononucleosis: a review. *Yale J Biol Med*. 1997;70(2):175-182.
24. Johnson MA, Cooperberg PL, Boisvert J, Stoller JL, Winrob H. Spontaneous splenic rupture in infectious mononucleosis: sonographic diagnosis and follow-up. *AJR Am J Roentgenol*. 1981;136(1):111-114.

25. Auwaerter PG. Infectious mononucleosis: return to play. *Clin Sports Med.* 2004;23(3):485-497, xi.
26. Hosey RG, Mattacola CG, Kriss V, Armsey T, Quarles JD, Jagger J. Ultrasound assessment of spleen size in collegiate athletes. *Br J Sports Med.* 2006;40(3):251-254.
27. Lockey TD, Zhan X, Surman S, Sample CE, Hurwitz JL. Epstein-Barr virus vaccine development: a lytic and latent protein cocktail. *Front Biosci.* 2008;13:5916-5927.
28. Elliott SL, Suhrbier A, Miles JJ, et al. Phase I trial of a CD8+ T-cell peptide epitope-based vaccine for infectious mononucleosis. *J Virol.* 2008;82(3):1448-1457.
29. Sokal EM, Hoppenbrouwers K, Vandermeulen C, et al. Recombinant gp350 vaccine for infectious mononucleosis: a phase 2, randomized, double-blind, placebo-controlled trial to evaluate the safety, immunogenicity, and efficacy of an Epstein-Barr virus vaccine in healthy young adults. *J Infect Dis.* 2007;196(12):1749-1753.
30. Hosey RG, Kriss V, Uhl TL, DiFiori J, Hecht S, Wen DY. Ultrasonographic Evaluation of Splenic Enlargement in Athletes with Acute Infectious Mononucleosis. *Br J Sports Med.* 2008;42(12):974-977.
31. Putukian M, O'Connor FG, Stricker P, et al. Mononucleosis and athletic participation: an evidence-based subject review. *Clin J Sport Med.* 2008;18(4):309-315.

Challenges in the Management of Urinary Tract Infections

Hynes NA; June 2008; Volume 1, Number 12

LEARNING OBJECTIVE

Describe the first-line antibiotic treatment of uncomplicated urinary tract infection, the impact of antibiotic resistance on treatment choice, and diagnostic issues particular to sexually active adolescents

Dr. Noreen A. Hynes from the Division of Infectious Diseases at The Johns Hopkins University School of Medicine reported on the management challenges that continually arise from antimicrobial resistance in both uncomplicated and complicated urinary tract infections (UTIs). Guidelines issued in 1999 by the Infectious Diseases Society of America (IDSA) provided evidence-based recommendations for treatment designed to stem the tide of antimicrobial resistance among the organisms that commonly cause UTIs.¹ However, a 2007 study analyzing antibiotic use for the treatment of uncomplicated UTIs among women in outpatient settings, before and after the guidelines were issued, reported no change in provider prescribing habits.² Dr. Hynes noted that the study found hospital-based providers and those caring for self-pay patients to be significantly more likely to use the first-line recommended therapy (trimethoprim-sulfamethoxazole [TMP-SMX]), suggesting that economic realities rather than concerns about evolving antimicrobial resistance may be a prime driver in antimicrobial selection.

In 2000, women made up more than 80% of the approximately 11 million outpatient visits by patients over 19 years of age with a UTI,³ and *Escherichia coli* (predominantly the O, K, and H antigen serotypes) accounted for 80% to 90% of those infections.⁴ A more complete picture of antibiotic resistance among *E. coli* urinary tract isolates came from a 2006 report on the results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA), an ongoing

surveillance study that assesses antibiotic resistance rates to five antimicrobial agents (ampicillin [AMP], TMP-SMX, ciprofloxacin [CIP], levofloxacin [LEV], and nitrofurantoin [NIT]).⁵ The investigators found that overall *E. coli* resistance was highest to AMP (37.7%), followed by TMP-SMX (21.3%), CIP (5.5%), LEV (5.1%), and NIT (1.1%).⁵ In addition, the authors noted that resistance to CIP was highest among those over 65 years of age compared with other age-groups ($P < .05$) and that the West South Central region of the United States (Arkansas, Louisiana, Oklahoma, and Texas) had the highest resistance rates across all five antibiotics.⁵ Dr. Hynes commented that, given the rates of fluoroquinolone resistance reported, prudent use of this class of agent is needed; such use should be based on region-specific and target group-specific urinary isolate antimicrobial resistance data.

Differentiation between UTIs and common sexually transmitted infections (STIs) — that include, *Chlamydia trachomatis*, *Trichomonas vaginalis*, and *Neisseria gonorrhoeae* — among sexually active adolescent/young adult females presents an ongoing challenge. A 20-month, cross-sectional study demonstrated that among members of this group, urinary symptoms alone or in combination with urinalysis data provided inadequate information to render an accurate clinical decision.⁶ The authors of the study recommended against empiric treatment, advocating instead an office-based evaluation that includes a history to elicit UTI and STI risk factors and symptoms, plus a urinalysis and urine culture, along with laboratory testing, for these common STIs.

UTI is the most common bacterial infection encountered in renal transplant recipients, and *Corynebacterium urealyticum*, a Gram-positive bacillus, has been recently recognized as a cause. The infection can lead to obstructive uropathy, graft malformation, and graft rejection/loss. A 2008 prospective cohort study to determine risk factors for and outcomes following infection with *C. urealyticum* among renal transplant patients demonstrated a much higher rate of *C. urealyticum*

bacteriuria (9.8%)⁷ than previously reported in less robust studies.⁸ Dr. Hynes recommended that if alkaline pH or struvite crystals are noted on urinalysis, the clinician should alert the microbiology laboratory that this organism may be present. Antimicrobial sensitivities should be used to guide treatment, as almost all isolates are multidrug-resistant.

Dr. Hynes also reviewed a randomized, double-blind, phase 2 clinical trial that compared the efficacy of a vaginal mucosa-delivered vaccine versus placebo for the prevention of recurrent UTIs.⁹ The vaccine contained ten uropathic strains, six of which were *E. coli*. It proved to be most effective in preventing *E. coli* UTI in the group that received primary immunization followed by booster intravaginal dosing.

In the podcast that originally accompanied this review, Dr. Hynes discussed the IDSA guidelines in greater detail, explaining the particular impact antibiotic resistance and cost-containment practices place on determining the choice of treatment agent. She also provided clinical practice pointers on diagnosing and differentiating uncomplicated from complicated UTIs. Other topics addressed in this newsletter issue were discussed from a clinical/practice change perspective.

Prior to this publication, Dr. Hynes updated this information with reports from two studies that highlighted the rapid evolution of fluoroquinolone-resistant *E. coli* UTIs, thus underscoring the need to consider changing first-line treatment for uncomplicated UTIs to NIT.

A case-control study conducted in Denver, Colorado, examined the impact of changes in prescribing policy on shifting trends in uropathogenic *E. coli* resistance to LEV and TMP-SMX over an 8-year period (1998 to 2005).¹⁰ The authors identified 123 adult, nonpregnant outpatients, 18 to 89 years of age, among whom 41 cases were defined with LEV-resistant UTIs during 2005, and they matched them with 81 controls with LEV-sensitive UTIs.

On multivariate, conditional logistic regression of the risk factors examined (diabetes, congestive heart failure, urinary catheter use, number of previous UTIs, past LEV use, and hospitalization within the past 12 months), only past LEV use (adjusted odds ratio [AOR]: 7.6; 95% confidence interval [CI]: 2.1 to 27.5) and hospitalization within the past 12 months (AOR: 2.0; 95% CI: 1.0 to 3.9) were found to be significantly associated with an LEV-resistant UTI among the age-matched (within five years) cases and controls.¹⁰ Based on their findings, the authors provided a treatment algorithm for uncomplicated UTIs, complicated UTIs, and pyelonephritis, in which clinicians recommend empiric therapy only for uncomplicated UTIs using NIT; clinicians should base treatment for the other types of UTI on the results of urinalysis with culture.¹⁰

The second study reported on a retrospective analysis of 10,417 uropathogenic *E. coli* isolate susceptibility patterns over a 5-year period at a medical center in Brooklyn, New York.¹¹ The objective of the study was to determine the most effective and relevant method of initially treating uncomplicated UTIs. Using inpatient and outpatient urine culture susceptibility data, the authors identified a decline in susceptibility to the four antimicrobial agents examined: CIP, LEV, NIT, and TMP-SMX. CIP sensitivity declined from 79.6% to 74.3%, LEV from 79.7% to 74.7%, TMP-SMX from 73.5% to 71.5%, and NIT from 97.8% to 93.6%. Based on these data, the authors also recommended using NIT as the first-line treatment for uncomplicated UTIs, given its activity against most *E. coli*, urinary enterococci, and *Staphylococcus saprophyticus*.¹¹

New guidelines for the treatment of uncomplicated UTIs are anticipated from the IDSA in the summer of 2009. In the interim, Dr. Hynes noted that it may be prudent for clinicians to use NIT 100 mg orally twice daily for five days as initial therapy in those areas of practice in which fluoroquinolone and

TMP-SMX resistance to uropathogenic *E. coli* is greater than 20%. However, it can be anticipated, based on the data presented here and previously in the NAUTICA trial described above, that resistance levels of 10% to 20% will develop in several years to this agent as well. In the absence of new classes of antibiotics for outpatient use in the treatment of uncomplicated UTIs — one of the most common reasons for antibiotic treatment in adults — a robust program for the rapid research, development, manufacturing, and licensure of an *E. coli* vaccine is needed.

References

1. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). *Clin Infect Dis*. 1999;29(4):745-758.
2. Taur Y, Smith MA. Adherence to the Infectious Diseases Society of America guidelines in the treatment of uncomplicated urinary tract infection. *Clin Infect Dis*. 2007;44(6):769-774.
3. Litwin MS, Saigal CS, eds. Urologic Diseases in America. Introduction. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: U.S. Government Printing Office, 2007; NIH Publication No. 07-5512: 5-6.
4. Ronald A. The etiology of urinary tract infection: traditional and emerging pathogens. *Am J Med*. 2002;113 (suppl 1A):14S-19S.
5. Zhanel GG, Hisanaga TL, Laing NM, et al; NAUTICA Group, Hoban DJ. Antibiotic resistance in *Escherichia coli* outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). *Int J Antimicrob Agents*. 2006;27(6):468-475.

-
6. Huppert JS, Biro F, Lan D, Mortensen JE, Reed J, Slap GB. Urinary symptoms in adolescent females: STI or UTI? *J Adolesc Health*. 2007;40(5):418-424.
 7. López-Medrano F, García-Bravo M, Morales JM, et al. Urinary tract infection due to *Corynebacterium urealyticum* in kidney transplant recipients: an underdiagnosed etiology for obstructive uropathy and graft dysfunction—results of a prospective cohort study. *Clin Infect Dis*. 2008;46(6):825-830.
 8. Ryan M, Murray PR. Prevalence of *Corynebacterium urealyticum* in urine specimens collected at a university-affiliated medical center. *J Clin Microbiol*. 1994;32(5):1395-1396.
 9. Hopkins WJ, Elkahwaji J, Beierle LM, Levenson GE, Uehling DT. Vaginal mucosal vaccine for recurrent urinary tract infections in women: results of a phase 2 clinical trial. *J Urol*. 2007;177(4):1349-1353.
 10. Johnson L, Sabel A, Burman EJ, et al. Emergence of fluoroquinolone resistance in outpatient urinary *Escherichia coli* isolates. *Am J Med*. 2008;121(10):876-884.
 11. Kashanian J, Hakiman P, Blute M Jr, et al. Nitrofurantoin: the return of an old friend in the wake of growing resistance. *BJU Int*. 2008;102(11):1634-1637.

>> PROCEED TO POST-TEST

<http://www.hopkinscme.edu/ofp/einfectionsmonograph.htm>