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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Current Trends and Outcomes for Infective Endocarditis

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

SYNOPSIS: Using large databases from New York and California, investigators found the overall incidence of infective endocarditis remained stable between 1998 and 2013, and 90-day mortality declined. Changes were noted in pathogen etiology and patient characteristics over time.

SOURCE: Toyoda N, Chikwe J, Itagaki S, et al. Trends in infective endocarditis in California and New York state, 1998-2013. *JAMA* 2017;317:1652-1660.

Infective endocarditis (IE) remains an uncommon yet serious illness. In 2007, a major change occurred in the IE prophylaxis guidelines, with the recommendation of fewer indications for prophylaxis. In light of this change, Toyoda et al used large databases to examine trends in the epidemiology and outcomes of IE between 1998 and 2013.

Patients for the study were identified using ICD-9 codes in statewide databases from New York and California. These databases included information on every hospital discharge, ambulatory surgery, and emergency room visit in their respective state. IE was characterized as native valve, prosthetic valve, cardiac device-related, or drug abuse-associated. Primary and secondary diagnostic codes were used to identify causal microorganisms, including *Staphylococcus aureus* (methicillin-resistant [MRSA] and methicillin-susceptible [MSSA]), other Staphylococcus species, Streptococcus species, gram-negative organisms,

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fungi, and unknown, which included both culture-negative cases and those without a code.

During the study period, 75,829 cases of first-episode IE were identified, 56% in California and 43% in New York. The crude annual incidence increased from 7.6 to 9.3 cases per 100,000 persons. However, after adjustment for age, sex, and race, there was no significant increase in IE over time (range, 7.6 to 7.8 cases per 100,000 annually), and 90-day mortality decreased annually by approximately 2%. During the latter part of the study, those diagnosed with IE tended to be older, more likely to be male, and more likely to have chronic obstructive pulmonary disease, cancer, or liver disease. Drug use-associated IE increased over the study period by 0.9% annually (95% confidence interval [CI], 0.4-1.3). There was a substantial increase in hemodialysis patients diagnosed with IE, from 14.9% to 17.9% and representing 35.0% of healthcare-associated cases of IE between 2010 and 2013.The proportion of patients with a history of valve surgery increased from 12.8% to 15.2%, and the proportion with implantable cardiac devices increased from 8.8% to 15.6%.

Overall, these trends resulted in a decreased proportion of patients with native-valve IE at the end of the study (74.5% to 68.4%) and an increased proportion with prosthetic-valve IE (12.0% to 13.8%) and device-related IE (1.3% to 4.1%). The proportion of healthcare-associated IE increased from 49.8% in 1998 to 51.2% by 2013. The standard incidence of *S. aureus* IE increased during the study period from 2.1 (95% CI, 2.0-2.2) to 2.7 (95% CI, 2.6-2.9) cases per 100,000 people annually, with MRSA increasing from 0.23 (95% CI, 0.19-0.27) to 1.13 (95% CI, 1.05-1.22). The incidence of oral streptococcal IE decreased from 0.84 (95% CI, 0.76-0.92) to 0.73 (95% CI, 0.67-0.80) cases per 100,000 people annually and there was not an increase after the prophylaxis guidelines were changed. More patients underwent cardiac surgery during or within 30 days of their index admission over the study period (10.6% to 13.3%). Finally, healthcare-associated IE was associated with greater mortality compared to community-onset IE (adjusted hazard ratio [aHR], 1.52; 95% CI, 1.48-1.56), and compared to streptococcal IE, mortality was greater with gram-negative IE (aHR, 1.22; 95% CI, 1.16-1.28), staphylococcal IE (aHR, 1.38; 95% CI, 1.34-1.42), and highest with fungal IE (aHR, 1.84; 95% CI, 1.72-1.99).

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This is an important study for several reasons: the large number of patients that were included, the timeframe studied, which ranged from before and after the guidelines changed for IE prophylaxis, and the findings about how IE has evolved in recent years. Indeed, there is reason for both optimism and concern. While the overall incidence of IE remained stable during the study period, it is encouraging that 90-day mortality decreased, perhaps as a result of improvements in diagnosis and management, such as earlier valve replacement. There was a 38% increase in patients with IE who were hemodialysis-dependent, which could be interpreted as either hemodialysis patients have a higher risk for IE or perhaps there are more hemodialysis patients now in the general population. Although further investigation about the risks associated with hemodialysis and IE is needed, clinicians currently caring for hemodialysis patients need to be vigilant and maintain a high index of suspicion for IE, especially in the setting of a bloodstream infection.

Regarding the decrease in oral streptococcal IE, this trend could mean more people are receiving better dental care. That no increase in IE cases was observed after 2007 lends further support to the current IE prophylaxis recommendations. Drug use-associated IE increased over the study period, which serves as an important reminder about how the ongoing epidemic of intravenous drug abuse (especially heroin) is a major and very costly problem for society. Thus, one could argue from a purely economic standpoint that more resources (e.g., needle-exchange programs and funding for substance-abuse programs) should be devoted to this issue. The increase in MRSA IE is not surprising given the higher incidence of community-

associated infections that began in the 1990s. What is unexpected given the high virulence of MRSA is that the overall mortality of IE declined during the study period. Perhaps the increase in MRSA cases was balanced by the decline of oral streptococcal ones.

As with all retrospective studies that use large databases, there is a chance that misclassification errors and unrecognized confounding variables affected the results. The IE data from New York and California might not be representative of other regions of the country, e.g., the Southern and Midwestern states. Moreover, the organisms were identified by ICD-9 codes and were assumed to be the causative pathogens, which may not have been the case. The data are already four years old and may not accurately reflect the current characteristics of IE. For example, there is evidence that the incidence of healthcare-associated MRSA infections is decreasing.[1] Finally, the investigators were not able to identify cases of IE acquired in skilled care facilities, which could have led to an underestimate of healthcare-associated cases.

The study by Toyoda et al presents a lot of interesting data that can serve as a starting point for many future investigations. IE is an important and dynamic disease whose trends must be monitored continuously to achieve optimal patient outcomes. ■

REFERENCE

1. Evans ME, Kralovic SM, Simbartl LA, et al. Eight years of decreased methicillin-resistant *Staphylococcus aureus* health care-associated infections associated with a Veterans Affairs prevention initiative. *Am J Infect Control* 2017;45:13-16.

ABSTRACT & COMMENTARY

Bambi Strikes Again — Encephalitis Due to the 'Deer Tick Virus' (Powassan Virus) May Be Increasing in Frequency

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Powassan virus is transmitted by the same tick that carries the etiologic agent of Lyme disease and several other pathogens. The number of cases of encephalitis caused by this virus may be increasing in the endemic areas.

SOURCES: Tutolo JW, Staples JE, Sosa L, Bennett N. Notes from the field: Powassan virus disease in an infant — Connecticut, 2016. *MMWR Morb Mortal Wkly Rep* 2017;66:408-409.

Doughty CT, Yawetz S, Lyons J. Emerging causes of arbovirus encephalitis in North America: Powassan, chikungunya, and Zika viruses. *Curr Neurol Neurosci Rep* 2017;17:12.

A 5-month-old infant living in eastern Connecticut was admitted to a hospital in November 2016 for evaluation and management of seizures that occurred a few days after onset of fever and vomiting. The history obtained at the time indicated that, two weeks earlier, the infant had been bitten by a tick, which was likely to have been attached for less than three hours before removal. CT of the brain was normal, and a lumbar puncture was performed; the cerebrospinal fluid (CSF) white blood cell (WBC) count was 125 cells/μL, with 81% lymphocytes. A symmetric pattern of restricted diffusion involving the basal ganglia, rostral thalami, and left pulvinar was detected on magnetic resonance imaging (MRI). Bacterial cultures of CSF yielded no growth and testing failed to detect evidence of infection with a number of arboviruses. Respiratory viral cultures also were negative.

An infectious diseases consultant requested that CDC test for evidence of Powassan virus infection, and IgM antibody directed against this virus was detected in a CSF sample obtained four days after the onset of illness. In addition, the antibody neutralizing titer was 1:32. Seizure control was achieved, and the patient was discharged on anticonvulsant therapy after seven days. At age 10 months, he was no longer receiving anticonvulsants and was reported to have normal motor and verbal development. MRI, however, revealed gliosis with encephalomalacia in both thalami and basal ganglia, along with volume loss and early

mineralization in the left basal ganglia.

COMMENTARY

Powassan virus is a tick-borne flavivirus that was first identified in 1958 in Powassan, Ontario, in the brain of a 5-year-old boy who died with encephalitis. Powassan virus and the tick-borne encephalitis virus belong to the tick-borne serocomplex, which causes encephalitis in parts of Eastern Europe, far eastern Russia, and Asia, in addition to North America. This complex is distinct from the mosquito-borne serocomplex, members of which include dengue virus, West Nile virus, Japanese encephalitis virus, and St. Louis encephalitis virus. Cases in the United States occur in the Great Lakes region and the Northeast (*see Figure 1*); although the virus has been identified previously in ticks in Connecticut, the case summarized above is the first human case reported.

Powassan virus is known to be transmitted by at least three distinct tick species: *Ixodes marxi*, *Ixodes cookei*, and *Ixodes scapularis*, the last of which also transmits *Borrelia burgdorferi*, *Borrelia miyamotoi*, *Anaplasma phagocytophilum*, and *Babesia microti*. There are two lineages of Powassan virus. Lineage 1, which includes the prototype virus identified in 1958, is transmitted by *I. cookei*, with skunks and groundhogs as the main reservoirs. Lineage 2 virus ("deer tick virus") is transmitted by *I. scapularis* and is maintained in the white-footed mouse.

Recognized infection is uncommon, with a median of seven cases reported each year from 2006 through 2015 in the United States (*see Figure 2*), although it has been suggested that the number of cases may be increasing, a conjecture that is consistent with a marked increase in seropositivity in deer in New England in recent decades. Approximately 3% of ticks examined in New York state are infected with Powassan virus. The virus is transmitted rapidly, requiring tick attachment for only 15 minutes and, as a consequence, one-half of infected patients remain unaware of having suffered a tick bite. In the case reviewed here, it is believed that the implicated tick likely was brought into the house on someone's clothing.

Most human Powassan virus infections are likely asymptomatic. Initial symptoms consist of fever and headache and, ominously, altered mental status. One-half have gastrointestinal symptoms and one-third have rash. Encephalitis, in some cases, may be delayed. In addition to encephalitis, meningitis, myelitis, or radiculitis is reported.

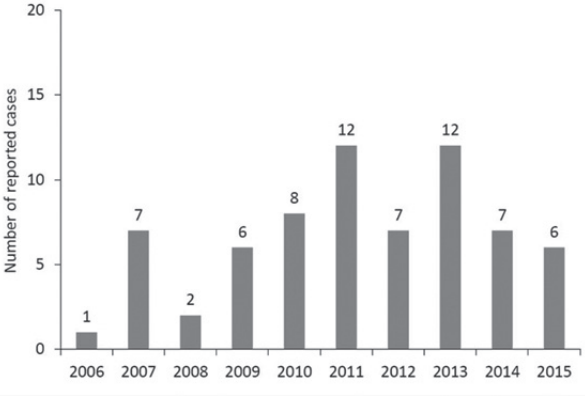
Examination of CSF demonstrates findings suggestive of a viral encephalitis, although occasional neutrophil predominance is seen early in the infection. T2 hyperintense lesions without enhancement commonly are seen on MRI and, as in the case reviewed here, diffusion restriction may be observed. Although lesions may occur elsewhere, involvement of the basal ganglia is common, as is the case with other flavivirus encephalitides such as that due to Japanese B encephalitis virus. As with West Nile virus, PCR testing is insensitive and the diagnosis is best made by detection of IgM antibody, preferably in CSF, with confirmation using a plaque reduction neutralization test to deal with potential cross-reactivity with other flaviviruses.

There is no specific treatment available, and an estimated 10-15% of patients with encephalitis die, while approximately one-half of survivors suffer residual neurological deficits. Prevention consists of avoiding tick bites, which, in brief, consists of wearing long pants and long-sleeved shirts, using effective tick repellent, performing effective screening,

Figure 1: Powassan Virus Neuroinvasive Disease Cases Reported by State, 2006-2015

Source: ArboNET, Arboviral Diseases Branch, Centers for Disease Control and Prevention.

Figure 2: Powassan Virus Neuroinvasive Disease Cases Reported by Year, 2006-2015



Source: ArboNET, Arboviral Diseases Branch, Centers for Disease Control and Prevention.

and performing tick checks. A more detailed set of preventive measures is available at the CDC web site.[3] ■

REFERENCES

1. Centers for Disease Control and Prevention. Powassan virus. Available at: https://www.cdc.gov/powassan/statistics.html/. Accessed May 6, 2017.
2. Piantadosi A, Rubin DB, McQuillen DP, et al. Emerging cases of Powassan virus encephalitis in New England: Clinical presentation, imaging, and review of the literature. *Clin Infect Dis* 2016;62:707-713.
3. Centers for Disease Control and Prevention. Preventing tick bites. Available at: https://www.cdc.gov/ticks/avoid/on_people.html. Accessed May 7, 2017.

ABSTRACT & COMMENTARY

Ready for Dengue in the United States?

By Julie L. Hanson, MD, and Philip R. Fischer, MD

Dr. Hanson is a resident in pediatrics at the Mayo Clinic in Rochester, MN. Dr. Fischer is professor of pediatric and adolescent medicine, Mayo Clinic, Rochester, MN.

Dr. Hanson and Dr. Fischer report no financial relationships relevant to this field of study.

SYNOPSIS: Dengue is increasingly recognized in the southern United States. When recently surveyed, however, clinicians in Texas seemed incompletely prepared to understand and manage patients with dengue.

SOURCE: Adam JK, Abeyta R, Smith B, et al. Clinician survey to determine knowledge of dengue and clinical management practices, Texas, 2014. *Am J Trop Med Hyg* 2017;96:708-714.

The vast majority of dengue cases in the United States have been imported from endemic regions by U.S. travelers. However, in recent years there has been increasing evidence of autochthonous dengue transmission in Texas, Florida, and Hawaii. The southern border of Texas is at particular risk of recurrent dengue outbreaks given the close proximity to Mexican states with relatively frequent dengue epidemics. Given this continual threat of dengue outbreaks at the Texas-Mexico border, Adam and eight coauthors from the Centers for Disease Control and Prevention (CDC) and Texas Department of State Health Services developed strategies to reduce morbidity and mortality associated with local dengue infections. As part of this effort, they developed a clinician survey to further understand local Texas clinicians' knowledge of dengue presentation and clinical management.

The clinician survey was sent to 2,375 physicians, physician extenders, and physician assistants in south Texas and the Houston metropolitan area. Two hundred seventeen clinicians (9%) fully completed the survey and were practicing within the catchment area. The clinician group was stratified further by specialty, practice site (i.e., inpatient, outpatient, or acute care), years of practice, and number of dengue cases diagnosed in their career. The survey questions focused on three knowledge areas, including dengue prevention and anticipatory guidance, clinical presentation and course, and clinical management. All clinician sub-divisions and categories of experience with dengue displayed a deficiency in knowledge of dengue.

Approximately half (56%) of participants were able to identify all clinical signs of dengue and could identify indicators of early shock. However, < 1% recognized all warning signs for severe dengue. Fifty-five percent of clinicians recognized that intravenous crystalloids should be the primary initial fluid replacement in patients with elevated hematocrit, but only 7% correctly identified all three indications for crystalloid use. A minority of clinicians (19%) orrectly identified situations in which patients with suspected dengue should return for reevaluation after discharge. This survey highlights the need for improved dengue education in the United States and, in particular, in regions at risk for continued dengue outbreaks.

■ COMMENTARY

As the continued geographic spread of dengue virus threatens the southern United States, it is helpful to review the basics of dengue virus presentation, management, and prevention. Returning to dengue disease basics will assist in closing knowledge gaps as displayed by the clinician survey conducted in Texas.

Epidemiology

Aedes aegypti and *Aedes albopictus*, the mosquitoes that serve as vectors for the four dengue virus types (DENV-1 to -4), have been able to reach subtropical and temperate regions, including North America. Dengue is thought to have been present in the United States since the end of the 18th century, with frequent

dengue epidemics occurring up until the mid-1900s. After 1945, there was a relatively quiescent period of dengue cases in the United States until 1980 when an autochthonous case of DENV-1 was identified in south Texas. Since 1980, surveillance studies have reported several additional cases of dengue in southern Texas associated with epidemics in northern Mexico, including outbreaks in 1999, 2005, and 2013. During the most recent outbreak in 2013, 53 cases of dengue virus were identified, with 49% of these patients acquiring the infection locally.[1] In addition to cases in southern Texas, an epidemic occurred on the island of Maui, Hawaii, in 2001, and the first autochthonous case of dengue in 75 years was identified in Florida in 2009.[2] Dengue also has been reported in several U.S. territories, with the largest number of cases reported in the U.S. Virgin Islands and Puerto Rico. While autochthonous dengue infections have been limited thus far to these three states and two U.S. territories, both dengue vector species are distributed widely throughout the southern parts of the United States, indicating that a larger portion of the continental United States may be at risk for dengue infection in the future.

Clinical Presentation

Infection by dengue viruses can lead to a wide variety of clinical presentations ranging from a mild, influenza-like illness to hypovolemic shock and death. This spectrum of dengue infection has been subdivided into three primary syndromes, including classic dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). Classic dengue fever, or "break bone fever," is characterized by onset of a high fever, headache, rash, myalgias, and arthralgias three to 10 days after sustaining a bite from an infected mosquito. As the fever begins to subside three to seven days after symptom onset, the patient may have complete resolution of symptoms, or go on to develop dengue hemorrhagic fever. DHF is defined by four characteristics: recent history of fever, any hemorrhagic manifestation, thrombocytopenia, and evidence of increased vascular permeability. The most common hemorrhagic manifestations are petechiae, a positive tourniquet test, and gingival bleeding. Increased vascular permeability can lead to an elevated hematocrit, presence of pleural effusion or ascites, or hypoalbuminemia. Cases of dengue shock syndrome meet the four criteria for DHF, but also show signs of circulatory failure, such as a rapid, weak pulse, narrow pulse pressure, or hypotension. The risk of progression to DHF or DSS is increased in secondary infections when the individual has been infected previously by a different virus serotype. The fatality rate of patients with DSS can be 10% or higher without proper recognition and management, but mortality can be decreased to < 1% with appropriate intervention.[3]

Diagnosis

Efficient and accurate diagnosis of dengue is important for prompt clinical care, disease surveillance, and outbreak control. In endemic regions, clinical diagnosis of dengue usually is sufficient, but laboratory testing can be useful when the diagnosis is uncertain or in regions where dengue is sporadic. Dengue can be diagnosed by isolation of the virus, molecular methods, or serologic studies. Virus isolation is the traditional diagnostic method for detecting dengue virus infection; however, it has been replaced by RT-PCR tests and the NS1 antigen ELISA. RT-PCR testing allows for viral identification from the onset of the illness and is fast, sensitive, and specific. Unfortunately, PCR-based testing requires specialized equipment and staff that may not be feasible in a resource-poor region.

In contrast, the NS1 ELISA has emerged as a simple, low-cost diagnostic tool to detect dengue virus in the early stage of infection. The qualitative NS1 ELISA has become the standard for dengue diagnosis worldwide, and quantitative NS1 ELISA continues to be researched as initial studies suggest a direct correlation between NS1 levels and the risk of progression to severe disease. Serological studies also are important tools in diagnosing dengue infection, especially outside of the acute phase. IgM antibodies typically are detectable three to five days after illness onset and peak several weeks after recovery. IgG is usually not present in the acute phase in a primary infection, but may appear as early as three days after illness onset in a secondary infection. The ratio of IgM and IgG in the acute phase of disease may provide an indication as to whether it is a primary or secondary infection. IgM and IgG serologies are susceptible to cross-reactivity with other flaviviruses, which can provide a diagnostic challenge in areas of the world where more than one flavivirus is circulating. Overall, no single assay can be used to definitively diagnose dengue at all stages of infection. Therefore, a combination of NS1 testing and IgM/IgG serologies is recommended to maximize disease detection. Several diagnostic kits, including rapid point-of-care devices, use this combination with nearly 100% detection sensitivity from disease onset through recovery.[4]

Treatment

While there are a wide variety of clinical manifestations of dengue, treatment is relatively simple and generally effective in reducing the morbidity and mortality associated with infection. Patients in the early febrile phase generally can be managed safely as

outpatients with adequate follow-up and anticipatory guidance. Warning signs of severe disease that should prompt return for care include abdominal pain, persistent vomiting, signs of bleeding, and change in mental status. Acetaminophen is safe for symptomatic management of the febrile patient, but nonsteroidal anti-inflammatory drugs should be avoided given the increased risk of bleeding complications. If the patient begins to show warning signs suggestive of more significant disease, or if there are co-existing risk factors, the patient should be hospitalized for further management. Initial treatment focuses on fluid resuscitation with the use of isotonic crystalloids, as well as monitoring of hematocrit and signs of plasma leakage. Patients who present with signs of shock, severe hemorrhage, or severe organ impairment should be hospitalized in a facility with access to intensive care services and blood products. Isotonic crystalloid infusion is still the most effective intervention for patients with severe dengue; however, blood products and more intensive hemodynamic and electrolyte monitoring may be required.[5]

Prevention and Control

Dengue prevention and control methods have been focused largely on vector management as well as the development of dengue-specific vaccines. Vector control efforts include the reduction of mosquito breeding sites, application of insecticides to high-yield targets (e.g., bed nets, window curtains, school uniforms), use of bacteria or fungi to decrease mosquito survivability, and genetic modification of wild mosquito populations to reduce transmission. Vector control is particularly challenging given the varying efficacies and costs of mosquito control measures, but efforts such as the World Health Organization's (WHO) Integrated Vector Management strategy seek cost-effective, efficacious, and ecologically appropriate solutions to vector control.[6]

A considerable amount of research has been devoted to the development of a dengue vaccine. The live attenuated tetravalent vaccine, CYD-TDV, has been registered in several countries. CYD-TDV is indicated for individuals 9-60 years of age who are living in an area with endemic dengue. Mathematical models have been carried out that demonstrate the possible effect of the CYD-TDV vaccine over time. The greatest effect of vaccination is in settings with high transmission intensity (seroprevalence > 70% at 9 years) where the reduction in symptomatic and hospitalized dengue ranged from 10-30% over a 30-year period. In contrast, the models predicted an increase in dengue hospitalization rates in very low transmission intensity settings (seroprevalence 10% at 9 years). This finding suggests that the vaccine may act like an asymptomatic infection in a previously seronegative individual, setting up the individual for a secondary-like infection if he or she is exposed to the dengue virus. Therefore, the WHO takes a stance that the vaccine should be considered for regions with seroprevalence > 70%, but it is not recommended for regions with seroprevalence < 50%.[7] The CYD-TDV vaccine, as well as other vaccines in development, will continue to be researched to provide an efficacious and safe method for dengue prevention. ■

REFERENCES

1. Thomas DL, Santiago GA, Abeyta R, et al. Reemergence of dengue in southern Texas, 2013. *Emerg Infect Dis* 2016;22:1002-1007.
2. Añez G, Rios M. Dengue in the United States of America: A worsening scenario? *Biomed Res Int* 2013;2013:678645.
3. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Dengue and dengue hemorrhagic fever. 2009.
4. Muller DA, Depelsenaire AC, Young PR. Clinical and laboratory diagnosis of dengue virus infection. *J Infect Dis* 2017;215(Suppl 2):S89-S95.
5. Hermann LL, Gupta SB, Manoff SB, et al. Advances in the understanding, management, and prevention of dengue. *J Clin Virol* 2015;64:153-159.
6. World Health Organization. *Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control: New Edition*. World Health Organization; 2009.
7. [No authors listed]. Dengue vaccine: WHO position paper — July 2016. *Wkly Epidemiol Rec* 2016;91:349-364.

ABSTRACT & COMMENTARY

Surviving Sepsis Campaign Guidelines Bundle: Studying How Improved Compliance Might Affect Outcomes

By Kathryn Radigan, MD

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

SYNOPSIS: Improved compliance with the Surviving Sepsis Campaign guidelines bundle was associated with a non-statistically significant decrease in the in-hospital mortality of severe sepsis patients.

SOURCE: Grek A, Booth S, Festic E, et al. Sepsis and Shock Response Team: Impact of a multidisciplinary approach to implementing Surviving Sepsis Campaign guidelines and surviving the process. *Am J Med Qual* 2016 Nov 10. [Epub ahead of print].

Although the Surviving Sepsis Campaign guidelines (SSCG) suggest a standardized, seven-element bundle to reduce sepsis mortality, national compliance rates are low. Grek et al hypothesized that improved compliance with SSCG would result in better outcomes in patients who suffer severe sepsis or septic shock. From December 2011 to March 2012, the authors conducted a baseline retrospective chart review of 25 consecutive patients discharged with the diagnosis of sepsis, severe sepsis, or septic shock. For each of these patients, compliance data were recorded for each of the seven bundle elements, including: initial lactate measurement followed by repeat if > 4; blood culture drawn prior to antibiotics; antibiotics within three hours of admission; fluid bolus of 30 mL/kg; placement of central venous line if lactate > 4; central venous pressure (CVP); and central venous oxygen saturation ($ScvO_2$) measurement. After data collection was completed on the initial 25 patients, data that included the same seven-element bundle were then collected prospectively for one year for all 116 patients who activated triggers, identifying them as patients in the ED with severe sepsis or septic shock. The primary outcome was to improve compliance with the seven-element bundle by 30%. This goal was to be achieved through high-impact interventions, including education, early identification of sepsis, and the development of a multidisciplinary team, the Sepsis and Shock Response Team (SSRT), which ensured early resuscitation of severe septic patients. Secondary outcomes, including hospital mortality and central line-associated bloodstream infection (CLABSI) rates, were measured and reported by the Infectious Disease and Infection Prevention and Control Committee.

Baseline data from the initial 25 consecutive patients with a diagnosis of sepsis, severe sepsis, and septic shock revealed poor compliance with the sepsis bundle. Lactate was measured in only 40% of patients, 76% received blood cultures prior to antibiotics, 60% received antibiotics within three hours of arrival, and only 33% received a fluid bolus of at least 30 mL/kg. None of the 25 patients were subjected to central line placement, CVP, or $ScvO_2$ measurements. There was 0% compliance for all elements of the bundle. After bundle implementation, 146 patients met the diagnosis of sepsis, severe sepsis, or septic shock criteria. Compliance for all elements of the bundle improved at three- and six-month intervals. At six months, all-or-none compliance was 51%. Additionally, there was 100% compliance with lactate measurements, along with 50% improvement with respect to antibiotics administered by three hours, fluid bolus administration, and blood cultures obtained prior to antibiotic administration. Overall, sepsis mortality for the study institution before and after the study period improved. Although not statistically significant, the overall observed/expected (O/E) sepsis mortality index decreased from 0.763 pre-SSRT to 0.642 post-SSRT implementation (P = 0.159); similarly, O/E sepsis mortality index for ED admits also decreased pre-SSRT from 0.745 to 0.591 post-SSRT (P = 0.069). For patients who were diagnosed with severe sepsis, there also was a drop in pre-SSRT O/E index from 0.864 to 0.701 post-SSRT (P = 0.102), with an O/E mortality index among ED admits showing a similar decrease from 0.884 to 0.662 (P = 0.049). CLABSI rates did not change during the study period.

■ COMMENTARY

Severe sepsis accounts for almost 10% of all deaths.[1] Ever since Rivers et al published the benefits of early goal-directed therapy (EGDT), the Surviving Sepsis Campaign guidelines were designed to implement a standardized, seven-element bundle to foster adherence to the guidelines, with the goal to reduce mortality by 25% over five years.[2] Unfortunately, adherence to bundles generally is exceedingly poor, and improved outcomes are challenging without adherence. Through their study, Grek et al could improve adherence to the bundle, which led to a trend toward reduction in overall mortality in patients presenting to the ED.

How did the researchers make a difference? To improve compliance with the bundle, quality improvement (QI) methodology was used to develop high-impact interventions. On initiation of the project, key stakeholders were identified and formed a multidisciplinary QI team. An SSRT was called to evaluate ED patients within 15 minutes to ensure completion of the bundle and expedite transfer to the ICU. The team consisted of an ICU physician, a fellow or resident, an advance practice provider (APP), nursing supervisor, and pharmacist. This was one of the most fundamental benefits to the project, as it created a spirit of consensus, cooperation, and teamwork. As appreciated in other studies, a multidisciplinary team approach to early recognition and treatment of sepsis is important.[3,4] Unfortunately,

the main barrier for initiation of these teams is culture change, which takes consistent follow-up, teamwork, and recurring interventions. During analysis, the team defined the three drivers for the effective treatment of sepsis. These included identifying severe sepsis and septic shock, standardizing quantitative resuscitation, and triage decisions.

Monitoring compliance also was key in making a difference in outcomes. Monitoring compliance during and after each intervention was followed closely with feedback to each individual provider through monthly staff meetings and biweekly emails. A sniffer computer algorithm was developed to improve early identification of systemic inflammatory response syndrome (SIRS) and sepsis. The alert triggered a text page to the lead nurse in the ED who would identify the ED physician once the trigger was verified and the sepsis resuscitation checklist was followed. A severe sepsis and septic shock activation flow sheet addressing triage and treatment was posted in the ED and ICU. Provider pocket cards addressing clinician roles for patients were created for nurses, fellows, residents, APPs, and ICU physicians. An internal SSRT website was developed detailing implementation plans, compliance data, and included an electronic suggestion box to invite feedback and suggestions. The team also included simulation center training targeting sepsis activation and standardized treatment protocols. Interestingly, the CVP and $ScVO_2$ measurements had the lowest compliance rates, most likely due to the coinciding release of the PROCESS, ARISE, and PROMISE trials.[5-7]

Multiple interventions, including education, early identification of sepsis, and the development of a multidisciplinary team to ensure early resuscitation of severe septic patients, led to dramatically improved adherence to the SSCG, with a decrease in the in-hospital mortality of severe sepsis patients presenting to the ED. Of course, improved adherence to the SSCG takes significant work with interdisciplinary collaboration and response infrastructure. Many of these same strategies may be adopted within our own hospitals with similar results. Although this study was promising, it must be interpreted cautiously, as its results were based on a small sample size without a randomized design. Future studies are needed to delineate the benefits of additional interventions that may be used to improve bundle compliance. ■

REFERENCES

1. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29:1303-1310.
2. Barochia AV, Cui X, Eichacker PQ. The Surviving Sepsis Campaign's revised sepsis bundles. *Curr Infect Dis Rep* 2013;15:385-393.
3. Sebat F, Musthafa AA, Johnson D, et al. Effect of a rapid response system for patients in shock on time to treatment and mortality during 5 years. *Crit Care Med* 2007;35:2568-2575.
4. Funk D, Sebat F, Kumar A. A systems approach to the early recognition and rapid administration of best practice therapy in sepsis and septic shock. *Curr Opin Crit Care* 2009;15:301-307.
5. Pro CI, Yealy DM, Kellum JA, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014;370:1683-1693.
6. Investigators A, Group ACT, Peake SL, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 2014;371:1496-1506.
7. Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015;372:1301-1311.

ABSTRACT & COMMENTARY

Oral Cholera Vaccine and Travelers

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

SYNOPSIS: The new oral cholera vaccine is recommended for adults 18-64 years of age who are planning to travel to areas at risk.

SOURCE: Wong KK, Burdette E, Mahon BE, et al. Recommendations of the Advisory Committee on Immunization Practices for Use of Cholera Vaccine. *MMWR Morb Mortal Wkly Rep* 2017;66:482-485.

In 2016, the Advisory Committee on Immunization Practices (ACIP) recommended the use of lyophilized CVD 103-HgR vaccine, which also was approved by the FDA in 2016, for prevention of cholera in individuals age 18-64 years traveling to areas with endemic or epidemic cholera caused by toxigenic *Vibrio cholerae* O1. It also recommended vaccination for travel to areas at risk of recurrence of epidemic cholera that had had cholera activity in the past 12 months.

■ COMMENTARY

While rare in the United States, cholera affects 2.9

million individuals globally each year, and these infections result in 95,000 deaths.

The vaccine has an estimated efficacy of 90% when tested by oral challenge with toxigenic *V. cholerae* 10 days after its receipt, an efficacy of 80% at three months, and is well tolerated. Travelers to selected areas who are considered at higher than usual potential risk include healthcare workers, epidemic response workers, those with extended residence in endemic areas, and, importantly, those visiting families and friends. Among those who become infected, the following are risk factors for adverse outcomes: those with reduced gastric acidity because of, e.g., partial gastrectomy or antacid therapy, those without ready access to medical care, and individuals with blood group O. The last risk factor is true of 45% of the U.S. population.

Vaccination should be avoided in individuals who received an antibiotic in the previous 14 days. Chloroquine may interfere with the immunogenicity of the vaccine, and its initiation, if indicated, should be delayed for at least 10 days after vaccination. The vaccine strain is shed in stool in 11.1% of recipients in the week after administration.

Receipt of the vaccine does not preclude the need for personal protection, including hygiene, food and water precautions, and effective sanitation. The duration of protection beyond three months is unknown. ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Colistin Resistance in Action

SOURCE: Rojas LJ, Salim M, Cobert E, et al. Colistin resistance in carbapenem-resistant *Klebsiella pneumoniae*: Laboratory detection and impact on mortality. *Clin Infect Dis* 2017:64; 711-718.

Colistin has become an important "last resort" agent for patients infected with increasingly drug-resistant gram negatives, especially carbapenem-resistant Enterobacteriaceae. This study examined colistin resistance in isolates from patients infected or colonized with carbapenem-resistant *Klebsiella pneumoniae* (CRKP) from December 2011 to October 2014, comparing the results from broth macrodilution (performed in a research laboratory) to those of standard clinical laboratory Etest, as well as to the results of polymyxin resistance testing. Only the first isolate from an individual patient was included in the assessment. Time to 30-day all-cause in-hospital mortality was determined.

A total of 246 patients with CRKP were identified. Of these, 22% had received prior treatment with colistin. Isolates were cultured from urine (59%), blood (18%), respiratory secretions (11%), wound (5%), or other (7%). Gene testing revealed that CRKP resistance was mediated by bla-KPC-3 (50%) and bla-KPC-2 (46%). Colistin resistance was identified for 31 (12.5%) of the isolates by broth macrodilution compared with 9% for the clinical laboratory, based on Etest. In comparison, 10% of the isolates tested were resistant to polymyxin B. Based on these results, the clinical laboratory underestimated colistin resistance for ~ 35% of isolates.

A variety of strain types were observed for both colistin-sensitive and colistin-resistant groups, suggesting that chromosomally mediated colistin resistance arises de novo. None of the isolates were found to be carrying MCR-1 or MCR-2 colistin resistance genes.

Kaplan-Meier confirmed that the 30-day all-cause mortality was significantly greater for patients with CRKP isolates resistant to colistin, regardless of whether the patients were actively infected or colonized (adjusted hazard ratio, 3.48; $P < 0.001$).

One of the difficulties infectious disease specialists have faced is the lack of interpretative standards for colistin resistance, and a lack of good clinical and PK/PD data for establishing breakpoints. A working group affiliated with the CLSI has been working to establish better data. For example, colistin breakpoints have been established for Acinetobacter spp. and *Pseudomonas aeruginosa* (≤ 2 micrograms/mL is considered susceptible). Based on epidemiological data, inferences can be made to support a similar cut-off value for Enterobacteriaceae. The CLSI has recommended that any Enterobacteriaceae isolate with an MIC to colistin of 4 micrograms/mL or higher should be tested for MCR genes.

PK-tailored High-dose Colistin May Not Be Beneficial

SOURCE: Benattar YD, Omar M, Zusman O, et al. The effectiveness and safety of high-dose colistin: Prospective cohort study. *Clin Infect Dis* 2016:63:1605-1612.

One of the difficulties in the use of colistin is understanding the optimal dose for patients with life-threatening infection with multidrug-resistant organisms. Not only is it difficult to interpret susceptibility data, but sufficient pharmacokinetic data are not available. These Israeli investigators examined the use of different dosing schemas of colistin in two prospective cohort studies performed between 2006 and 2009 and 2012 and 2015 at two different facilities. Pharmaco-directed therapy, using higher doses of colistin, aimed at maintaining the drug level above a breakpoint of 2 mg/L (see above article) was compared with standard dosing. High-dose colistin consisted of a loading dose of 9 MIU followed by 4.5 MIU twice daily, with daily renal-dose adjustment as needed to maintain at least 80% of the target dose. Mortality and toxicity were compared between those receiving higher-dose colistin vs. standard dosing in adult patients with carbapenem-resistant infection requiring colistin.

A total of 529 patients were included in the analysis, including 144 treated with high-dose colistin and 385 receiving standard dosing. Not including the loading dose, the median daily dose in the high-dose group was 9 MIU compared with 4 MIU in the standard dosing group. After adjustment in multivariate analysis and for propensity scoring, no significant difference in 28-day mortality was observed between the two groups. In looking at overall mortality, there were 50 (34.7%) deaths in the high-dose group compared with 165 (42.9%) in the standard-dose group (P = NS). However, the adjusted odds ratio for mortality was 1.07 (95% confidence interval, 0.63-1.83) for high-dose colistin, suggesting a possible trend in favor of standard dosing. Patients in the high-dose group were more likely to have pneumoniae from *Acinetobacter baumannii*, while the most frequent infection in the standard dose group was *Klebsiella pneumoniae* bacteremia. Mortality in patients with bacteremia was significant in both groups: 14/32 (43%) of bacteremic patients receiving high-dose colistin died vs. 91/175 (52%) of those in the standard dosing group.

Not unexpectedly, toxicity was greater in patients receiving high-dose colistin compared with standard dosing. Almost twice as many patients developed increased serum creatinine in the high-dose group. Three times the increase in creatinine was observed in 16.7% of high-dose vs. 8.8% of standard-dose group. Seizures occurred in 4.9% of those receiving high-dose colistin compared with 1% in the standard dosing group.

'Dragon's Blood' Yields Possible Antibacterial

SOURCE: Bishop BM, Juba ML, Russo PS, et al. Discovery of novel antimicrobial peptides from *Varanus komodoensis* (Komodo dragon) by large-scale analyses and de-novo-assisted sequencing using electron-transfer dissociation mass spectrometry. *J Proteome Res* 2017;16:1470-1482.

The search is on for new antimicrobials that may prove useful against increasingly resistant organisms. Such bioprospecting is focused on the discovery of new products from biological and natural resources, as well as systematically reviewing centuries-old homeopathic products and drugs shelved years ago. Amphibians and reptiles are widely recognized for their ability to resist infection, despite a constant risk of wounds and wound infection. For example, different species of frogs secrete various antimicrobial peptides from their skin that have a broad range of activity against bacteria and fungi, and a couple have made their way into preliminary clinical trials as potential topical antimicrobials for humans. Thus far, more than 800 such organisms have been isolated from different species, including frogs, toads, spiders, scorpions, and fish.

These authors have turned their attention to crocodiles and lizards, such as the Komodo dragon, which lives on a series of islands in Indonesia. The Komodo is thought to kill its prey with the use of strong scissor-like teeth that inflict a bacterial-laden wound, resulting in fatal infection, much the same as the big cats (or your own cat) do. And yet, the Komodo itself seems resistant to these wound infections.

The first task was finding a cooperative Komodo willing to donate a blood specimen — a zookeeper managed to collect four tablespoons of blood from the tail of a 100-pound Komodo at a zoological park in Florida for use. Using mass spectrometry, 48 potentially useful cationic peptides were isolated from blood — referred to as CAMPS (for cationic antimicrobial peptides). Eight of these have been synthesized and tested in vitro against laboratory strains of *S. aureus* and *Pseudomonas aeruginosa*. All eight had activity against pseudomonas, while seven had activity against *S. aureus*. Researchers are still working on the other 40 compounds.

While researching this article, it was interesting to learn that the traditional Chinese remedy

"Dragon's blood" has nothing to do with Komodo or other dragons. Dragon's blood is a bright red plant resin, acquired from the rattan palms in Indonesia or certain trees native to the Canary Islands, Morocco, and South America. Used for centuries as a cure-all for wound infections, stomach upset, mouth ulcers, and postpartum bleeding, it still can be found in use in commercial sculpting gels and night creams. It also has been found in furniture varnish and adds color to string instruments. This resin is a complex product containing phenols, flavonoids, sterols, etc., which also have been examined for their potential antimicrobial and antioxidant properties. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. Dengue fever:

a. has not yet occurred in the continental United States.

b. has an incubation of up to two months between mosquito bite and symptom onset.

c. may be complicated by hemorrhage and shock shortly after the resolution of the initial fever.

d. is potentially fatal without early administration of antiviral agents.

2. Which of the following is correct regarding infective endocarditis in New York and California between 1998 and 2013?

a. The adjusted mortality significantly increased.

b. The proportion affecting prosthetic valves and other intracardiac devices (as compared to native valves) increased.

c. The incidence caused by oral streptococci increased, especially after the indications for dental antibiotic prophylaxis were restricted.

d. The mortality rate was greater in patients with community-acquired endocarditis compared to those with nosocomial endocarditis.

3. Which of the following is correct regarding Powassan virus?

a. It is a flavivirus related to the tick-borne encephalitis virus that causes infections in parts of Europe and Asia.

b. It is transmitted by three tick species, including *Ixodes scapularis*, which also can transmit *Borrelia burgdorferi*, among other pathogens.

c. It can be transmitted by a tick bite that lasts only 15 minutes.

d. All of the above.

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.