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Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

A Negative Nares Screen for MRSA Helps Exclude MRSA Pneumonia

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

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

SYNOPSIS: A meta-analysis determined that nares screening for methicillin-resistant *Staphylococcus aureus* (MRSA) has a high specificity and negative predictive value for MRSA pneumonia. MRSA nasal screening can be a useful tool for antimicrobial stewardship personnel to de-escalate empiric anti-MRSA therapy.

SOURCE: Parente DM, Cunha CB, Mylonakis E, Timbrook TT. The clinical utility of methicillin-resistant *Staphylococcus aureus* (MRSA) nasal screening to rule out MRSA pneumonia: A diagnostic meta-analysis with antimicrobial stewardship implications. *Clin Infect Dis* 2018;67:1-7.

Although methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia is a serious illness associated with significant morbidity and mortality, its overall prevalence is low, especially as a cause of community-acquired pneumonia (CAP). Thus, clinicians frequently must deal with the dilemma of when to use empiric anti-MRSA therapy (e.g., vancomycin and linezolid), factoring in the inherent drawbacks, such as cost, adverse reactions, toxicities, and the promotion of antimicrobial resistance, associated with these agents. To address this concern, Parente and colleagues sought to determine the value of MRSA nasal screening in the management of MRSA pneumonia.

The investigators conducted a meta-analysis that included studies with information about both rates of positive MRSA nasal screening and the rates of

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MRSA pneumonia that were confirmed by culture. All classes of pneumonia were included: CAP, hospital-acquired pneumonia (HAP), healthcare-associated pneumonia (HCAP), and ventilator-associated pneumonia (VAP). Studies that used MRSA surveillance cultures from sites other than the nares were excluded from the analysis. Researchers employed a bivariate random-effects model to calculate the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

There were 22 studies with 5,163 patients who met the inclusion criteria. Of these, 18 (81.1%) were retrospective, three were prospective (13.6%), and one was not reported. The diagnostic criteria for MRSA pneumonia differed in the various studies, with most using radiographic, microbiological, and clinical criteria to determine the diagnosis. The MRSA nares surveillance method differed in the studies as well, with 11 (50%) using polymerase chain reaction (PCR), four (18.35%) using culture, one study (4.5%) using both methods, and for the remaining six studies (27.3%) the method was not described. The timing for obtaining MRSA screening was reported in most of the studies (95.5%).

For all pneumonia types, the sensitivity of MRSA nares screen to predict pneumonia was 70.9% (95% confidence interval [CI], 58.8-80.6%], specificity was 90.3% [95% CI, 86.1-93.3%], PPV was 44.8%, and NPV was 96.5%. For CAP and HCAP, the values were 85% sensitivity [95% CI, 59.7-95.6%], 92.1% specificity [95% CI, 81.5-96.9%], 56.8% PPV, and 98.1% NPV. For VAP, the values were somewhat different, with a sensitivity of 40.3% [95% CI, 17.4-68.4%], specificity of 93.7% [95% CI, 77.1-98.4%], PPV of 35%, and NPV of 94.8%. There was a low probability of publication bias as determined by funnel plot testing.

■ COMMENTARY

The overuse of vancomycin is a serious concern in clinical practice. The study by Parente and colleagues is welcome because it provides solid evidence that can help antibiotic stewardship efforts in reducing the amount of anti-MRSA antibiotics prescribed for pneumonia.

Even though a positive MRSA screen was not diagnostic, if the screen result was negative, pneumonia essentially could be ruled out in instances of CAP/HCAP. The sensitivity and NPV were lower for VAP, which the authors blamed on artificial airways providing a secondary source of MRSA besides the nares. However, in the absence of risk factors for MRSA and the presence of a negative MRSA nasal screen, it seems reasonable to stop anti-MRSA therapy and then observe closely. Further clinical studies will need to be conducted to determine outcomes in patients with pneumonia whose therapy is modified based on the results of MRSA nasal screening.

There are a couple of exceptions for which MRSA nasal screening might not be reliable to predict pneumonia. These include patients who were decolonized recently, those with a MRSA infection in the preceding 30 days, those with structural lung disease such as cystic fibrosis or bronchiectasis, and those who are critically ill.

As with all meta-analyses, the strength of the findings is directly proportional to the robustness of the studies that are included. That being said, most of the studies (81.8%) in the present meta-analysis had a retrospective design, which makes them subject to confounding by indication and sampling bias. Moreover, verification bias is a concern because nasal screening results often influence culture collection and clinical diagnosis. It is notable that the confidence interval for the sensitivity associated with VAP was particularly wide (17.4-68.4%), which may reduce the value of this variable. Finally, not all of the studies clearly defined the time that nasal swabs were collected compared to when the sputum cultures were taken.

The meta-analysis by Parente and colleagues has shown that a negative nasal screen for MRSA is a rapid, easy, and inexpensive way to exclude MRSA pneumonia. This will allow the discontinuation of anti-MRSA antibiotics to occur sooner, thus sparing patients unnecessary therapy and reducing costs. One potential strategy is to allow pharmacists to order MRSA nasal screens

whenever a patient is prescribed vancomycin or linezolid for pneumonia. A negative result then could be discussed with the prescribing physician. Whether future pneumonia guidelines incorporate these new data remains to be seen. ■

ABSTRACT & COMMENTARY

Using Multilocus Sequence Typing for Surveillance and Discovery of *Borrelia* Species

By Dean L. Winslow, MD, FACP, FIDSA

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

SYNOPSIS: Broad polymerase chain reaction screening followed by multilocus sequence typing is a useful method to understand the geographic distribution of *Borrelia* species causing human disease. *Candidatus B. johnsonii* (carried by bat ticks) was not known previously to infect humans. Its identification in a human patient suggests it may cause a relapsing fever syndrome.

SOURCE: Kingry LC, Anacker M, Pritt B, et al. Surveillance for and discovery of *Borrelia* species in U.S. patients suspected of tickborne illness. *Clin Infect Dis* 2018;66:1864-1871.

Providers throughout the United States submitted 7,292 de-identified blood and other body fluid specimens from patients who were suspected to have a tickborne disease to the U.S. Centers for Disease Control and Prevention (CDC). Researchers screened the specimens initially by employing a *Borrelia* genus-level TaqMan polymerase chain reaction (PCR) followed by characterizing the species and sequence types of *Borrelia* with multilocus sequence typing (MLST) using next-generation sequencing. Researchers identified five *Borrelia* species among these 7,292 specimens. The two species causing the clinical syndrome of Lyme borreliosis (LB) were *Borrelia burgdorferi* (n = 25) and *Borrelia mayonii* (n = 9). The three species causing the clinical syndrome of relapsing fever (RF) were *Borrelia hermsii* (n = 1), *Borrelia miyamotoi* (n = 8), and *Candidatus Borrelia johnsonii* (n = 1). The latter species was identified previously only in *Carios kelleyi* (bat ticks). The researchers found that sequence type (ST) diversity was greatest for specimens that were positive for *B. burgdorferi*, and these diverse STs were identified primarily in synovial fluids.

■ COMMENTARY

I found this to be a very interesting study. The novel species *Candidatus B. johnsonii* was identified in a human patient with a relapsing fever illness in Wisconsin. Previously, this species had been identified only in bat ticks from a farmhouse in Iowa. The one specimen positive for *B. hermsii* came from a patient in Montana. The *B. miyamotoi*-positive specimens came from patients in Minnesota, Wisconsin, and New Jersey. The *B. mayonii*-positive specimens all came from Minnesota or Wisconsin. Not surprisingly, the specimens of *B. burgdorferi* all originated from eight states in the regions of the Midwest, mid-Atlantic, and Northeast (Iowa, Maryland, Minnesota, Missouri, New Jersey, New York, Pennsylvania, Virginia, and Wisconsin). This study emphasizes the growing clinical importance of broad-range PCR and NGS to identify human pathogens. ■

ABSTRACT & COMMENTARY

The Viral World Keeps on Going — Some Recent Activity

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: Ebola makes a comeback, but meets a vaccine. Lassa fever and Rift Valley fever also make their mark, while Keystone virus infects a teenager in Florida.

SOURCE: International Society for Infectious Diseases. ProMED Mail. Available at: http://www.promedmail.org/index.php. Accessed July 8, 2018.

Lassa Fever

Between Jan. 1, 2018, and June 10, 2018, 1,999 suspected cases of Lassa fever were reported from 22 Nigerian states and 437 of these cases were laboratory-confirmed. The case fatality among confirmed cases was 24.9%. Thirty-eight healthcare workers have been infected. Among the 5,328 identified contacts who have completed 21 days of follow-up, 84 were symptomatic and 29 have been confirmed. The outbreak has been diminishing for a number of weeks.

Lassa fever is a viral hemorrhagic illness that is caused by Lassa virus, which is an arenavirus present in West Africa, particularly in the countries of Benin, Ghana, Guinea, Liberia, Mali, and Sierra Leone, in addition to Nigeria. Humans typically can become infected via exposure to aerosol or through contact with droppings of infected multimammate rats; contact may be direct or via food or items that have been contaminated with excreta from rodents. In addition, person-to-person transmission occurs in healthcare settings from exposure to body fluids of infected patients.

Approximately four-fifths of patients are asymptomatic or have quite mild symptoms. The incubation period is 2-21 days in symptomatic patients with progression to hemorrhagic fever in a small proportion. Although the overall case fatality rate is approximately 1%, it is 15% in those who require hospitalization. Ribavirin administration beginning within six days of fever onset generally is recommended, but this is based on limited and low-quality evidence.

Rift Valley Fever

In Kenya, a Rift Valley fever outbreak started with recognition of the index case identified on May 11, 2018. As of June 20, 90 cases had been reported. This was accompanied by an epizootic that also is occurring in Rwanda, which, along with Uganda, has suspected human cases.

Rift Valley fever virus is a Phlebovirus (family *Bunyaviridae*) that is primarily a disease of livestock in Africa, with frequent transmission into human populations. Although originally apparently confined to the Rift Valley of eastern Africa, it now is present in much of Africa, including Madagascar, as well as the Arabian peninsula. Humans acquire the infection either through contact with infected animals or through mosquito bites. Most human infections are asymptomatic, but approximately 10% of patients with symptoms develop uveitis, retinitis, and/or retinal hemorrhage. The illness may progress to hemorrhagic fever.

Ebola

Ebola reemerged on April 1, 2018, this time in the Equateur province in the Democratic Republic of Congo, with, as of July 3, 53 cases (38 laboratory-confirmed and 15 probable cases). The 29 deaths represent a case fatality rate of 55%.

This outbreak provided an opportunity for further testing of a recombinant vaccine, rVSV-ZEBOV, consisting of a vesicular stomatitis virus expressing Ebola surface glycoprotein. A ring strategy was employed with vaccine administration to case contacts. The vaccine also was administered to healthcare and other frontline workers in the affected areas, as well as in areas to which spread of the outbreak was of concern.

Keystone Virus

Keystone virus, a California serogroup Orthobunyavirus, was detected by non-biased

sequencing and cell culture from a 16-year-old male in Florida with fever and a non-pruritic erythematous papular eruption that had begun on his chest and spread to abdomen, arm, back, and face.[1] The infection resolved within a few days. This was the first reported detection of the Keystone virus in humans, although older serological studies suggested prior exposure to it. The virus infects a variety of small vertebrates as well as mosquitoes. The findings reported here are highly suggestive of the virus causing symptomatic infection, but they do not prove it.

These represent just a small fraction of recent viral activity. Middle East Respiratory Syndrome continues to cause disease in the Middle East, Nipah has affected several individuals in the Kerala state of India, a new virus (Ntwetwe) was detected in cerebrospinal fluid of a child in Uganda with encephalitis, and more. ■

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ABSTRACT & COMMENTARY

Encephalitis, Fever, and Doxycycline

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: Scrub typhus is a significant cause of acute encephalitis in north India and other parts of Asia and Africa. Doxycycline is a safe and effective treatment option.

SOURCE: Mittal M, Bondre V, Murhekar M, et al. Acute encephalitis syndrome in Gorakhpur, Uttar Pradesh, 2016: Clinical and laboratory findings. *Pediatr Infect Dis J* 2018;37: doi: 10.1097/INF.0000000000002099. [Epub ahead of print].

Outbreaks of acute encephalitis occur seasonally in northern India, with about 10,000 cases per year and with case fatality rates of approximately 25%. Japanese encephalitis virus accounted for the majority of cases in the past, but the incidence of disease due to that agent has decreased with use of vaccines. Nonetheless, outbreaks of encephalitis continue. Investigations earlier this decade suggested that scrub typhus was common in northern India and might be responsible for some encephalitis cases. Mittal and colleagues prospectively evaluated patients presenting with acute encephalitis to determine current causes.

Patients of any age were included if they had acute fever with altered mental status and/or new onset of seizures during three months in 2016 (August-October). Of 1,242 patients at a single center meeting the clinical case definition, 1,037 had cerebrospinal fluid evaluation showing at least five cells per cubic milliliter; 407 of the patients with acute encephalitis and spinal fluid pleocytosis were selected randomly for study inclusion. Researchers tested serum samples for IgM antibodies to the agents of scrub typhus (*Orientia tsutsugamushi*), Japanese encephalitis, and dengue fever. The investigators also tested spinal fluid for IgM antibodies against Japanese encephalitis virus and *O. tsutsugamushi*. They performed polymerase chain reaction testing on whole blood and on spinal fluid for *O. tsutsugamushi* and for the spotted fever group of *Rickettsia*.

All patients were from rural areas. About half were 5 to 10 years of age. Of the 407 studied patients, 65% had scrub typhus, 10% had Japanese encephalitis, and 8% had dengue fever. Less than 1% (four patients) had evidence of infection with the spotted fever group of *Rickettsia*. Of the 266 patients with scrub typhus, 36 had coinfection: 23 with dengue, 10 with Japanese encephalitis virus, two with spotted fever group *Rickettsia*, and one with triple infection (scrub typhus, dengue, and Japanese encephalitis).

For patients with scrub typhus, symptoms of fever, altered sensorium, and seizures were characteristic. About half had vomiting, and 15% had abdominal pain; 5% had diarrhea. Headache was reported by 14%. Patients had been sick with fever for a median of six days between the onset of fever and the development of central nervous system findings. Hepatomegaly was seen in 44%, splenomegaly in 10%, and periorbital edema in 33%. Eschar was not seen. About three-fourths of patients were hyperreflexic. Peripheral white

blood cell counts were elevated mildly, and platelet counts were diminished mildly. Spinal fluid white cell counts were elevated mildly (median 24 per cubic milliliter). In this study, patients with acute encephalitis were treated routinely with intravenous azithromycin. Sadly, 15% of patients did not survive the scrub typhus infection.

The researchers compared their results to those of other studies of etiologies that account for acute encephalitis in India. In other studies in which *O. tsutsugamushi* infection was not sought, the majority of patients had no identified causal microbe.

■ COMMENTARY

A couple of years ago, I performed teaching rounds with a pediatric team in the capital city of the Himalayan mountain kingdom of Bhutan. We saw a child with acute encephalitis who had come from the southern part of Bhutan, at low elevation near the border with India. I thought through a differential diagnosis for this febrile child who presented semi-comatose and seizing with spinal fluid pleocytosis. Bacterial testing was negative, as was a test for Japanese encephalitis. I wondered about herpes infection and arboviral diseases. Fortunately, even the Bhutanese trainees had a broader differential diagnosis than I did, and they thought to start doxycycline for possible scrub typhus. As exemplified by the other Indian studies reviewed by Mittal and colleagues, those who don't seek scrub typhus fail to find it, and those who don't think of scrub typhus fail to treat for it.

Obviously, the geographic epidemiology of febrile illnesses, including encephalitis, varies. Scrub typhus is borne by mites and is common in eastern and southern Asia, on western Pacific islands, and on the islands of the Indian Ocean. More than 1 million new cases are thought to occur each year.[1] The epidemiology also varies over time. Even as my senior colleagues and I remember frequently seeing patients with bacterial meningitis due to *Haemophilus influenzae* and *Streptococcus pneumoniae*, those diseases are markedly rare in our current era of improved vaccination. Similarly, the likelihood of Japanese encephalitis causing illness in countries like India has dropped with more widespread Japanese encephalitis virus vaccine use.

In a study reported last year from Tanzania, researchers evaluated 57 potential causes of fever in 1,007 febrile patients.[2] *Plasmodium* was the most common etiology identified, but *Leptospira* was found in 3% and *Rickettsia* in 1%; scrub typhus was not included in the testing for this study. However, as malaria becomes less common in Africa, other infections become relatively more common. In a recent study in Kenya, researchers looked specifically at other treatable causes of fever in children; during 13 months spanning 2011-2012, researchers evaluated 370 febrile children.[3] They identified spotted fever group *Rickettsia* in 22% of the children, typhus group *Rickettsia* in 1%, and scrub typhus in 4%. In Asia and Africa, patients with fever and patients with acute febrile encephalitis should be cared for by professionals who are aware of the possibility of scrub typhus.

Patients with rickettsial diseases and patients with scrub typhus do not respond favorably to common antibacterial agents. Doxycycline usually is considered the treatment of choice, but there have been concerns about the safety of doxycycline use in children because of the concern about staining of teeth. However, a recent systematic review gives reassurance about the use of doxycycline.[4] Although tetracycline has potential side effects, there is no correlation between the use of doxycycline and either staining of children's teeth or teratogenicity when the medication is used during pregnancy.[4]

Mittal and colleagues chose to treat scrub typhus with azithromycin. Researchers conducted a comparison study of azithromycin and doxycycline for complicated scrub typhus using retrospective propensity score matching.[1] Outcomes were similarly favorable between the two groups, suggesting that intravenous azithromycin is a valid alternative to doxycycline for treatment of patients with scrub typhus.

Thus, scrub typhus is a significant cause of acute encephalitis in parts of Asia, Oceania, and, increasingly, Africa. Patients with acute encephalitis in or from these parts of the world should be tested and/or presumptively treated with doxycycline or intravenous azithromycin to cover the possibility of scrub typhus. ■

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SPECIAL FEATURE

Re-evaluating Steroid Therapy in Septic Shock

By Samuel Nadler, MD, PhD

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

Septic shock carries a significant risk of mortality despite increasing knowledge of its pathophysiology and clinical management. Studies dating back to the 1960s suggested steroid treatment may alter the course of septic shock and led to the concept of critical illness-related corticosteroid insufficiency.[1]

In 2002, Annane et al demonstrated a mortality benefit for patients with septic shock given the combination of hydrocortisone and fludrocortisone, generating interest in this therapy and changing guidelines.[2] However, the 2008 CORTICUS trial demonstrated no mortality benefit and a reevaluation of this guideline.[3]

Two recent trials, ADRENAL and APROCCHSS, have provided more data regarding steroid therapy for septic shock.[4,5] Comparing these seminal studies provides context for the decision about whether to treat septic shock with steroid therapy.

PAST AND CURRENT STUDIES

Annane et al published results from a placebo-controlled, randomized, double-blind trial of 299 patients with septic shock.[2] The authors enrolled adult patients with documented or strong suspicion of infection, alterations in body temperature, tachycardia, systolic blood pressure < 90 mmHg for one hour despite fluid administration, and vasopressors with organ dysfunction defined by low urine output, elevated arterial lactate, or need for mechanical ventilation. Patients were excluded if they presented with acute myocardial infarction, pulmonary embolism, advanced cancer, AIDS, or contraindications to or pre-existing indications for steroid therapy. Participants were stratified further by a 250 mcg tetracosactrin stimulation test as responders or non-responders. The intervention group received hydrocortisone 50 mg intravenously every six hours and enteral fludrocortisone 50 mcg daily for seven days. Regarding the primary endpoint, 28-day mortality in non-responders was significantly lower in the steroid group (53%) than in the placebo group (63%), with an odds ratio (OR) of 0.54 (95% confidence interval [CI], 0.31-0.97; $P = 0.04$).

In all patients, the OR for 28-day survival was 0.65 (95% CI, 0.39-1.01; $P = 0.09$) in the steroid vs. placebo groups. The non-responders also demonstrated both decreased ICU mortality and hospital mortality when given steroids. Time to vasopressor therapy withdrawal with steroid therapy was shorter in both the non-responder group (7 days vs. 10 days; $P = 0.001$) and the overall patient population (7 days vs. 9 days; $P = 0.01$). No adverse events were ascribed to steroid replacement therapy. Specifically, there were no increased rates of infections, bleeding, or delirium.

The authors of the CORTICUS study, published in 2008, enrolled 499 patients with sepsis and examined the response to 50 mg of hydrocortisone intravenously every six hours.[3] The inclusion criteria included evidence of infection, the systemic response to infection, and onset of shock within 72 hours. Exclusion criteria included poor prognosis and recent steroid use. All patients underwent a cosyntropin stimulation trial. The primary endpoint was 28-day mortality in non-responders. Notably, power calculation of this trial cited a sample size of 800 patients to achieve a statistical power of 80% to detect a 10% decrease in absolute mortality, assuming 50% mortality.

This trial demonstrated no difference in mortality with hydrocortisone compared with placebo in non-responders (39.2% vs. 36.1%; $P = 0.69$) or all patients (34.3% vs. 31.5%; $P = 0.51$). There was no difference in ICU mortality, death during hospitalization, death at one year, or length of stay. Oddly, time to reversal of shock with steroids was statistically lower in those patients who responded to cosyntropin (2.8 days vs. 5.8 days; $P < 0.001$) and all patients (3.3 days vs. 5.8 days; $P < 0.001$), but not in non-responders (3.9 days vs. 6.0 days; $P = 0.06$).

The authors of the HYPRESS trial, published in 2016, further evaluated the effect of hydrocortisone alone in patients with severe sepsis.[6] The inclusion criteria for this trial included evidence of infection with a systemic response, organ dysfunction not present for more than 48 hours, but excluded patients with septic shock, defined by persistent hypotension despite fluids and vasopressors. The study population received hydrocortisone 50 mg bolus followed by a continuous infusion of 200 mg per day for five days with tapering over the next six days. The primary endpoint was the occurrence of septic shock within 14 days. Power calculation in this study planned an 80% chance to detect a 15% difference, assuming a rate of septic shock in the study population of 40% with 380 total patients.

Of the 353 patients who were included in the intention-to-treat analysis, the rates of septic shock at 14 days in the placebo and study group were very similar (22.9% and 21.2%, respectively; P = 0.70). No significant differences were noted in many secondary endpoints, although the rates of delirium were lower in the hydrocortisone group. The rate of hyperglycemia was significantly higher with steroid administration. Another notable difference was the relatively higher proportion of patients with pneumonia and respiratory tract infections in the placebo group compared with the study group.

Most recently, the authors of two additional studies (ADRENAL and APROCCHSS) examined the response of patients with sepsis to steroids.[4,5] ADRENAL investigators randomized adult patients on mechanical ventilation with suspicion of infection, two or more systemic inflammatory response syndrome (SIRS) criteria, and the need for vasopressors or inotropes for at least four hours. Patients who received etomidate, exhibited other indications for steroids, or were expected to die within 90 days were excluded. The study compared a continuous infusion of hydrocortisone 200 mg daily for seven days vs. placebo. The primary outcome was all-cause mortality at 90 days. A population of 3,800 patients provided the trial a 90% power to detect a 5% absolute difference in the primary outcome, with an estimated baseline mortality of 33%. However, there was no difference in 90-day mortality between the treatment and control groups (27.9% and 28.8%, respectively; P = 0.50). There were improvements in the secondary outcomes of median time to shock resolution, median time to discharge, and median time to cessation of mechanical ventilation. These authors also noted more adverse events in the hydrocortisone group, including hyperglycemia, hypernatremia, hypertension, and myopathy.

In contrast, APROCCHSS originally was designed to be a 2 × 2 factorial study examining activated protein C (APC) and steroids in septic shock. During the trial, APC was removed from the market, but the trial continued, focusing on the steroid effects. Inclusion criteria included indisputable or probable septic shock for < 24 hours as defined by a sequential organ failure assessment score of 3-4 in at least two organ systems and vasopressor therapy. Exclusion criteria included septic shock for > 24 hours, pregnancy or lactation, or underlying conditions that could affect short-term survival. The study group received 50 mg hydrocortisone intravenously every six hours and 50 mcg enteral fludrocortisone daily for seven days. Again, cosyntropin stimulation trials were performed. The primary outcome was 90-day all-cause mortality.

Here, the baseline mortality was assumed to be 45% and a total of 1,280 patients would be required to detect an absolute 10% difference. The primary outcome was realized in 43% of the steroid group and 49.1% of the placebo group, with a relative risk of death of 0.88 (P = 0.03). Mortality at ICU discharge, hospital discharge, and day 180 were all statistically less in the steroid-treated group. Furthermore, the secondary outcomes of vasopressor-free, ventilator-free, and organ failure-free days were fewer in the treatment arm. Again, more hyperglycemia was noted with steroid administration, but there was no difference in infection, bleeding, or myopathy rates between the two groups.

COMPARISONS

With these trials demonstrating conflicting outcomes with differing interventions, how can providers make decisions regarding steroid treatment for sepsis? By comparing each study design and specific patient factors within each study, some conclusions can be drawn. (*See Table 1.*)

In terms of study design, the most important differences were in the intervention arms. Those studies that demonstrated mortality benefits included both hydrocortisone and fludrocortisone. It might be that both medications are required for benefit. However, the authors of the 2010 COIITS study compared hydrocortisone to hydrocortisone plus fludrocortisone, which showed no difference in mortality, although this study did not include a placebo arm without steroid therapy and was not powered specifically to detect differences in mortality.[7]

The power of each study to evaluate mortality also differed. After the 2002 study generated excitement for steroid therapy, the CORTICUS study in 2008 failed to show an improvement in

Table 1. Comparison of Major Studies of Steroids for Sepsis

Study	Number of Patients	Intervention	Length of Treatment (Days)	Study Mortality	Change in Mortality	Power to Detect Change?
Annane et al[2]	299	Hydrocortisone and fludrocortisone boluses	7	28-day mortality of 58%	6%	Yes
CORTICUS[3]	499	Hydrocortisone bolus	11	28-day mortality of 33%	Not significant	No
HYPRESS[6]	353	Hydrocortisone infusion	11	28-day mortality of 8.5%	Not significant	No
ADRENAL[4]	3,713	Hydrocortisone infusion	Up to 7	90-day mortality of 28%	Not significant	Yes
APROCCHSS[5]	1,241	Hydrocortisone and fludrocortisone boluses	7	90-day mortality of 46%	6.1%	Yes

mortality. However, this study was underpowered to detect changes in mortality. Both 2018 studies were adequately powered for their primary outcomes, although both the overall mortality and number of patients enrolled in the ADRENAL study were lower than the figures used in the power calculation. An additional difference was the length of steroid treatment. Both positive studies used steroids for seven days, then stopped. ADRENAL specified treatment up to seven days, while the other negative trials tapered steroids up to 11 days. It is possible that the adverse effects of steroid treatments increasingly outweighed the benefits with longer treatments. Patient factors also differed considerably between these studies. Studies with positive results demonstrated higher overall mortality. (*See Table 1.*) This is a result of differing inclusion criteria. The inclusion criteria in the two positive studies specified significant organ dysfunction with few exclusion criteria.

CORTICUS included patients with organ dysfunction, but excluded patients with poor prognosis, immunosuppression, or life expectancy of < 24 hours, not an uncommon occurrence with severe sepsis. HYPRESS specifically excluded patients with septic shock and demonstrated the lowest overall mortality of the studies. ADRENAL included SIRS criteria, but did not specify organ dysfunction, and excluded patients who were expected to die within 90 days from comorbidities. Also notable was the much higher proportion of patients with pulmonary infections in the positive studies.

While in ADRENAL, 33.8% and 36.5% of the steroid and placebo groups, respectively, had pulmonary infections; in the APROCCHSS study, 58% and 60.7%, respectively, had pulmonary infections. This is notable, as a growing body of literature suggests steroid therapy can alter the outcomes of severe pneumonia.[8]

What the outcomes of each study had in common also are informative. The 2002 Annane et al study demonstrated that steroids led to a decreased time to vasopressor therapy withdrawal in both non-responders and all patients. CORTICUS reported a decreased time to reversal of shock for all patients as well as decreased time on mechanical ventilation. ADRENAL demonstrated that hydrocortisone administration was associated with decreased median time to shock reversal, ICU length of stay, and median time on mechanical ventilation. APROCCHSS demonstrated statistically significant improvements in vasopressor-free days and organ failure-free days, with a nonsignificant trend toward increased ventilator-free days. Except for the original Annane et al study, all reported hyperglycemia as an adverse effect of steroid treatment.

However, the COIITSS study did not demonstrate that intensive control of hyperglycemia with insulin in steroid-treated patients improved outcomes, raising the question of the clinical significance of transient hyperglycemia in this population.[7]

CONCLUSION

Much uncertainty remains regarding the benefits of steroid therapy for sepsis. Furthermore, it seems unlikely that additional, well-powered studies will be undertaken to address the questions of patient selection, treatment intervention, duration of therapy, or infusions vs. bolus therapy.[9] Current studies seem to indicate potential benefits for patients with

higher levels of sepsis severity, especially in those presenting with pneumonia as the causative factor. As the only positive trials included fludrocortisone, the best evidence would be to use both intravenous hydrocortisone and enteral fludrocortisone if treating severe sepsis with steroids. There seems to be some agreement that steroid therapy in sepsis leads to shorter time to vasopressor withdrawal and the duration of need for mechanical ventilation. Predicting which patients will require longer duration of vasopressors and mechanical ventilation is difficult. Ultimately, in those patients presenting with severe sepsis with rising vasopressor needs who no longer appear to be fluid responsive, the addition of hydrocortisone and fludrocortisone may improve outcomes. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Worse Than Snake Oil

SOURCE: Bottichio L, Webb LM, Leos G, et al. Notes from the field: *Salmonella oranienburg* infection linked to consumption of rattlesnake pills — Kansas and Texas, 2017. *MMWR Morb Mortal Wkly Rep* 2018;67:502-503.

Of all *Salmonella* serotypes, *Salmonella oranienburg* is an unusual cause of clinical illness. Occasional infections and small outbreaks have occurred worldwide, and a recent 2016 CDC posting attributed a small outbreak of *S. oranienburg* in three states involving eight individuals to shell eggs from Missouri. National *Salmonella* surveillance data, last published for 2016, indicate that 1.5% of 32,271 clinical *Salmonella* isolates reported from humans were due to *S. oranienburg*. Parallel 2016 data from the National Veterinary Services Laboratory described 5,258 clinical isolates from animals, including reptiles, with none ascribed to *S. oranienburg*.

A bottle of rattlesnake pills seized by the Texas Department of State Health Services during an investigation of *Salmonella* infection yielded *S. oranienburg*. The isolate was forwarded to PulseNet, the national molecular subtyping network, which identified multiple similar isolates by pulsed-field gel electrophoresis (PFGE). These cases included a man in Kansas with a recent *S. oranienburg* infection. During his initial interview, which included various questions about vitamins and supplements, the individual did not report taking rattlesnake pills. On a subsequent interview, he admitted to purchasing such pills in Mexico and took five capsules in the week before getting sick.

Rattlesnake "pills" are basically dehydrated, ground up rattlesnake meat stuffed into gel caps. These may be sold locally in health food stores and are available on the internet, and have not been reviewed or approved by the FDA. A quick search found an advertisement for a bottle of 150 "capsulas vibora de cascabel" for acne for only $24, promising that snake pills "clean out your system and gets rid of built up toxins." Other ads target individuals with cancer and HIV, and soap products made from rattlesnake are purported to be useful for rashes and psoriasis.

In December 2017, the CDC issued a health alert warning that rattlesnake meat or pills may be a source for *Salmonella* infection. In addition to *S. oranienburg*, rattlesnake pills and meat have resulted in infection from *S. enterica spp. arizonae*.

Contact Tracing Using WHO Network

SOURCE: Pieracci EG, Stanek D, Koch D, et al. Notes from the field: Identification of tourists from Switzerland exposed to rabies virus while visiting the United States — January 2018. *MMWR Morb Mortal Wkly Rep* 2018;67:477-478.

A couple found a dead bat in a parking lot of a shopping mall, picked it up, and brought it

to a veterinary clinic in Naples, FL. The woman was described as in her 50s-60s and visiting from Switzerland. Five days later, the bat tested positive for rabies. During the next nine days, the Florida Department of Health, in conjunction with the CDC, tried to locate the couple, even issuing a press release asking the couple to contact health officials, all to no avail.

After weighing the potential seriousness of the situation and the need for timely intervention, the CDC contacted the World Health Organization's International Health Regulations (IHS) network, and was directed to the IHS national focal point identified in Switzerland. They, in turn, notified the Swiss government, which quickly issued a national press release for the couple on Jan. 25. Amazingly, the couple contacted the government within five hours. They confirmed that they had handled the bat using their bare hands but had not been bitten, and started the recommended prophylaxis.

The WHO IHS network has proven to be a useful tool in international rabies exposure investigation; since January 2017, the CDC Poxvirus and Rabies Branch has accessed the WHO IHS network for potential rabies exposure to help locate 12 different people. Fortunately, the Swiss are so organized, they communicated an effective message to the public within hours.

Preparing Your Hospital for *Candida auris*

SOURCE: ProMED-mail post. Candida Auris — Europe: 2013-2017. April 25, 2018. Available at: www.promedmail.org. Accessed July 12, 2018.

While everyone is worrying about multidrug-resistant bacteria, it's a plain old yeast that may upend things. *Candida auris* is a non-albicans *Candida* species that is broadly resistant to antifungal therapy, can easily establish itself in the environment, and, as a skin colonizer, has a high potential for nosocomial transmission and outbreak. In the United States, index cases of *C. auris* most often are the result of the inadvertent introduction into the hospital environment from a patient who has received healthcare outside the United States, with dangerous consequences. Estimates of mortality from invasive infection vary from 28% to as high as 50%, and delays in recognition of *C. auris* infection may increase the risk of death.

As of May 2018, 311 clinical cases of *C. auris* infection have been reported in the United States, the majority of which have occurred in New York (59%), New Jersey (23%), and Illinois (12%). A local San Francisco Bay Area hospital has the distinction of being the first acute care facility west of the Rockies with a case of *C. auris* in August 2017. This remains the first and only case in California to date. Notably, the patient had been hospitalized recently in India, and within weeks of entry to the United States, was hospitalized at our facility and found to have clinical infection with New Delhi metallo-beta-lactamase (NDM)-containing *Escherichia coli*. The patient was hospitalized multiple times, both at our facility and the other hospital, where, two months later, *C. auris* was identified in urine. The patient undoubtedly had been colonized with *C. auris*, presumably on entry to the United States. Subsequently, our microbiology lab was required to perform a retrospective analysis of every clinical and non-clinical, non-albicans isolate over the past year.

Meanwhile, in Europe, from 2013 to 2017, a total of 620 *C. auris* cases were reported in six of 29 European Union/European Economic Area countries. Most of these occurred in Spain (63%) and the United Kingdom (36%), while isolated cases have occurred in Germany, France, and Belgium. Austria just reported its first case in January 2018. Most of these resulted in colonization (75%), but bloodstream and other invasive infections were reported in 150 cases (24%). Two countries have been mired in four different outbreaks, one of which lasted two years, and another is ongoing.

This report summarizes what hospitals must consider to prepare for this emerging infection:

- Microbiology labs should develop protocols for accurately identifying all non-albicans *Candida* isolates, even for isolates causing simple colonization; this is a big step up for microbiology labs, which may disregard small amounts of yeast in many clinical samples, such as stool and skin swabs. This will require much more labor and expense. Such isolates require identification based on molecular means. If this is not possible at your facility, then all clinical non-albicans *Candida* isolates must be forwarded to a reference lab.
- Clinical isolates of *Candida* resistant to fluconazole similarly should prompt further study.
- Measures should be put in place to identify patients admitted or transferred from other facilities with a recognized case (and, based on our experience, perhaps this should include patients with NDM and other CRE from India).
- Prompt notification of suspect isolates to infection control teams is essential.
- Infection control teams need to develop specific policies for managing *C. auris* cases. As of February 2018, the CDC still recommends the use of contact precautions. This report suggests that hospitals consider implementing enhanced control measures, including single rooms with dedicated nursing staff and equipment.

- These policies should include cleaning procedures, with an emphasis on daily cleaning and terminal cleaning and disinfection of rooms, and especially equipment, using chlorine-based disinfectants, hydrogen-peroxide, or other disinfectants with antifungal activity following discharge.
- A single case should prompt review and screening of close contacts (i.e., axillary and groin cultures, as well as appropriate cultures of clinical sites, such as urinary catheters, tracheostomy sites, open wounds, and other tubing sites).
- More extensive contact tracing should be considered on a case-by-case basis.
- Environmental sampling/surveillance is not recommended presently. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. Which of the following is true regarding scrub typhus?

a. It is caused by *Rickettsia orientia*.

b. It is a rare cause of acute encephalitis in Asia.

c. It is a benign, self-limited illness in children.

d. It is treatable safely with doxycycline, even in children.

2. Which of the following is *not* a cause of relapsing fever?

a. *Candidatus Borrelia johnsonii*

b. *Borrelia mayonii*

c. *Borrelia hermsii*

d. *Borrelia miyamotoi*

3. Which of the following is correct?

a. Detection of nasal MRSA has a positive predictive value > 90% for the diagnosis of MRSA pneumonia.

b. Detection of a nasal MRSA has a sensitivity > 95% for the diagnosis of MRSA pneumonia.

c. Failure to detect nasal MRSA has a negative predictive value > 95% for the diagnosis of MRSA pneumonia.

d. Failure to detect a nasal MRSA has no value in excluding the diagnosis of MRSA pneumonia.

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.