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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Dual Antibiotic Therapy Is Not Routinely Necessary for Uncomplicated Cellulitis

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

SYNOPSIS: A randomized, multicenter, placebo-controlled clinical trial that enrolled patients presenting to emergency departments with uncomplicated cellulitis found the addition of trimethoprim-sulfamethoxazole to cephalexin did not lead to better outcomes.

SOURCE: Moran GJ, Krishnadasan A, Mower WR, et al. Effect of cephalexin plus trimethoprim-sulfamethoxazole vs cephalexin alone on clinical cure of uncomplicated cellulitis: A randomized clinical trial. *JAMA* 2017;317:2088-2096.

The increase in skin infections caused by community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) over the last 10 to 15 years has led many clinicians to prescribe antibiotics with anti-MRSA activity to treat cellulitis. However, guidelines from the Infectious Diseases Society of America recommend that in cases without systemic illness, penetrating trauma, intravenous drug use, or evidence of MRSA elsewhere, therapy should be directed only against streptococci.[1] Therefore, Moran et al sought to determine whether covering for MRSA improves outcomes in cellulitis.

The study was a randomized, double-blind, placebo-controlled clinical trial that enrolled patients aged 12 years and older who presented to five U.S. emergency departments with uncomplicated cellulitis, defined as erythema without an abscess, purulent drainage, or wound. All patients had an ultrasound to rule out an underlying abscess at enrollment. They were assigned in a 1:1 ratio to receive either a seven-day course of cephalexin plus placebo or cephalexin plus trimethoprim-sulfamethoxazole (TMP-SMX). The primary outcome was clinical cure of cellulitis at the test-of-

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cure visit, 14 to 21 days after enrollment in the study. Failure was defined at day 3 or 4 as fever, an increase in erythema by 25% from baseline, or worsening of swelling and tenderness by the visit. Failure at days 8 to 10 was defined by fever, no decrease in erythema, or no decrease in swelling or tenderness. Failure at days 14 to 21 was defined as fever or more than minimal erythema, swelling, or tenderness. For patients who met failure criteria, assigned antibiotics were stopped and another non-study antibiotic was given along with assessment for possible surgical drainage. The study was designed as a superiority trial. The modified intention-to-treat analysis was defined as patients who took at least one dose of study medication and had an interview through the test-of-cure visit or withdrew from the study and/or were lost to follow-up. The per-protocol population was defined as those patients who took at least 75% of the total doses of study medicines during the first five days and had an in-person test-of-clinical-cure visit.

In the per-protocol population, clinical cure was achieved at 14 to 21 days in 182 (83.5%) of 218 patients enrolled in the cephalexin/TMP-SMX group and in 165 (85.5%) of 193 in the cephalexin/placebo group ($P = 0.50$). However, in the modified intention-to-treat analysis, the cephalexin/TMP-SMX group showed a numerically (but not statistically significant) higher clinical cure rate (189/248, 76.2%) compared to those who received cephalexin/placebo (171/248, 69.0%) ($P = 0.09$). Of the 36 who experienced treatment failure with cephalexin/TMP-SMX, 10 (27.8%) had an abscess at the time of clinical failure and nine (25%) developed purulent drainage. Of the 28 patients with clinical failure in the cephalexin/placebo group, 10 (35.7%) had an abscess at the time of clinical failure and 10 also developed purulent drainage. Among the 60 patients with clinical failure who had culture data available, MRSA was isolated from 41 (68.3%), methicillin-susceptible *S. aureus* (MSSA) from eight (13.3%), and streptococci from two (3.3%). Regarding adverse events, there were no significant differences between the groups, and 90% of the reactions were considered mild. The most common adverse event was gastrointestinal upset, which occurred in 46% of the cephalexin/TMP-SMX group and in 38.7% of the cephalexin/placebo group. One case of *Clostridium difficile* infection occurred, which was attributed to clindamycin given after a treatment failure with cephalexin/TMP-SMX. One patient who received cephalexin/TMP-SMX developed acute-on-chronic kidney injury that subsequently resolved.

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This study supports the notion that routine antibiotic coverage for MRSA is not necessary when treating uncomplicated cellulitis. As an accompanying editorial notes, the different findings between the modified intention-to-treat analysis and the per-protocol population likely can be explained by the large number of patients in the analysis who did not complete the recommended course of therapy and, thus, were excluded.[2] Indeed, adherence actually was lower in the cephalexin/placebo group, making it unlikely that drug intolerance led to post-randomization bias. The most common reason for clinical failure was the development of an abscess, for which the primary management is incision and drainage. Thus, it should not come as a surprise that many cases of treatment failure occurred when only antibiotics (including those that treat MRSA) were prescribed and an abscess was present. The study has some limitations worth mentioning. First, despite enrolling nearly 500 patients, the power was limited such that it is possible the effect of TMP-SMX therapy could have improved outcomes in some of the subgroups. Second, bedside ultrasound may not be available in some settings and using physical examination alone is not reliable to detect abscesses. Third, there are many cases of uncomplicated cellulitis that resolve without antibiotics, which could have biased the results toward the null hypothesis.

Despite some uncertainty in the different findings between the per-protocol group and the modified intention-to-treat analysis, the present study suggests the addition of a second antibiotic to cover for MRSA in cases of uncomplicated cellulitis is unnecessary. One caveat is that

patients with clinically undetectable abscesses or with abscesses in evolution likely will experience treatment failure, although it can be argued that in these cases incision and drainage is more important than the antibiotic chosen. Finally, the dangers of unnecessary and excessive antibiotics are well-described, and Moran et al should be commended for helping advance antibiotic stewardship from an ambulatory standpoint. ■

REFERENCES

1. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2014;59:e10-52.
2. Shuman EK, Malani PN. Empirical MRSA coverage for nonpurulent cellulitis: Swinging the pendulum away from routine use. *JAMA* 2017;317:2070-2071.

ABSTRACT & COMMENTARY

Not Just Ebola — Lassa Fever Rears its Ugly Head Once Again

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: Outbreaks of Lassa fever are occurring in Nigeria and several other West African nations, some of which also are endemic for Ebola virus infections.

SOURCE: Lassa Fever – West Africa. ProMED Mail June 6, 2017. Available at: http://www.promedmail.org.

At the end of December 2016, a report appeared on ProMED indicating that a nurse in Ogun State, Nigeria, who had cared for a patient with suspected Lassa fever had died, as had the morgue attendant who had handled the patient's corpse. Since Lassa fever is endemic in Nigeria, as it is in several other countries of West Africa, this was not surprising. In fact, in October 2016, the Ministry of Health stated that there had been 10 cases reported so far in that year in Ogun State. By the last day of the year, however, the Ministry of Health had to raise the threat level for fear of an epidemic.

Additional cases occurred in other Nigerian states — a total of nine states by February. By mid-February, 196 suspected and 53 laboratory-confirmed cases and 31 deaths had been detected nationally. The case fatality rate for confirmed cases was 53.4%.

By the end of February, two fatal cases were reported in the adjacent country of Benin as well as additional cases in the more distant countries of Togo, Burkina Faso, Sierra Leone, and Liberia. Meanwhile, cases continued to occur in Nigeria, with 262 cases reported by June 7, 2017, 59 of which were laboratory confirmed; 48 patients died.

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Lassa fever is caused by a single-stranded RNA virus of the Arenavirus family, which includes, among others, lymphocytic choriomeningitis virus, and Junin, Guanarito, and Machupo viruses. Its eponymous name derives from its first identification in association with the village of Lassa in northwestern Nigeria.

Rodents are the reservoir of Lassa fever virus. Humans are infected by exposure to rat excreta either directly or by inhalation of contaminated dust or, in some cases, by eating rats. Human-to-human transmission appears to be limited to direct contact with secretions, but the period of risk is potentially prolonged (as with Ebola virus), with excretion of the virus in urine lasting for as long as six weeks and in semen for as long as three months. Nonetheless, the experience with cases exported to the more developed world indicate that the risk of person-to-person transmission is very low.

Exposure to the virus in the most highly endemic countries of Nigeria, Liberia, and Sierra Leone is frequent, with seroprevalence rates ranging from 7% to 20%. It is estimated that the number of cases may be as high as 300,000 per year and that these result in 5,000 deaths. The geographic overlap in some countries (e.g., Liberia) with Ebola virus makes clinical confusion with this viral infection an ongoing issue.

The usual incubation period is seven to 10 days, but it may be as short as three days and as long as 21 days. However, approximately four-fifths of infections are asymptomatic. In those with clinically evident illness, the severity may range from a mild illness with non-specific symptoms to full-blown hemorrhagic fever. While the overall mortality rate is only 1-2%, that of patients hospitalized in Africa is approximately 20%. The diagnosis is best made by PCR, when available, and patients are treated with ribavirin, also when available. Within the endemic areas, the differential diagnosis includes all the usual suspects, especially malaria, yellow fever, and Ebola virus infection.

In the endemic area, the major method of prevention is rodent control, although recent evidence suggests that it may be possible to develop a vaccine. Transmission to healthcare workers may occur, and the World Health Organization recommends the following precautions[1]:

"Health-care workers caring for patients with suspected or confirmed Lassa fever should apply extra infection control measures to prevent contact with the patient's blood and body fluids and contaminated surfaces or materials such as clothing and bedding. When in close contact (within 1 metre) of patients with Lassa fever, health-care workers should wear face protection (a face shield or a medical mask and goggles), a clean, non-sterile long-sleeved gown, and gloves (sterile gloves for some procedures)."

These recommendations are of relevance outside the endemic area since more than two dozen infections have been identified in returning travelers. ■

REFERENCES

1. World Health Organization. Lassa fever – Nigeria. Disease outbreak news. May 27, 2016. Available at: http://www.who.int/csr/don/27-may-2016-lassa-fever-nigeria/en/. Accessed June 12, 2017.
2. Brosh-Nissimov T. Lassa fever: Another threat from West Africa. *Disaster Mil Med* 2016;2:8.

Bug Bytes from Barcelona: Report of the 15th Conference of the International Society of Travel Medicine

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: In addition to issues of malaria, vaccination, and trauma in travelers, viral diseases and the management of diarrhea were key topics at the biannual meeting of the International Society of Travel Medicine in Barcelona, Spain, during May 2017.

Celebrating its 25th anniversary, the International Society of Travel Medicine looks back on decades of establishing and advancing the field of travel medicine. With a certifying exam, a focused medical journal, a robust research network, regional and international conferences, and a growing (3,500) membership, this organization continues to lead at the frontier of ensuring that travelers have safe and healthy international experiences. A total of 1,543 participants from 68 countries met in Barcelona. Some aspects of the May meeting are noted here to give readers of *Infectious Disease Alert* a view of some new advances in the field of travel medicine.

Viral Diseases

Arthropod-borne virus infections, including Zika, dengue, and chikungunya, have garnered recent headlines in the popular press. The vectors' lives are not shortened despite ongoing infection; this allows them to spread the infection to many animals or humans. Human hosts usually are "dead-end" victims without high enough levels of viremia to allow further spread of illness. Symptoms overlap, as fever, musculoskeletal pain, and rash occur with each of these infections. Reverse polymerase chain reaction testing can identify infections. Symptomatic care can be helpful.

Up to half of the million people who contract chikungunya each year go on to develop chronic pain that can persist for up to six years. Patients often have synovitis with edema, but actual joint effusion is less common. Bilateral distal joints usually are involved symmetrically, and larger proximal joints can be involved after the first six months of illness. Physical

therapy is helpful; acetaminophen helps with pain; low-dose steroids sometimes are offered, although steroid use has not yet been proven to be effective.

Several neurotropic viruses are common. Japanese encephalitis virus mostly affects children in Asia (although there was a recent report of a case in Africa). Acutely, about 10% of affected subjects have brain involvement; about half of infected individuals fully recover. West Nile virus infection of the nervous system is more common in adults, especially immunocompromised adults. West Nile virus infection, even with meningitis, usually resolves without neurologic sequelae; two of three anecdotally treated Israeli patients seemed to be helped by intravenous immune globulin.

The effects of the West Africa Ebola epidemic linger, even as Ebola is now active again in the Democratic Republic of the Congo. There is emerging evidence of post-Ebola arthralgia with fatigue and some visual changes. Sequelae are most common in those who experienced seizures or melena with the initial infection. Ebola antigen has been identified in semen in about 25% of subjects nine months out from symptomatic infection and has been found up to 500 days after recovery. While not all detectable antigen represents live virus, sexual transmission has occurred six months after a man recovered from Ebola. Ocular symptoms are identified in 60% of Ebola survivors, with 18% with uveitis.

Nearly 2,000 cases of Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) have been identified in 27 countries; 81% of cases are tied to Saudi Arabia. Camels are clearly linked to infection, but 27% of subjects lack known camel contact and contact with someone known to be ill. Some affected individuals seem to be especially contagious; one returned traveler was linked directly to 153 of the 186 patients who had MERS-CoV in a South Korean outbreak. Thus far, no MERS-CoV infection has been linked to the Hajj, probably because of careful camel restrictions with that event.

Travelers' Diarrhea

No controversy was greater in Barcelona than that of antibiotic use for presumptive management of travelers' diarrhea. It is well-established that bacterial diarrhea is common in travelers, affecting about 30% of those visiting resource-limited countries. It is accepted that antibiotic treatment with azithromycin, even in a single dose, can shorten the duration of illness. And, it has been common practice to provide a prescription of an antibiotic during pre-travel consultations so that treatment can be started quickly in the event of a bothersome bout of travelers' diarrhea.

In recent years, however, it has been well-documented that travelers undergo changes in the intestinal microbiome, often with emergence of multi-resistance enteric pathogens. Former travelers then risk the development of subsequent resistant infections, and communities risk more rapid global spread of antimicrobial resistance. Antibiotic treatment augments the travel-related risk of developing antimicrobial resistance in the intestinal flora.

Research and practice leaders generally agreed that travelers with mild diarrhea who don't experience any change in planned activities can allow their self-limited gastrointestinal infection to run its course without using antibiotics; loperamide or bismuth subsalicylate can provide some symptomatic relief. At the other end of the spectrum, travelers with severe diarrhea (fever, bloody diarrhea, bed-bound) should receive antimicrobial therapy (with a single 1,000 mg dose of azithromycin usually being fully effective for adults, otherwise 500 mg daily for up to three days in adults). The controversy arose about self-treatment of moderate bouts of diarrhea (not severely sick but unable to participate in some planned activities). While newly released guidelines[1] say that "azithromycin may be used to treat moderate travelers' diarrhea," some thought that "may" was too permissive and encouraged overuse of antibiotics, while others said "may" was too restrictive when all suffering travelers with diarrhea should receive helpful antibiotic treatment.

Provision of Pre-travel Care

A survey of 100 primary care providers in 35 U.S. states revealed that most felt uncomfortable providing pre-trip care. Their discomfort was not unreasonable since most were unable to identify accurately which vaccines would be useful, and most were not able to advise accurately about the prevention and management of travelers' diarrhea.

A community program was established to determine how best to provide care to West Africans traveling from Minnesota to visit friends and relatives. There were high levels of engagement by community members, and culturally appropriate surveys and strategies were developed.

In general, travelers are satisfied with multi-faceted input during pre-travel consultations. In a Swiss survey, travelers were satisfied with the information they received about malaria, diarrhea, rabies, and fever. However, they did not feel adequately informed about safety, sexually transmitted infections, and skin protection. Professionals providing pre-travel care should be adequately knowledgeable about all aspects of travel health, capable of clear educational

presentations of information for travelers, and organized with adequate time to provide comprehensive pre-travel care.

In Indiana, a statewide vaccine registry helped give necessary immunizations and avoid repeat doses of vaccines in children visiting a travel clinic. Electronic systems can facilitate improvements in efficiency and quality of care.

Data about acute mountain sickness were presented on two posters. Acetazolamide did not seem to alter the incidence of symptoms significantly in either travelers in Peru or in travelers from Spain. Of course, further study will be needed before abandoning the use of acetazolamide to prevent mountain sickness. ■

REFERENCE

1. Riddle MS, Connor BA, Beeching JN, et al. Guidelines for the prevention and treatment of travelers' diarrhea: A graded expert panel report. *J Travel Med* 2017;24 (Suppl 1):S57-S74.

ABSTRACT & COMMENTARY

Sepsis Management: What We Think We Know

By Dean L. Winslow, MD, FACP, FIDSA

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

SYNOPSIS: In the Protocolized Resuscitation in Sepsis Meta-Analysis (PRISM), 3,723 patients' outcomes from the ProCESS, ARISE, and ProMISe randomized, controlled trials of early goal-directed therapy (EGDT) were evaluated. EGDT did not result in better outcomes than usual care and was associated with higher costs. The authors of a second study looked at outcomes of 49,331 patients with sepsis treated in New York from April 2014 to June 2016. More rapid completion of the three-hour sepsis bundle and antibiotic administration (but not rapid bolus administration of IV fluids) was associated with reduced in-hospital mortality.

SOURCES: The PRISM Investigators, Rowan KM, Angus DC, et al. Early, goal-directed therapy for septic shock — A patient-level meta-analysis. *N Engl J Med* 2017;376:2223-2234.

Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med* 2017;376:2235-2244.

In the PRISM meta-analysis, data were pooled across the three large prospective randomized, controlled trials (ProCESS, ARISE, and ProMISe) of early goal-directed therapy (EGDT) vs. usual care. The primary outcome was 90-day mortality. Secondary outcomes included one-year survival, organ support, and hospitalization costs. Included in the analysis were 3,723 patients from 138 hospitals in seven countries. Mortality at 90 days was 24.9% in the EGDT arm and 25.4% in the usual care arm. The EGDT arm was associated with greater use of intensive care unit (ICU) and cardiovascular support and higher costs, but resulted in no benefit in any of the secondary outcomes. Subgroup analysis showed no benefit of EGDT even in patients with more severe septic shock (higher lactate levels and other factors predicting higher risk of death).

In the large 49,331 patient analysis of New York sepsis data from 149 hospitals, 82.5% of patients had the three-hour sepsis bundle (consisting of blood cultures, administration of antibiotics, and lactate measurements) completed within three hours. Among patients who had the three-hour bundle completed within 12 hours, a longer time to the completion of the bundle was associated with higher risk-adjusted in-hospital mortality, as was a longer time to the administration of antibiotics, but not a longer time to the completion of a bolus of intravenous fluids.

■ COMMENTARY

The famous Rivers trial,[1] in which the term "early goal-directed therapy" of sepsis was coined, has influenced the management of sepsis positively throughout the world. The small, single-center Rivers trial emphasized, and the results of subsequent larger and better-quality randomized, controlled trials made clear, that patients who have sepsis recognized earlier and receive appropriate antibiotics and appropriate

fluid resuscitation in a timely fashion experience better outcomes than patients who have diagnosis and appropriate treatment delayed.

Unfortunately, since the Rivers trial was published in the *New England Journal of Medicine* in 2001, many of the specific interventions in the EGDT arm (including measurement of CVP, central venous O_2 saturation, use of serum lactate to guide fluid resuscitation, the mandated "one-size-fits-all" 30 mL/kg IV saline bolus) have not been shown to be helpful in subsequent trials. Despite this, many of these interventions now have been codified into "sepsis bundles" mandated by the Centers for Medicare & Medicaid Services (CMS). Compliance with these bundles is tracked by hospitals' QI committees, is publicly reportable, and soon reimbursement will be tied to adherence to these bundles, with little room given for thoughtful deviation.

Another unwanted side effect is that the wide net that is cast to define sepsis ends up catching many patients who are not really septic. An extreme example I saw recently was a patient with a bad asthma attack, who, despite being normotensive, was labeled as having "sepsis" since the patient had HR > 90, high respiratory rate, and leukocytosis (from stress or glucocorticoid administration). This then triggered the drawing of a serum lactate (which is often elevated due to the inhaled β-agonists patients with wheezing are generally receiving in the ED). This then triggers the 30 mL/kg fluid challenge. In a young, healthy person, this generally is tolerated but could easily put an older patient with diastolic dysfunction into pulmonary edema. I also recently saw a 90-year-old lady from a skilled nursing facility receive 2.1 liters of IV saline because she was tachycardic, had leukocytosis, and had a minimally elevated lactate in the setting of PCR+ influenza (and no evidence of sepsis, but had received an albuterol treatment) despite a blood pressure of 150/100. She ended up in the ICU and needed BiPAP as well as 40 mg of IV furosemide as a result of the pulmonary edema that developed.

Similarly, I have seen residents order IV saline boluses in patients with atrial flutter with 2:1 conduction, multifocal atrial tachycardia, and supraventricular tachycardia (rather than treating the underlying arrhythmia). Just recently Kalil et al[2] also published a wonderful meta-analysis of 19,998 patients from 31 observational studies and six randomized trials. As in the two studies discussed above, he also showed that survival was not correlated with sepsis bundle compliance but rather that survival was associated with more rapid administration of appropriate antibiotics that occurred in the EGDT arms of the studies he examined.

As I was writing this piece, it occurred to me that the effect of EGDT on survival in sepsis may be analogous to the improvement that we saw in survival of acute myocardial infarction and unstable angina after critical care units (CCUs) became common beginning in the 1960s. When I did my Medicine residency in the 1970s, the "CCU bundle" (although we didn't call it that) consisted of: admission to a dedicated CCU where the patient had continuous cardiac monitoring; care generally provided by internists or cardiologists rather than general practitioners; nursing care from experienced nurses trained in ACLS who could defibrillate patients rapidly if necessary; O_2 administered by nasal cannula at 2 L/min; prophylactic heparin SQ; and at the sight of the first VPC, the patient was given a lidocaine bolus and drip. Over the years, it was shown that supplemental O_2 wasn't helpful unless the O_2 saturation was low, and prophylactic lidocaine was actually harmful, but the survival advantages afforded by CCU-level care were real, and we eventually eliminated the interventions that were found to be unhelpful or harmful.

I am hoping that some of our professional societies and both ID and critical care experts will be able to persuade CMS to allow thoughtful deviation from these mandated sepsis bundles and also to modify them by eliminating some elements (like serum lactate levels and "one-size-fits-all" 30 mL/kg fluid bolus) that actually drive inappropriate care. ■

REFERENCES

1. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-1377.
2. Kalil AC, Johnson DW, Lisco SJ, Sun J. Early goal-directed therapy for sepsis: A novel solution for discordant survival outcomes in clinical trials. *Crit Care Med* 2017;45:607-614.

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2016 Surviving Sepsis Guidelines Update

By James McFeely, MD

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

The Surviving Sepsis Campaign recently published an update to the 2012 guidelines for management of sepsis and septic shock.[1,2] The document incorporates literature published through July 2016. Pediatric guidelines, included in previous documents, have been removed from this version. Although the length of the paper is somewhat intimidating (74 pages, with 93 statements or recommendations regarding sepsis management and 655 references), fortunately for the bedside clinician, recommendations have been enumerated in table form. In addition, there is an accompanying article with recommendations on how this guideline may be approached.[3]

The panel of experts was divided into five different study sections: hemodynamics, infection, adjunctive therapies, metabolic, and ventilation. Professional librarians performed independent literature searches. There was no industry input into guideline development, and no industry representatives were present during any of the deliberations. The 2012 guidelines were reassessed for relevance, and new questions were submitted for inclusion based on research since the last revision.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to assess the quality of the information and to determine the strength of recommendations.[4] Three levels of statements or recommendations were made: strong ("most patients would accept that intervention and most clinicians should use it in most situations"), weak ("desirable effects of adherence to a recommendation probably will outweigh undesirable effects but with less confidence in these trade-offs"), and best practice statements, which are strong recommendations with unequivocal benefit but where evidence is hard to summarize or access using GRADE methodology.[5] Examples of best practice statements include: Treat sepsis as a medical emergency, minimize level of sedation in ventilated patients, and discuss goals of care and prognosis with patients and families.

The campaign goes so far as to state that strong recommendations could be used as quality criteria or performance metric indicators. Several strong recommendations list therapies that are not appropriate for the septic patient. Table 1 lists those interventions not recommended by the current guidelines.

Any references to the three- and six-hour bundles of care have been removed; these are replaced with strong recommendations for rapid administration of fluids (within three hours) and antibiotics (within one hour) and flexible options for dynamic reassessment of adequacy of resuscitation.

One striking recommendation is the strong recommendation for using prone positioning in acute respiratory distress syndrome (ARDS) patients. Tables 2 and 3 list the strong recommendations sorted by section. The bedside clinician would be well-served to review all the tables included in the article, paying particular attention to the strong recommendations in each subsection.

The weak recommendations also are very important, but require more risk/benefit analysis before implementation in any given case. The best

Table 1: Strongly NOT Recommended by 2016 Guidelines

- Routine combination antibiotic therapy for neutropenic sepsis/bacteremia
- Hydroxyethyl starches for volume repletion
- Renal dose dopamine
- Erythropoietin for sepsis-associated anemia
- Anti-thrombin III
- High-frequency oscillatory ventilation for sepsis-induced ARDS
- Beta-agonists without evidence of bronchospasm
- Routine use of pulmonary artery catheters with sepsis-induced ARDS
- Total parenteral nutrition in the first seven days
- Omega-3 fatty acids as an immune supplement
- Selenium
- Glutamine

Table 2: Strong POSITIVE Recommendations (Hemodynamics, Infection)

• 30 mL/kg crystalloid within the first three hours
• Initial target mean arterial pressure of 65 mmHg in septic shock requiring vasopressors
• Norepinephrine as first-line vasopressor
• Administer antibiotics as soon as possible, preferably within one hour of recognition
• Empiric broad-spectrum therapy to cover all likely pathogens
• Conservative fluid strategy in ARDS in patients without hypoperfusion

Table 3: Strong POSITIVE Recommendations (Adjunctive Therapies, Metabolic, and Ventilation)

• Transfuse packed red blood cells when Hgb < 7 unless extenuating circumstances (bleeding, myocardial infarction, severe hypoxemia)
• Target tidal volume 6 mL/kg for ARDS, plateau pressure upper limit 30 cm H_2O
• Prone positioning for ARDS where PaO_2/FiO_2 < 150
• Raise head of bed 30-45 degrees in mechanically ventilated patients, spontaneous breathing trials, and a weaning protocol
• Blood glucose control via protocol targeting blood glucose < 180
• Pharmacologic venous thromboembolism prophylaxis where able, low molecular weight heparin preferred
• Stress ulcer prophylaxis for patients with risk factors
• Incorporate goals of care into treatment planning including palliative care principles where appropriate

practice statements, by and large, appear to be non-controversial, common sense recommendations that most clinicians already should be following.

With this update, the Surviving Sepsis Campaign has done a remarkably good job summarizing the current state of the sepsis literature. It will serve as a reliable reference for bedside providers, administrators, and third-party payers as they develop their performance metrics.

In addition, its robust reference section is a valuable resource for researchers or others who wish to conduct a thorough investigation on any of the specifics recommended in the article.

All ICU clinicians need to review these guidelines, compare them with their current practices, and develop plans for implementation in the near future. ■

REFERENCES

1. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* 2017;45:486-552.
2. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017;43:304-377.
3. Dellinger RP, Schorr CA, Levy MM. A users' guide to the 2016 Surviving Sepsis Guidelines. *Intensive Care Med* 2017;43:299-303.
4. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-926.
5. Guyatt GH, Schünemann HJ, Djulbegovic B, Akl EA. Guidelines panels should not GRADE good practice statements. *J Clin Epidemiol* 2015;68:597-600.

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Antibiotic Increases Honeybee Mortality

SOURCE: Raymann K, Shaffer Z, Moran NA. Antibiotic exposure perturbs the gut microbiota and elevates mortality in honeybees. *PLoS Biol* 2017;15:e2001861.

The investigators examined the gut microbiome of wild honeybees fed tetracycline, and determined the mortality of treated vs. untreated bees. Honeybee gut flora is highly conserved, meaning honeybees throughout the world share similar bacteria, probably as a social phenomenon. It has been theorized that this gut flora is essential to honeybee health and natural resistance to opportunistic pathogens. Metagenomic analysis of colonies with colony collapse disorder (CCD) have shown an increase in certain gut bacteria while other "core" bacteria are diminished (e.g., Bifidobacteria, Alphaproteobacteria, Lactobacillus) when compared with healthy hives.

The authors collected healthy honeybee hives, brought them into the laboratory, and fed them sterile sucrose syrup with or without tetracycline for five days before placing the colony back in the hive.

Bees were sampled at different time-points post-antibiotic exposure. Tetracycline treatment resulted in significant changes to gut flora, with reductions in the relative and absolute abundance of eight core bacterial species. None of the core bacteria were completely eliminated, but Lactobacillus species, FIRM-4, FIRM-5, and Bifidobacteria were substantially reduced, as well as a gram-negative bacilli called *Snodgrassella alvi*. In contrast, a relative increase in *Gilliamella apicola* was observed in treated bees. Even at seven days post-treatment, significant reductions in normal gut flora persisted. Keep in mind that worker honeybees (who are all female) only live about four to six weeks, and only the largest and oldest bees are sturdy enough to carry their burden home at the end of the day.

Once honeybees were transplanted back to their hives, recovery of foraging bees was only 32% in treated hives compared with 64% in untreated hives — meaning only half the number of the treated bees returned home at the end of their day compared to untreated controls. More mature bees also died in the treated hives compared with untreated hives.

The authors exposed treated bees to a strain of Serratia, a potential opportunistic pathogen, which appeared to reduce survival further in both age-controlled and non-age-controlled Kaplan-Meier analysis.

The basis for colony collapse disorder is not yet known. Preliminary work suggests it is the result of a complex interplay of multiple factors. Apiarists in some countries have tried various anti-mite treatment, as well as antibiotics, hoping to keep larval bees alive. Unfortunately, tetracycline may have an adverse effect on honeybee gut flora and survival. From personal experience — the effects of CCD are devastating — I've kept up to seven hives at a time, and overnight, the bees seem to vanish. I have given up on beekeeping, leaving it to those more expert than myself, hoping they will have better success. For one, it's become quite expensive: A five-pound package of bees used to cost $15, mailed by USPO, and a queen in a matchbox was $2. Now, a starter hive costs upwards of $150. The Obama administration pushed for further research in honeybee mortality. Let's hope the Trump administration continues this funding.

Sustained Hepegivirus Infection in Injection Drug Users

SOURCE: Kandathil AJ, Breitwieser FP, Sachithanandham J, et al. Presence of human hepegivirus-1 in a cohort of people who inject drugs. *Ann Intern Med* 2017; doi: 10.7326/M17-0085. [Epub ahead of print].

Molecular "deep diving" using such techniques as next-generation metagenomic sequencing (NGMS) is resulting in the discovery of new viruses almost every year. Previously, Kapoor and colleagues identified a novel RNA flavivirus in two individuals with hemophilia who had received multiple blood products.[1] Viremia persisted in one of these individuals for 5.4 years without apparent symptoms or disease. This new virus was characterized as human hepegivirus, or HHpgV-1, which shares features with hepatitis C virus and the apparently non-pathogenic human pegivirus, HPgV, formerly called hepatitis G virus or GBV-C. HHpgV-1 also was found in two individuals who had received blood transfusion, but both individuals had cleared their viremia in subsequent specimens. Researchers now are sequencing and comparing these viruses with other similar viruses from chimpanzees, rodent variants, and several different groups of pegiviruses and hepaciviruses from bats to form a phylogenetic tree.

Armed with this information, Kandathil and colleagues examined serum samples obtained from a prospective national clinical cohort study for persons using injection drugs who received interferon for HIV/HCV co-infection. To enhance the likelihood of interesting findings, samples were selected from those previously known to be positive for GBV-C RNA (n = 20), SEN virus DNA (n = 24), HCV RNA (n = 42), and HCV antibody but not HCV RNA (n = 20). Plasma samples were obtained before and after interferon administration at 72 and 168 hours and stored.

Using these samples, NGMS generated 600 million reads, most of which were the expected HIV and HCV sequences. But a small number of samples generated different reads — leading to the discovery of HHpgV-1 in four samples from two persons. These reads were detected both pre- and post-interferon, and the reads from one participant were so numerous as to be nearly sufficient to assemble a complete genome.

This led to the creation of a specific quantitative PCR, which was used on a subset of 156 individuals with a history of injection drug use. Seventeen (10.9%) were found to have HHpgV-1 in plasma samples. HHpgV-1 viremia was detected in eight of these individuals at two different time-points spanning a median of 5,886 days, suggesting that these individuals were viremic, on average, for many years (or repeatedly re-infected). Further testing of another six individuals at three different time-points confirmed sustained viremia for a median of 4,538 days (range, 1,524 to 6,158 days).

The implications of this finding and how long HHpgV-1 may have been in circulation in human beings are not known. Since more than half of the participants in the original cohort study had sustained HHpgV-1 viremia and active HCV infection, it is not known whether the viruses simply coexist or are, in some way, interdependent — or whether their presence is simply a marker of ongoing risky behavior. What blood banks are going to do with all this new information is even less clear.

REFERENCE

1. Kapoor A, Kumar A, Simmonds P, et al. Virome analysis of transfusion recipients reveals a novel human virus that shares genomic features with Hepaciviruses and Pegiviruses. *MBio* 2015;6:e01466-15. doi: 10.1128/mBio.01466-15.

Decrease SSIs: Take August Off

SOURCE: Anthony CA, Peterson RA, Polgreen LA, et al. The seasonal variability in surgical site infections and the association with warmer weather: A population-based investigation. *Infect Control Hosp Epidemiol* 2017; doi: 10/1017/ice/2017.84. [Epub ahead of print].

Previous studies have hinted at an increase in surgical site infections (SSIs) in the summer months. To determine the seasonal variation of SSIs, the investigators examined a large population database (from the Healthcare Cost and Utilization Project by the Agency for Healthcare Research and Quality) for all hospital discharges with a primary diagnosis of SSI from 1998-2011. This database contains data from 20% of nonfederal acute care hospitals in the United States (but does not contain outpatient data). Ten surgical procedures were the focus of the investigation, including colon resection, small bowel resection, knee arthroplasty, hip replacement, lower extremity fracture repair, spine fusion, cesarean section, inguinal or femoral hernia repair, another hernia repair, and exploratory laparotomy. Cases were aggregated by month, year, region, sex, age, and type of institution. Monthly average ambient temperatures were determined for each hospital location. Subgroup analysis with logistic regression was performed using two separate models.

After eliminating cases without adequate data, the sample size was 55,665,828 procedures performed at 2,512 unique hospitals. The monthly incidence of SSI clearly peaked in August of every year, and nadired in January, with an average difference of 26.5% ($P < 0.001$). SSI cases had higher rates of diabetes (19% vs. 14.7%) and obesity (9.5% vs. 5.6%) compared with controls, but were otherwise similar with regard to mean age, comorbidities, latitude, and region. Further, the odds of SSI were similar whether the procedure was performed in a teaching hospital or a nonteaching hospital.

After controlling for demographics and hospital cofactors, the odds of SSI increased by 2.1% for every five degrees Fahrenheit increase in average monthly temperature.

Remarkably, the increased odds of SSI from the warmest month to the coldest month (January) was double the effect of diabetes. And if July and August cases were eliminated from the database, the rate of SSI would decrease by 20.6%.

As yet, there is no good explanation for this observation. Is it really because of changes in the weather? Do people sweat more in the hospital? Are bandages not as secure in the heat? What I did not understand was the study focused on in-hospital SSI data, not outpatient data. Presumably, most hospital temperatures are controlled, with air conditioning in the summer months and heating in the winter. Shouldn't the "ambient" temperature within hospitals be similar, more or less, regardless of whether you are in Minneapolis in January or Tucson in August? Some have theorized that the introduction of new house staff in July-August might affect SSI rates, and yet there was no apparent difference between teaching and nonteaching facilities in this study. Is there simply reduced or less capable staffing in hospitals in July-August because of vacations? Staff dreaming of that fish they caught last weekend and not focusing on dressing changes? Whatever the reason, this study suggests that if we were more like the French, took August entirely off, and moved all elective surgical cases to the winter months, the total annual burden of SSI would be reduced by approximately 20%. ■

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CME QUESTIONS

1. Which of the following statements is true?

a. Most U.S. primary care providers have the knowledge and comfort required to provide good pre-travel care.

b. Steroids are effective in reducing joint pain in patients with chronic dengue infection.

c. Azithromycin 1,000 mg is effective as a single dose in presumptively treating severe travelers' diarrhea.

d. Middle East Respiratory Syndrome due to a novel coronavirus is now endemic in South Korea.

2. Which of the following is correct regarding the treatment of pure (non-purulent) cellulitis?

a. Cephalexin alone is relatively ineffective.

b. The addition of trimethoprim-sulfamethoxazole to cephalexin significantly improves outcomes.

c. Failure of therapy is associated with the presence of abscesses that were occult on presentation, even with the use of ultrasound examination.

d. Most cases are due to MRSA.

3. In the PRISM meta-analysis, which of the following is correct regarding early goal-directed therapy of septic shock?

a. It was associated with reduced use of the intensive care unit.

b. It was associated with reduced need for cardiovascular support.

c. It was associated with reduced costs.

d. It was associated with no significant improvement in survival.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the diagnosis of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.

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