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Infectious Disease [ALERT]

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ABSTRACT & COMMENTARY

Oral Antibiotics Are Noninferior to Intravenous for Bone and Joint Infections

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

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

SYNOPSIS: In a randomized, controlled trial of adult patients with bone or joint infections, researchers found oral antibiotic therapy was noninferior to intravenous therapy based on treatment failure at one year.

SOURCE: Li HK, Rombach I, Zambellas R, et al. Oral versus intravenous antibiotics for bone and joint infection. *N Engl J Med* 2019;380:425-436.

The standard management of bone and joint infections for more than 40 years has been surgical debridement followed by a prolonged (i.e., four to six weeks) course of intravenous (IV) antibiotics. However, this paradigm has become increasingly questioned because of recent evidence showing similar efficacy between oral and IV therapy. Li and colleagues sought to clarify outcomes at one year between IV and oral antibiotics administered during the initial six weeks of treatment for bone and joint infections.

The Oral Versus Intravenous Antibiotics for Bone and Joint Infections (OVIVA) trial was conducted at 26 sites in the United Kingdom. Patients 18 years of age and older were enrolled if they had one of the following conditions: native osteomyelitis of the extra-axial skeleton, native joint infection requiring excision arthroplasty, prosthetic joint infection (PJI), orthopedic fixation device infection, or vertebral osteomyelitis with or without associated discitis or soft-tissue infection. The patients were randomized 1:1 within seven days of surgery or the start of antibiotics to either six weeks of IV or oral

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therapy. The choice of antibiotics was left to the judgment of the infectious disease physician, and adjunctive oral therapy (e.g., rifampin) was permitted for patients in the IV group. Therapy beyond six weeks was permitted for both groups.

The primary endpoint was treatment failure within one year, which was defined as the presence of at least one clinical criterion (draining sinus tract from the bone or prosthesis or the appearance of frank pus adjacent to the bone or prosthesis), microbiological criterion (phenotypically indistinguishable bacteria isolated from two or more deep-tissue samples or a pathogenic organism from a single aspirate or biopsy), or histologic criterion (the presence of characteristic inflammatory infiltrates or microorganisms). Secondary endpoints included probable or possible treatment failure, early discontinuation of the treatment strategy, IV catheter complications, *Clostridioides difficile* infection, serious adverse events, resource use, health status, the Oxford hip and knee scores, and adherence to treatment.

The modified intention-to-treat (ITT) analysis included 1,015 patients, of whom 639 (61%) had hardware-related infection and 80 (7.6%) were treated without surgical intervention. The identified pathogens were *Staphylococcus aureus* (38%), coagulase-negative *Staphylococcus* (27%), *Streptococcus* species (15%), *Pseudomonas* (5%), Gram-negatives besides *Pseudomonas* (16%), and culture negative (16%). Ten percent of the patients had methicillin-resistant *S. aureus* (MRSA). The most commonly prescribed IV antibiotics were glycopeptides (41%) and cephalosporins (33%), while quinolones (44%) and combination therapy excluding rifampin (14%) were the most common oral agents.

Therapy was continued past six weeks for 805 of 1,049 participants (76.7%). The median total duration of therapy was 78 days (interquartile range, 42 to 99 days) in the IV group and 71 days (interquartile range, 43 to 94 days) in the oral group ($P = 0.63$). Treatment failure based on clinical, microbiological, or histological criteria occurred in 74 of 506 (14.6%) in the IV group and 67 of 509 (13.2%) in the oral group. Furthermore, the ITT analysis showed a difference in the risk of definitive treatment failure between the oral group and the IV group of -1.4 percentage points (90% confidence interval [CI], -4.9 to 2.2; 95% CI, -5.6 to 2.9), which indicated noninferiority. A post-hoc subgroup analysis did not reveal any advantages of IV therapy over oral therapy.

For the secondary endpoints, there were no significant differences between oral and IV therapy in terms of *C. difficile* infection rates or the percentage of patients reporting at least one serious adverse event. More patients discontinued therapy earlier in the IV group than in the oral group (18.9% vs. 12.8%, respectively; $P = 0.006$). Not surprisingly, catheter complications were more common in the IV group (9%) than in the oral group (1%), with the latter reflecting the fact that 10% of those in the oral group received IV therapy at any time during the study. The median hospital stay was significantly greater in the IV group (14 days [interquartile range, 11 to 21]) compared to the oral group (11 days [interquartile range, 8 to 20], $P < 0.001$). There was no significant difference between the groups in Oxford hip scores, but better Oxford knee scores were observed in the oral group compared to the IV group at days 120 and 365 ($P = 0.01$ and $P = 0.04$, respectively). Finally, the use of rifampin did not lead to a significant difference in outcomes ($P = 0.22$).

■ COMMENTARY

The results of the study by Li and colleagues challenge the practice of administering six weeks of IV antibiotics to treat bone and joint infections, which is widely accepted as the standard of care. Although this is not the first study to show the effectiveness of oral antibiotics for these indications, it was well designed and directly compared the two regimens in the same settings and in the same patient population. Indeed, not only was oral therapy noninferior to IV therapy, it also was associated with shorter hospital stays and fewer complications, although the latter was

due mostly to adverse events related to catheters. These findings likely will shift the treatment paradigm for orthopedic infections away from prolonged IV therapy.

Another interesting finding was the lack of benefit found from adding rifampin, which many experts view as an important adjunctive agent when treating biofilm. One explanation might be related to the timing, such that in many cases, rifampin was not used during the entire course of therapy.

The study had some limitations. First, there were few cases of MRSA, a highly virulent organism that often does not respond as well as other pathogens in orthopedic infections. Thus, oral antibiotics might be riskier for MRSA, and IV antibiotics (e.g., vancomycin, daptomycin, or ceftaroline) likely should continue to be the recommended therapy. Second, the treatment regimens were heterogeneous, as were the surgical interventions, which does not allow for comparisons of one treatment to another. Finally, the open-label design may have introduced selection bias, although it would have been unethical to give IV placebo.

Has the time come for the use of oral antibiotics to treat bone and joint infections? The answer is probably yes, with some exceptions, such as patients with poor gastrointestinal absorption or those with antibiotic-resistant pathogens, like MRSA. Questions remain about optimal therapy regimens and surgical management. It also seems prudent to recommend close outpatient monitoring with oral therapy and a switch to IV therapy if clinical improvement is suboptimal. ■

ABSTRACT & COMMENTARY

Viruses, Food Allergies, and Childhood Wheezing

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: Infants with severe bronchiolitis sometimes develop subsequent recurrent wheeze and asthma. Among infants hospitalized with bronchiolitis, the risk of developing asthma is greatest in those with rhinovirus C infection, especially if they also are sensitized with IgE against foods.

SOURCE: Hasegawa K, Mansbach JM, Bochkov YA, et al. Association of rhinovirus C bronchiolitis and immunoglobulin E sensitization during infancy with development of recurrent wheeze. *JAMA Pediatr* 2019; April 1. doi:10.1001/jamapediatrics.2019.0384. [Epub ahead of print].

Bronchiolitis accounts for 130,000 hospitalizations each year in the United States. Approximately one-third of infants sick enough to be hospitalized with bronchiolitis go on to develop recurrent episodes of wheezing and asthma. After respiratory syncytial virus, rhinovirus is the next most common cause of bronchiolitis.

A study of children in Australia revealed that those with atopic dermatitis who became ill with bronchiolitis C were more likely than other children to have further episodes of respiratory illness with wheezing.

With that background, Hasegawa and colleagues at 17 United States medical centers evaluated 716 children hospitalized during the first year of life with bronchiolitis to see if the risk of subsequent wheezing illness depended on the specific viral etiology of the initial bout of illness. They also performed immunoglobulin E (IgE) tests during the initial admission to determine if pre-illness allergic sensitization (to food and/or aeroallergens) altered the risk of subsequent asthma. The study covered three bronchiolitis seasons (November 2011 to April 2014).

The median age of study subjects was 2.9 months. Seventy-six percent of patients had respiratory syncytial virus bronchiolitis; the others had rhinovirus A (12%), B (2%), or C (11%). Overall, 32% developed recurrent wheeze by 3 years of age. Rhinovirus C-infected infants had a 1.58-fold higher risk of developing recurrent wheeze. Those with rhinovirus C who also had IgE sensitization at the time of their initial hospitalization were

at greatest risk (3.03-fold risk) of developing recurrent wheeze.

■ COMMENTARY

Several key lessons emerge from this study. Rhinovirus is not merely a cause of runny nose and "colds." After respiratory syncytial virus, rhinovirus is the second most common cause of bronchiolitis, a common infection that accounts for the more than 100,000 infant hospitalizations in the United States each year. In addition, not all rhinoviruses are equal. The rhinovirus family includes viruses with 170 different genotypes, and these viruses are classified into three species, grouped as A, B, and C. Rhinovirus C, identified in 2006, now is known to be the rhinovirus most responsible for severe infant illness and is linked the most to the development of subsequent respiratory difficulties.

The development of recurrent wheeze is multifactorial. Many of us have long believed that some of the children who get sick enough with bronchiolitis to be hospitalized are more genetically predisposed to develop subsequent wheeze and asthma compared to those children who do not require hospitalization. Approximately one-third of subjects in this study had a parent with asthma, thus suggesting a genetic risk for the child to develop asthma as well. However, beyond host-specific genetic risks, this study informs us that the development of childhood asthma also relates to infant infection (with rhinovirus C being more dangerous than rhinovirus A, rhinovirus B, or respiratory syncytial virus) and concurrent infantile hypersensitivity to food. Personal genetics, specific viruses, and food sensitization combine to increase the risk of a young child developing recurrent wheeze and asthma.

Previous efforts to vaccinate children for respiratory syncytial virus caused vaccine recipients to mount more aggressive immune responses to subsequent infection and, thus, to become more ill than non-vaccinated individuals. To date, no good active immunization exists for respiratory syncytial virus or rhinovirus. Of course, high-risk children such as babies born very prematurely and those with chronic cardiopulmonary disease (who were not included in the current study) can benefit from passive respiratory syncytial virus infection. ■

ABSTRACT & COMMENTARY

When to Screen for and Treat Asymptomatic Bacteriuria

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: New guideline recommendations indicate that the only unequivocal indications for screening and treatment of asymptomatic bacteriuria are pregnancy and undergoing endoscopic urologic procedures associated with mucosal injury.

SOURCE: Nicolle LE, Gupta K, Bradley SF, et al. Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2019; March 21. doi: 10.1093/cid/ciy1121. [Epub ahead of print].

The Infectious Diseases Society of America has published their recommendations, which are few in number, regarding the indications for screening and treatment of asymptomatic bacteriuria.

Groups to screen and treat are:

- Pregnant patients;
- Patients undergoing endoscopic urologic procedures with associated mucosal trauma; target antimicrobial therapy with administration of only one to two doses with initiation 30 to 60 minutes prior to the procedure.

Groups for whom screening and treating asymptomatic bacteriuria is NOT recommended include:

- Infants and children;
- Healthy pre- and postmenopausal nonpregnant women;
- Functionally impaired older women and men residing in the community or long-term care facilities;
- Diabetic individuals;
- Patients who received renal transplants more than one month previously;
- Recipients of non-renal solid organ transplants;
- Patients with impaired voiding resulting from spinal cord injury (taking into account that symptoms may

be atypical, such as due to autonomic dysfunction);
• Patients with short- or long-term bladder catheterization;
• Patients undergoing non-urologic surgery;
• Patients undergoing placement of an artificial urinary sphincter or penile implant or living with such a device; patients undergoing this surgery should receive standard operative antibiotic prophylaxis.

The guideline authors were unable to provide a recommendation for the following because of inadequate evidence:
• Patients with high-risk neutropenia (absolute neutrophil count < 100 cells/mm^3 with anticipated duration ≥ 7 days);
• Patients undergoing removal of a bladder catheter.

Older patients with functional and/or cognitive impairment with or without a fall who have known bacteriuria but without local urinary symptoms or systemic signs of infection but with acute mental status change should undergo evaluation for other causes of their symptoms rather than antibiotic administration. For those with sepsis syndrome and no localizing source, broad-spectrum antimicrobial therapy directed at both urinary and non-urinary pathogens is indicated.

■ COMMENTARY

The prevalence of asymptomatic bacteriuria is approximately 1% in school-age girls, almost 5% in sexually active premenopausal women (in whom it is often transient) and in pregnancy, and > 20% in community-dwelling women > 80 years of age. It is rarely present in healthy males, but occurs at elevated frequency in elderly community-dwelling men.

In general, antibiotic treatment of asymptomatic bacteriuria is contraindicated because the personal and societal risks of this approach are real and the benefit is nonexistent. A recent study of 68,265 veterans concluded that "receipt of antimicrobial therapy with activity against asymptomatic bacteria organisms identified in preoperative cultures was not associated with reductions in the risk for postoperative infections, including urinary tract infections and surgical site infections."[1] In a 2018 systematic review and meta-analysis, the authors found no benefit from screening and treatment of asymptomatic bacteriuria in patients undergoing joint arthroplasty.[2]

Prevention of inappropriate screening and treatment of asymptomatic bacteriuria is an important antimicrobial stewardship activity and, frequently, a frustrating one. Adherence to this guideline will be associated with decreased occurrence of adverse reactions to unnecessarily administered antibiotics, the decreased occurrence of *Clostridioides difficile* infection, and reduced selective pressure that leads to antimicrobial resistance. However, altering clinician behavior in this domain often is difficult and frustrating — but increasingly important. ■

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ABSTRACT & COMMENTARY

Corticosteroid Administration in Sepsis May Be Associated With Lower 28-Day Mortality

By Drayton A. Hammond, PharmD, MBA, BCPS, BCCCP

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

SYNOPSIS: In this systematic review and meta-analysis of randomized, controlled trials comparing administration of corticosteroids with placebo or standard supportive care in sepsis, corticosteroids were associated with reduced 28-day mortality.

SOURCE: Fang F, Zhang Y, Tang J, et al. Association of corticosteroid treatment with outcomes in adult patients with sepsis: A systematic review and meta-analysis. *JAMA Intern Med* 2019;179:213-223.

The current Surviving Sepsis Campaign guidelines provide a weak recommendation based on low-quality evidence against the routine use of IV hydrocortisone in patients with septic shock if adequate fluid resuscitation and vasopressor therapy can restore hemodynamic stability.[1] However, the guidelines suggest its use if hemodynamic stability cannot be restored. No recommendation is provided for or against its use in sepsis without shock. Because of the low-quality evidence and potential benefits alongside minimal adverse effects, two randomized, controlled trials (RCTs) with the largest sample sizes to date were conducted.[2,3] Fang and colleagues sought to critically evaluate all relevant literature for corticosteroids in sepsis to better inform contemporary practice. Their study was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols study (PRISMA-P) and registered a priori in the PROSPERO database.[4] They hypothesized that relevant clinical outcomes would differ between those who did or did not receive corticosteroids and could be affected by other factors, including corticosteroid dose, year of publication, illness severity, and quality of evidence. Articles indexed in Medline, Embase, and/or the Cochrane Central Register of Controlled Trials by March 20, 2018, were considered for inclusion, resulting in 37 RCTs that included 9,564 patients. Random effect models were used for all outcomes, although fixed effect models were evaluated as a sensitivity analysis. Corticosteroids were found to reduce the risk of the primary outcome of 28-day mortality compared to placebo or standard supportive care (26.3% vs. 29.2%; risk ratio [RR], 0.90; 95% confidence interval [CI], 0.82-0.98; I^2 = 27%) in the full analysis. Similar results were observed when relevant sensitivity analyses were performed, such as excluding studies published earlier than 2000, those reporting only ICU or in-hospital mortality, those with a non-low risk of bias, and those with fewer than 200 patients. Although a funnel plot analysis suggested some asymmetry between positive and negative trials and sample sizes, a trial sequential analysis confirmed the required information size was met to make confident statements regarding 28-day mortality. Lower doses (< 400 mg hydrocortisone/day) and longer course (≥ 4 days) of corticosteroids demonstrated mortality benefit at 28 days (RR, 0.82; 95% CI, 0.85-0.98 and RR, 0.92; 95% CI, 0.85-0.98, respectively). Additionally, patients with septic shock (RR, 0.91; 95% CI, 0.82-1.02) may show reduced 28-day mortality rates, but those with sepsis do not (RR, 0.89; 95% CI, 0.61-1.31). Secondary outcomes for which corticosteroids were favored included ICU and in-hospital mortality (RR, 0.85; 95% CI, 0.77-0.94; I^2 = 0% and RR, 0.88; 95% CI, 0.79-0.99; I^2 = 38%, respectively), time to resolution of shock (mean difference [MD], -1.35 days; 95% CI, -1.78 to -0.91 days), vasopressor-free days (MD, 1.95 days; 95% CI, 0.80-3.11 days), shock reversal at day 7 (MD, 1.95 days; 95% CI, 0.80-3.11 days), and ICU length of stay (MD, -1.16 days; 95% CI, -2.12 to -0.20 days). Outcomes were similar between groups for 90-day mortality (RR, 0.94; 95% CI, 0.85-1.03; I^2 = 27%). Corticosteroids were associated with higher incidences of hyperglycemia (RR, 1.19; 95% CI, 1.08-1.30) and hypernatremia (RR, 1.57; 95% CI, 1.24-1.99).

■ COMMENTARY

Despite the use of corticosteroids in sepsis for more than 50 years, clinical equipoise has persisted because studies evaluating corticosteroids have been of inadequate sample size and design to confidently and precisely make statements of benefit and harm. Supportive care for sepsis has become protocolized and evolved to reduce the clinical impact of most individual interventions. Nevertheless, two well-designed trials[2,3] were conducted recently. The authors of a meta-analysis have incorporated the outcomes from those trials into their results.[5]

The trials with the greatest weight in this and another meta-analysis were the Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock trial (ADRENAL) and Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial.[3,4] In the ADRENAL trial, 3,713 patients with septic shock who were mechanically ventilated were randomized to hydrocortisone or placebo.[2] Those who received hydrocortisone experienced multiple benefits, including faster resolution of shock and shorter duration of the initial episode of mechanical ventilation, but exhibited similar 90-day all-cause mortality and adverse effect profiles. A subgroup analysis of patients randomized to an intervention within six to 12 hours of shock onset suggested those randomized to hydrocortisone were at lower risk for 90-day mortality. In the APROCCHSS trial, 1,241 patients with septic shock who had a similar or greater degree of critical illness as those in the ADRENAL trial initially were randomized to one of four groups: drotrecogin alfa or placebo paired with hydrocortisone and fludrocortisone or placebo.[4] The investigators paused their work when drotrecogin alfa was removed from the market; later, investigators continued their work with two arms: hydrocortisone and fludrocortisone or placebo. The trial sponsor terminated the study after 97% of the expected sample size had been achieved because the trial agents expired. Nevertheless, 90-day all-cause mortality was lower in the corticosteroid

arm. Adverse events were grossly similar between groups, except hyperglycemia (defined as at least one episode of blood glucose ≥ 150 mg/dL), and occurred more frequently in the steroid arm. While both trials had their limitations, their overall strengths were plentiful. Including these trials in an updated meta-analysis was both logical and needed.

The meta-analysis by Fang et al suggests particular nuances to providing corticosteroids in sepsis that may help guide clinicians' decisions. Providing hydrocortisone at lower doses (< 400 mg/day, most commonly provided as 200 mg/day in bolus or continuous infusion dosing) and for longer durations (four or more days) appears most beneficial. Additionally, patients with septic shock may benefit most from their use. Notably, the authors only considered one long-term mortality endpoint, 90-day mortality, which was similar between the groups. However, another contemporary meta-analysis considered mortality between 60 days and one year as long-term mortality, which was subjective but defensible, and revealed a lower relative risk of mortality with corticosteroids (relative risk, 0.94; 95% CI, 0.89-1.0).[5] This may be the endpoint of greatest importance for evaluating the efficacy of a therapy in sepsis and warrants further consideration. The authors also evaluated serious adverse effects and found a greater relative risk for hyperglycemia and hypernatremia with corticosteroids; however, the definitions for these effects varied widely between studies. Regardless of their rates of occurrence, these adverse effects are relatively benign and controllable in most critically ill patients. Overall, corticosteroid use in septic shock appears reasonable and potentially advantageous. ■

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ABSTRACT & COMMENTARY

Staphylococcus aureus Bloodstream Infections in the United States

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: Although the rate of hospital-onset MRSA bacteremia has decreased since 2012, the rate of decrease has slowed. The National Action Plan goal of a 50% reduction by 2012 compared to 2015 seems out of reach.

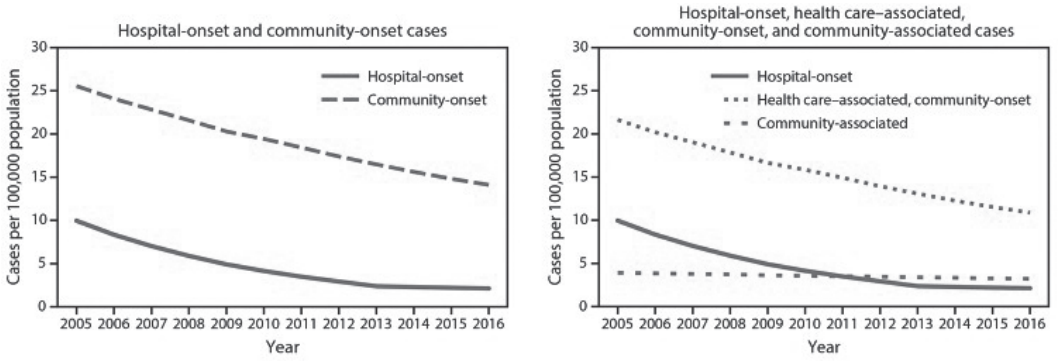
SOURCE: Kourtis AP, Hatfield K, Baggs J, et al; Emerging Infections Program MRSA author group. Vital Signs: Epidemiology and recent trends in methicillin-resistant and in methicillin-susceptible *Staphylococcus aureus* bloodstream infections — United States. *MMWR Morb Mortal Wkly Rep* 2019;68:214-219.

Staphylococcus aureus, both methicillin-susceptible (MSSA) and resistant (MRSA), are among the most important bacterial pathogens in the community and in healthcare facilities. The Centers for Disease Control and Prevention (CDC) has evaluated the epidemiological trends in bloodstream infections (BSI) caused by each of these pathogens from 2012 to 2017 in the United States. To accomplish this, they examined both the Emerging Infections Program (EIP) MRSA and the Premier and Cerner Electronic Health Record (EHR) databases. (*See Figures.*)

Based on EIP surveillance data, the incidence of hospital-onset MRSA BSI decreased by 74% from 2005 to 2016, while that of community-onset cases decreased by 40%. Although the rates of hospital-onset bacteremia decreased by 17.1% annually during that time, the rate of decline diminished beginning in 2013 such that the reduction was not statistically significant ($P = 0.25$). The annual rate of decline for community-onset MRSA bacteremia was 6.9%, with much of this decrease due to a reduced occurrence of healthcare-associated infections, which decreased by 7.8% annually.

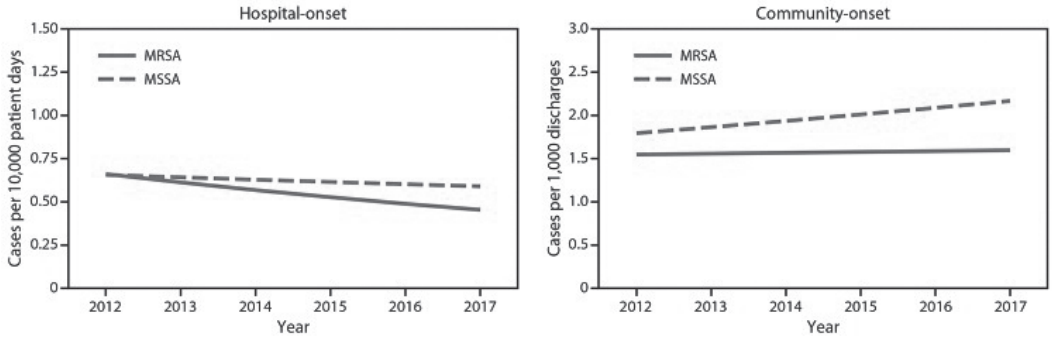
Based on EHR data from 447 hospitals, adjusted hospital-onset MRSA BSI decreased at a rate of 7.3% per year ($P < 0.0001$) with no significant change in community-onset MRSA BSI. At the

Figure 1: Adjusted Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infection Rates 2005-2016



Source: Centers for Disease Control and Prevention

Figure 2: Adjusted Hospital-Onset and Community-Onset Rates of *Staphylococcus aureus* Bloodstream Infection — Premier and Cerner Hospitals, United States, 2012-2017



Source: Centers for Disease Control and Prevention

same time, there was no significant change in hospital-onset MSSA rates, while community-onset MSSA BSI rates increased 3.9% annually ($P < 0.001$). The unadjusted overall in-hospital mortality rates for all *S. aureus* BSI was 18% and was higher for hospital-onset than community-onset cases.

The CDC estimated that 119,247 cases of *S. aureus* BSI occurred in the United States in 2017 and that there were 19,832 associated deaths.

■ COMMENTARY

One contribution of this analysis is that related to MSSA BSI — something for which national data largely has been missing. This report indicates that the rates of hospital-onset MSSA BSI have not changed significantly since 2012, while there may have been a slight increase in that of community-onset MSSA BSI — findings that contrast to those regarding MRSA BSI.

The U.S. National Action Plan to Prevent Health Care-Associated Infections calls for a 50% reduction in hospital-onset MRSA BSI in 2020 compared to the rate in 2015.[1] Despite the observed (albeit recently slowed) progress, this goal is unlikely to be achieved. The CDC stresses the need to continue effective infection control practices that have been implemented contemporaneously with the observed decrease in hospital-onset BSI infections — the chief of which, in my opinion, was the introduction of alcohol gels making handwashing more convenient.

One question that can be raised is that since many infection control practices, such as handwashing, central line bundles, and the like, are not organism-specific, why was there not a decrease in MSSA BSI? The CDC also suggests greater implementation of decolonizing activities, which are MRSA-specific, but which remain somewhat controversial. ■

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Multi-Modal Interventions for Controlling CRE: Which Is Best?

SOURCES: Tomczyk S, Zanichelli V, Grayson ML, et al. Control of carbapenem-resistant *Enterobacteriaceae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* in healthcare facilities: A systemic review and re-analysis of quasi-experimental studies. *Clin Infect Dis* 2019;68:873-884; Bleasdale SC. Do we need another study to control carbapenem-resistant organisms, or do we just need to get better at the basics? *Clin Infect Dis* 2019;68: 885-886.

No one doubts that the emergence of carbapenem-resistant Gram-negative organisms (CRO), specifically carbapenem-resistant *Enterobacteriaceae* (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), presents a serious threat to healthcare facilities, resulting in outbreaks and increased mortality. A United Kingdom Review on Antimicrobial Resistance published in May 2015 estimated that 10 million people will die annually by the year 2050 because of antimicrobial resistance and ineffective antimicrobials. Some of this resistance has the potential for widespread transmission based on the presence of mobile plasmids, which can readily jump strains of bacteria, while others persist in the environment and successfully resist ordinary cleaning measures.

[Infection prevention strategies aimed at reducing infection do not readily lend themselves to randomization.]

Hospitals are under siege as patients unwittingly carry these organisms with them into the hospital. The trick is, who are these people and what do we do about it before transmission or an outbreak actually occurs?

Both the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) have urged measures to stop the spread of carbapenem-resistant organisms within healthcare facilities, although clear guidelines, based on rigorous research, are lacking about how to best accomplish this task. For one reason, infection prevention (IP) strategies aimed at reducing infection do not readily lend themselves to randomization, and even the largest hospitals would not be able to produce a clinical trial with sufficient statistical power. Tomczyk and colleagues performed a systematic analysis of published articles and abstracts on carbapenem-resistance IP measures, yielding 76 articles with meaningful data, most of which were performed in the United States and Europe (46 concerning CRE, 26 on CRAB, and 13 on CRPA). Seventeen of these studies were non-randomized before-and-after or interrupted time series studies, providing an opportunity to assess the effect of bundled IP interventions on outcomes. The most common outcome in these studies was the incidence of infection. Hardly a meta-analysis, the interventions were too varying and the data were "of low or very low quality." The authors termed their effort a "quasi-analysis."

Most of these studies combined three or more IP interventions in a "multi-modal strategy," including 10 (91%) CRE studies, four (80%) CRAB studies, and three (100%) CRPA studies. Interventions included contact precautions (variously defined, but at a minimum including gowns and gloves) in 90%, active surveillance (80%), monitoring, audit and feedback (80%), isolation of patients in private rooms (or cohorting; 70%), hand hygiene (50%), and environmental measures (40%). Active surveillance strategies varied but included culture of feces or rectal swabs from all patients (e.g., ICU) or high-risk patients (e.g., those with previous colonization or infection), either on admission or at various intervals. Hand hygiene may have been included as a stated intervention in only half of the studies since it was considered a baseline or standard of care measure and not explicitly an intervention. Contact precautions in some studies were described as "strict" or "enhanced."

All of these IP measures were observed to reduce the incidence of outcomes significantly over time. The most effective strategy reported at several facilities appeared to be a combination of active surveillance, pre-emptive contact precautions with isolation pending those results, contact isolation measures, and

healthcare worker education with renewed focus on hand hygiene. Another successful study combined an even broader range of interventions, including active surveillance of at-risk patients, pre-emptive isolation for all patients, patient and staff cohorting, chlorhexidine bathing, limiting public access to rooms and common areas, terminal cleaning, audit and feedback on hand hygiene, contact isolation, environmental cleaning, and antibiotic stewardship. (Our facility does all of this.) Even with this extensive effort, the effect was perhaps a 50% reduction in outcome. Other less commonly used interventions included chart flagging, alerts, temporary ward closure, task force meetings, and analysis of workflow to examine how equipment is passed from patient to staff to patient.

The intervention with the strongest supportive evidence appeared to be active surveillance for CRE, although surveillance strategies varied between studies, the types of cultures performed varied, and the targeted populations differed. At-risk patients were defined most often as those with a history of an overnight stay in a healthcare setting in the past 12 months; dialysis dependence; receipt of cancer chemotherapy; known previous infection or colonization in the previous 12 months; or linkage to another recognized CRE case. In addition, patients presenting from long-term care or with long-term mechanical ventilation were targeted by some as high risk. Studies that favored active surveillance also often pre-emptively isolated high-risk patients pending the results. (Our facility does this.)

Only three (30%) of the CRE studies, three (60%) of the CRAB studies, and two (70%) of the CRPA studies included environmental cleaning measures in their interventions. Again, various strategies were employed, but as part of a bundle of interventions, they appeared to reduce the incidence of outcomes over time.

Although bundled interventions uniformly had some beneficial effect on reducing outcomes, the contribution of any particular intervention remains cloudy. An interesting question remains whether a combined approach is truly necessary to achieve a beneficial outcome, or whether performing one good intervention really well 100% of the time is sufficient. Although the latter approach may have appeal, it is my opinion (having worked in this area for years) that a combined approach is necessary. How can you best isolate the highest risk patients but not perform some kind of surveillance? What good is isolation if your staff have lax hand hygiene, or if the bedrails, tray tables, and sinks are not well cleaned?

Perhaps our success with controlling hospital-onset *Clostridioides difficile* (HO-CD) infection can best illustrate this point. Once a facility with the highest HO-CD rate in California, our hospital implemented 10 years of successive IP interventions that have resulted in a clear step-wise reduction in our rate. These interventions began with a hand hygiene campaign in 2009-2010, an effort to strengthen contact precautions in 2012-2013, and then continued with active surveillance of high-risk individuals and pre-emptive isolation in 2013-2015. Gradually, our rate was cut by > 75%. But it was not until we implemented more aggressive daily and terminal

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cleaning measures, including UVC of all *C. diff*. and ICU rooms, in 2016 that we saw our rates drop by > 90%. More recently, we implemented a nurse-driven protocol for pre-emptive isolation and testing of patients with diarrhea. I hesitate to confess that this 10-year effort was not conducted with logic of forethought, but, as the editorialist suggested, more of a "hierarchy of hazard control" with step-wise implementation of interventions as they gained support in the literature and were driven by need. Using this combined approach, our HO-CD rates are the best in California.

Although everyone knows that something obviously needs to be done with CRO, it is not entirely clear what works best for hospitals. Our very own success story with CD is my best justification for a multi-modal approach for controlling CRO in our facility. ■

Antimicrobial Resistance Genes — in the Arctic

SOURCE: Antibiotic resistance — Norway: (Svalbard) NDM, high arctic region. ProMED-mail post. International Society for Infectious Diseases. Feb. 7, 2019. Available at: www.promedmail.org. Accessed April 8, 2019.

For a recent study, researchers combined sophisticated geochemistry and high throughput qPCR technique to examine the frequency of antimicrobial resistance genes (ARGs) and mobile genetic elements (plasmids) in the remote Kongsfjorden region of Svalbard, Norway.

Surprisingly, in this remote region, researchers found several ARGs, including the *blaNDM-1* gene, which was first detected in India in 2008. Soil samples from eight areas yielded detectable levels of ARGs much higher than chance would allow. The levels of ARGs ranged from 10 (-6) to 10 (-4) copies/16s rRNA gene copy, suggesting these bits of genetic material were not naturally occurring but had been introduced into the area. Soil clusters with higher levels of ARGs showed elevated secondary nutrients, whereas soil clusters with lower readings were more likely to be consistent with rock with low nutrient levels. These results led to the supposition that bird or other wildlife guano, or dissemination of human waste, somehow had resulted in the dissemination of these resistance genes to this northern outpost.

Svalbard is a cluster of islands in the Arctic Ocean, directly north of continental Norway and about 810 miles south of the North Pole. Remarkably, it is not barren of human life, but it sports a longstanding mining community, a local government, and a research station. A secure seed bank is sequestered there, buried in a local mountain. It is also apparently a tourist "end-destination" for those interested in dog sledding or glacier watching. How many people populate the area in a year, and how human waste is managed, is not clear from this article. I was curious to know how much CRO-colonized guano or human waste theoretically could result in this miniscule environmental finding. ■

Updated PEP Guidelines for Hepatitis A Vaccine

SOURCE: Nelson NP, Link-Gelles R, Hofmeister MG, et al. Update: Recommendations of the Advisory Committee on Immunization Practices for the use of hepatitis A vaccine for postexposure prophylaxis and for preexposure prophylaxis for international travel. *MMWR Morb Mortal Wkly Rep* 2018;67:1216-1220.

In November 2018, the Advisory Committee on Immunization Practices provided updated guidelines on the use of hepatitis A (HAV) vaccine and immune globulin (IG) for postexposure prophylaxis (PEP) and for pre-travel prophylaxis. Previous recommendations for PEP included HAV for those ≥ 12 months and ≤ 40 years of age, at which point, IG was to be administered to older adults > 40 years of age. Children < 12 months also received IG, since HAV has not been licensed for infants. However, the administration of IG for pre-travel prophylaxis often precludes the receipt of other necessary vaccines, such as measles, mumps, and rubella (MMR), which is increasingly necessary for travel abroad.

Updated recommendations include:
1) Postexposure prophylaxis with a single dose of HAV vaccine within two weeks of exposure for children and adults ≥ 12 months of age, including those older than 40 years of age;
2) In addition to HAV vaccine, individuals > 40 years of age also may receive IG depending on the provider's risk assessment of the exposure;
3) Children 6-11 months of age also may receive HAV vaccine for travel outside of the United States to areas of HAV risk; this travel dose does not count toward their later routine two-dose HAV vaccination;
4) For those adults and children 12 months of age or older who have not completed the usual two-dose HAV vaccine series, a second dose of HAV vaccine should be administered at least six months after the first dose to complete their vaccine series;
5) Adults and children 12 months of age or older with compromised immunity or chronic liver disease who have not completed the usual two-dose HAV vaccine series should receive both HAV vaccine and IG.

When administered within two weeks of exposure, the HAV vaccine's protection historically has approached that of IG in healthy adults and children. However, there are concerns that IG for HAV prophylaxis may be losing its efficacy, based on diminishing antibody titers. Therefore, a higher dose of IG (0.1 mL/kg) was recommended in 2017, which has been updated throughout these recommendations. IG should be administered in an area separate from HAV vaccine when given concurrently. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. In the United States, which of the following statements is true?

a. Bronchiolitis accounts for more than 1 million childhood hospitalizations each year.

b. Rhinoviruses cause more bronchiolitis than respiratory syncytial virus.

c. Infants hospitalized with bronchiolitis usually go on to develop asthma.

d. Serious rhinovirus C infection increases the risk of subsequently developing asthma.

2. Which of the following is correct regarding the results of the OVIVA trial by Li et al dealing with treatment of bone and joint infections?

a. The addition of rifampin to the treatment regimens was associated with a marked improvement in outcomes.

b. The median duration of hospitalization was four days longer in the group treated with orally administered antibiotics.

c. The risk of *Clostridioides difficile* infection was greater in those treated with oral rather than IV antibiotics.

d. Treatment with orally administered antibiotics was noninferior to treatment with IV antibiotics.

3. Based on the new Infectious Diseases Society of America guidelines, which of the following is an indication for screening for and treating asymptomatic bacteriuria?

a. Pregnancy

b. Presence of an indwelling bladder catheter

c. Diabetes mellitus

d. Any surgery

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.