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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Pediatric Pneumonia — Evolving Diagnosis and Management

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: Tachypnea has long been considered to identify which children with acute fever and cough might benefit from antibiotic treatment, especially in resource-limited parts of the world. Now, with declining rates of vaccine-preventable infections with *Haemophilus influenzae* and pneumococcus, new data suggest that approximately 90% of febrile, tachypneic, coughing (but still well enough for outpatient treatment) preschoolers do fine without antibiotics.

SOURCE: Ginsburg AS, Mvalo T, Nkwopara E, et al. Placebo vs amoxicillin for nonsevere fast-breathing pneumonia in Malawian children aged 2 to 59 months: A double-blind, randomized clinical noninferiority trial. *JAMA Pediatrics* 2019;173:21-28.

With nearly 1 million children around the world dying of pneumonia before reaching school age, it is important to identify which febrile coughing children would benefit from an antimicrobial agent. The World Health Organization's (WHO's) Integrated Management of Childhood Illness guidelines suggest using the presence of tachypnea to identify which children with acute respiratory infection might respond to antibiotic treatment. This strategy maximizes sensitivity to ensure that as few children as possible go untreated; of course, this strategy lacks specificity and might lead to overtreatment and worsened antimicrobial resistance.

Thus, Ginsburg and colleagues evaluated whether antibiotic treatment even helped generally healthy (no HIV) preschoolers with tachypnea and a respiratory illness but without retractions or poor oral intake. Investigators compared placebo to three days of oral amoxicillin (the current WHO-recommended treatment for nonsevere pneumonia)

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in 1,126 Malawian children. Children who developed worsened respiratory distress during or after treatment were considered to have failed treatment.

By day 4, 4% of amoxicillin-treated children had failed treatment; 7% of placebo-treated children failed (95% confidence interval [CI], 1.07-2.97). Of those who had not failed by day 4, 6.4% of amoxicillin-treated and 5.1% of placebo-treated patients failed treatment by day 14 (with the difference between groups not statistically significant). The number-needed-to-treat analysis suggested that 33 children would need to be treated to help the one who would fare better on antibiotics.

While fast-breathing children in Africa still can benefit statistically from antibiotics during respiratory illnesses, approximately 90% of children would do fine without an antibiotic. The authors pointed out that these data suggest that the African situation now more closely approximates the North American situation in which antibiotics generally are not recommended for community-acquired pneumonia if there are no signs of severe disease (i.e., poor feeding, retractions).

■ COMMENTARY

For years, pneumonia has been a frequent killer of children, especially in resource-limited areas of the world where not all children have access to physician care. Based on good evidence, the WHO has advocated for the use of tachypnea as a key discriminating factor to determine which children would benefit from antibiotic therapy.[1] With widespread implementation of WHO teaching, the death rate from pneumonia has dropped significantly, and fewer children receive unnecessary antibiotics.

In resource-rich areas of the world where viral lower respiratory tract infection is relatively more common than bacterial pneumonia, tachypnea has been less reliable in determining which children might benefit from antibiotic treatment.[2,3,4] With widespread immunization against *Haemophilus influenzae* and pneumococcus, the relative rates of bacterial pneumonia are declining in resource-limited areas, too. Ginsburg and colleagues wisely evaluated whether tachypnea is still a key discriminator to identify which children would benefit from antibiotic treatment.

Indeed, most children who had acute fever and cough with tachypnea without signs of more serious infection (that is, without poor feeding or retractions) were fine whether they received antibiotic treatment or not. This suggests that even in resource-limited areas where viral lower respiratory tract illnesses are relatively more common, tachypnea lacks good specificity for identifying children with bacterial pneumonia. However, there still were more treatment failures with placebo than with amoxicillin, so tachypnea should not be disregarded; rapid breathing still is a sign of risk for bacterial pneumonia even if it is not as specific as in past years.

How should we diagnose bacterial pneumonia? Wheezing and diffuse findings on auscultation can point toward a nonbacterial cause of illness. Leukocytosis might provide a clue but also lacks specificity. Even consolidation on chest radiographs is subject to subjective interpretation. Studies over the past two decades showed that blinded pediatric radiologists disagreed with themselves and with colleagues a significant amount of time about specific radiographic findings in children with lower respiratory tract infection.[5,6] Ultrasound offers some help for point-of-care use in identifying some pneumonias,[7,8] but there still is no fully adequate gold standard to determine which children with acute fever, cough, and tachypnea will benefit from antibiotics.[9]

Physicians caring for children with possible pneumonia still need to be judicious with their diagnosis and with treatment. Many children with bronchiolitis receive treatments (antibiotics, bronchodilators) that have been proven to lack effectiveness. Even in resource-rich areas of the world with readily available blood counts, antigen detection methods, and radiographs, doctors sometimes overtreat children with lower respiratory infection, and helpful

guidelines for the management of viral respiratory infections are available.[10] Thoughtful clinicians must carefully balance the benefits and risks of antibiotic treatment in each child.

At the same time, nearly 1 million children die of pneumonia each year, mostly in resource-limited areas of the world. Children who are more severely ill, as evidenced by poor oral intake and/or retractions, are more likely to benefit from an antibiotic. For these sicker children, early antibiotic therapy still can be life-saving. In addition, children who are immunocompromised might fall outside the new data from Malawi since that study was done in a population with low HIV prevalence. At the same time, children with malaria can have high temperatures and tachypnea, so clinicians must carefully consider management of the whole child with multiple possible causes of his or her symptoms.

What should we anticipate in the future? Medication for influenza already can help reduce morbidity and mortality in sick children with influenza. Perhaps a medication for respiratory syncytial virus infections will emerge on the horizon. It could be that one day, the odds will favor antiviral treatment of children in Africa with fever, cough, and tachypnea. In the meantime, though, competent clinicians still will consider various clinical findings to try to focus antibacterial treatment on those who truly might benefit. ■

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ABSTRACT & COMMENTARY

The Downsides of High Vancomycin Troughs: No Longer 'Mississippi Mud,' but Still Hazardous

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: A retrospective cohort study from a large healthcare system found that elevated vancomycin troughs were common and associated with a higher body mass index and reduced baseline renal function, and led to more acute kidney injury and a longer hospital length of stay.

SOURCE: Zonozi R, Wu A, Shin JI, et al. Elevated vancomycin trough levels in a tertiary health system: Frequency, risk factors, and prognosis. *Mayo Clin Proc* 2019;94:17-26.

Vancomycin is one of the most commonly prescribed antibiotics for hospitalized patients. It was referred to informally as "Mississippi mud" when first introduced

because of impurities that caused significant nephrotoxicity. Modern formulations are much purer and, hence, less nephrotoxic, but this issue remains a legitimate concern. Monitoring vancomycin trough levels is seen as a possible way to mitigate the risk. Zonozi et al aimed to determine the risk factors that lead to elevated vancomycin troughs and assess patient outcomes for those who have them.

The study was a retrospective cohort analysis from a large healthcare system that included hospitalized patients aged 18 years or older who received IV vancomycin and had at least one vancomycin trough measured. An elevated trough was defined as > 30 mg/L, while a sensitivity analysis used a lower cutoff of > 20 mg/L. A trough was defined as a vancomycin level drawn at least eight hours after the last dose.

Researchers used the first elevated level as the index event if multiple troughs were high. They calculated a baseline estimated glomerular filtration rate (eGFR) based on the closest antecedent value to the time of the first dose of vancomycin. Acute kidney injury (AKI) was defined as a creatinine increase of 0.3 mg/dL within 48 hours or a 50% increase within seven days of the elevated vancomycin level.

Of the 21,285 patients who received vancomycin during the study period of August 2007 to October 2014, 7,422 had at least one vancomycin trough drawn. Of these, 755 (10.2%) were elevated. Higher troughs occurred more frequently in younger patients, women, and those with diabetes or heart failure. Furthermore, elevated troughs occurred in 332 of 1,668 patients (19.9%) who received more than seven days of vancomycin.

Compared to patients with a normal vancomycin level, those with an elevated trough had a longer therapy duration (median 6.0 days vs. 3.4 days; $P < 0.001$), received higher doses (mean 1.72 g vs. 1.58 g; $P < 0.001$), and had a higher body mass index (BMI) and a lower eGFR. Propensity matching determined that a vancomycin trough > 30 mg/L was associated with a higher risk for developing AKI (hazard ratio [HR], 1.55; 95% confidence interval [CI], 1.09-2.20; $P = 0.02$), a longer hospital stay (relative risk [RR], 1.14; 95% CI, 1.02-1.28; $P = 0.03$), but similar in-hospital mortality. Researchers observed a linear relationship such that the higher the trough, the longer the hospital stay (RR, 1.59; 95% CI, 1.40-1.80 for a trough of 50 mg/L). When the trough level was lowered to > 20 mg/L, the risk associations were slightly attenuated.

■ COMMENTARY

Dosing vancomycin appropriately sometimes can be a challenge in routine practice, especially in patients with unstable renal function. The study by Zonozi et al is interesting because the authors reported the rate of elevated vancomycin troughs and subsequent outcomes using real-world data from a large healthcare system. Notably, the finding that elevated troughs were more common in those with higher BMIs may be related to the way the vancomycin dose is calculated. This is because the Cockcroft-Gault formula overestimates the glomerular filtration rate at higher BMIs.

Furthermore, it is very difficult to truly know whether an elevated vancomycin trough is the cause or consequence of renal dysfunction. The onset of AKI often is preceded by an increase in creatinine by one to two days, such that it often is unclear whether an unrecognized subclinical event led to an accumulation of vancomycin. However, Zonozi et al recognized this dilemma and took appropriate steps to increase the plausibility that the nephrotoxicity was caused by vancomycin. For example, the sensitivity analysis included only patients with creatinine values available within 24 hours of the drug level. These data were consistent with the overall finding that high troughs led to AKI.

There remains a need for more accurate vancomycin dosing models than are currently available. The authors of an accompanying editorial discussed cystatin C, an alternative biomarker recently validated in an independent cohort that was used to construct a simple dosing nomogram that was made available to clinicians through the electronic medical record. Cystatin C is a relatively new renal biomarker that is inexpensive and responds more quickly than creatinine to renal function changes. Cystatin C is not affected by factors such as sex, age, dietary intake, muscle mass, or deconditioning.[1] After implementation, the frequency of initial vancomycin troughs within goal among intensive care unit patients increased from 28% to 50%. One hopes that this innovative strategy will be validated in other settings in the near future.

Despite the large sample size, there are some limitations to the study that need to be mentioned. First, there were no data on concurrent nephrotoxic agents. For example, there is an increased risk for nephrotoxicity when vancomycin is combined with piperacillin-tazobactam.[2] Second, it is more common in clinical practice to consider a trough of > 20 mg/L than 30 mg/L as elevated. Finally, the observational design still might be affected by unmeasured confounding variables despite the advanced statistical

methods employed by the authors. In summary, the study by Zonozi et al found that elevated vancomycin troughs are common and have important negative consequences, especially for patients who are overweight or have baseline kidney disease.

This study adds to the growing body of evidence associating modern formulations of vancomycin with nephrotoxicity and reinforces the practice of monitoring vancomycin troughs to avoid supratherapeutic levels and the resulting increase in hospital morbidity. ■

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ABSTRACT & COMMENTARY

Infection After Placement of Antibiotic Spacers in Prosthetic Joints

By Dean L. Winslow, MD

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

SYNOPSIS: Researchers reviewed a case series of 51 patients who received retained "destination spacers" after resection of infected joint prostheses. The researchers noted a significant association between the presence of preoperative sinus drainage and re-infection. Long-term antimicrobial suppression after retention of a destination spacer did not result in significant prevention of re-infections.

SOURCE: Valencia JCB, Abdel MP, Virk A, et al. Destination joint spacers, reinfection, and antimicrobial suppression. *Clin Infect Dis* 2019; Jan 28. doi: 10.1093/cid/ciz062. [Epub ahead of print].

Researchers reviewed 51 consecutive patients from Mayo Clinic who underwent "destination joint replacement" for prosthetic joint infection (PJI). The cases included 34 with retained knee and 17 with retained hip antibiotic spacers. The median patient age was 77 years. The most common reason for choosing "destination replacement" vs. a two-stage procedure with re-implantation of a prosthetic joint was the presence of a medical comorbidity that was considered to preclude a second joint replacement in 67%. Thirty-three percent of patients had good joint function and declined a second-stage re-implantation of the prosthesis. The destination spacers all were secured to the bone surface using cement loaded with vancomycin and an aminoglycoside (tobramycin or gentamicin); amphotericin B also was included in 16% of cases. After implantation of the destination spacer, all patients received six weeks of systemic antimicrobials guided by cultures.

After the initial six weeks of systemic antibiotics, 11 patients (21%) received long-term oral antibiotic suppression for a median duration of three years. Of these 11 patients, two experienced diarrhea, one experienced renal dysfunction, and two experienced hyperpigmentation or photosensitivity after minocycline and doxycycline treatment, respectively. During the median follow-up period of 31 months, five patients experienced re-infection, and the re-infecting pathogens were completely different from the original pathogens isolated. Four of 17 patients with preoperative draining sinus vs. only one of 34 patients without preoperative draining sinus developed re-infection.

■ COMMENTARY

I must confess that PJI is one of my least favorite infectious diseases. PJI complicates about 2% of primary hip and knee replacements in the United States. Although the orthopedic surgeons at our university hospital, community hospital, and affiliated VA (where I proudly receive my own healthcare) all are excellent, I have chosen to cut back running to three days per week in hopes of putting off a knee replacement during this lifetime.

Recommended management of PJI generally includes removal of all hardware, debridement of periprosthetic tissue, insertion of a temporary antibiotic-impregnated spacer, six weeks of systemic antibiotics guided by culture results, and re-insertion of a joint prosthesis after the infection is determined

to be eradicated. Sometimes, our surgeons will attempt surgical debridement with "liner exchange" but leaving most of the hardware in place. We often are consulted to provide long-term "suppressive antibiotics" in these liner exchange cases, but I have been disappointed in the low success rate of this approach. These patients often have to undergo eventual removal of hardware, debridement, and insertion of an antibiotic-impregnated spacer anyway. Occasionally, these temporary antibiotic-impregnated spacers are retained permanently because of either patient comorbidities that preclude additional surgery or patient preference not to undergo a second (or third) surgery to re-implant a joint prosthesis. This case series actually is reassuring that recurrent infection is rare in patients who have a destination spacer. They often do well and, in most cases, when re-infection is encountered, it is due to new pathogens in patients who had a preoperative draining sinus.

The study also suggests that long-term antibiotic suppression in patients who undergo placement of a "destination antibiotic-impregnated spacer" likely does not improve outcomes following the usual six weeks of systemic antibiotics after initial hardware removal, debridement, and placement of the antibiotic-impregnated spacer. ■

PHARMACOLOGY UPDATE

Eravacycline (Xerava)

By Emily Mui, PharmD

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

Eravacycline is a novel fluorocycline antibiotic under the tetracycline antibacterial class. With a modified fluorine atom at the C7 position and pyrrolidinoacetamido group at the C9 position, eravacycline retains activity against tetracycline-specific resistance mechanisms.[1] Eravacycline binds to the 30S ribosomal subunit, which results in disruption of bacterial protein synthesis. Eravacycline is FDA approved for the treatment of complicated intra-abdominal infections that are caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii*, *Enterobacter cloacae*, *Klebsiella oxytoca*, *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus*, *Streptococcus anginosus* group, *Clostridium perfringens*, *Bacteroides* species, and *Parabacteroides distasonis*.

In Phase 3 clinical trials (IGNITE1 and IGNITE4), researchers found eravacycline to be noninferior to ertapenem and meropenem for the treatment of complicated intra-abdominal infections with the primary endpoint of clinical response in the micro-ITT population.[2,3] However, eravacycline did

Table 1: Eravacycline Is Shown to Be Active Against Most Isolates of the Following Organisms in In-Vitro and Clinical Trials

Gram-Positive Bacteria	**Gram-Negative Bacteria**
• *Enterococcus faecalis* • *Enterococcus faecium* • *Staphylococcus aureus* • *Streptococcus anginosus* group	• *Citrobacter freundii* • *Enterobacter cloacae* • *Escherichia coli* • *Klebsiella oxytoca* • *Klebsiella pneumoniae*
Gram-Positive Anaerobic Bacteria	**Gram-Negative Anaerobic Bacteria**
• *Clostridium perfringens*	• *Bacteroides caccae* • *Bacteroides fragilis* • *Bacteroides ovatus* • *Bacteroides thetaiotaomicron* • *Bacteroides uniformis* • *Bacteroides vulgatus* • *Parabacteroides distasonis*

not demonstrate noninferiority in the complicated urinary tract infection Phase 3 studies (IGNITE 2 and IGNITE 3) and carries a warning against its use for treatment of complicated urinary tract infections.

MICROBIOLOGY

Eravacycline has a broad range of activity against many Gram-positive and Gram-negative aerobic and anaerobic organisms, including those that harbor multidrug resistance mechanisms, such as extended-spectrum beta-lactamase (ESBLs), carbapenem-resistant *Enterobacteriaceae*, carbapenem-resistant *Acinetobacter baumannii*, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and anaerobes.

Compared to tigecycline, eravacycline is more than twice as potent against Gram-negative bacilli and Gram-positive cocci.[4] Gram-negative organisms found to have lower MICs include *A. baumannii*, *A. lwoffii*, *C. freundii*, *E. aerogenes*, *K. oxytoca*, *M. catarrhalis*, *M. morganii*, *P. mirabilis*, *P. vulgaris*, *P. stuartii*, *Salmonella* spp., *S. marcescens*, and *S. maltophilia*, as well as certain panels with I/R phenotypes for third-generation cephalosporins. A greater than two-fold potency for eravacycline was seen for the following Gram-positive organisms: *E. faecalis* (VRE and VSE), *E. faecium* (VRE), *Enterococcus* spp., *S. aureus* (MRSA), coagulase-negative staphylococci (methicillin sensitive), *S. pneumoniae*, *S. pyogenes*, *S. anginosus*, *S. intermedius*, and *S. mitis*. Like tigecycline, eravacycline does not have activity against *Pseudomonas aeruginosa*.

RESISTANCE

Eravacycline resistance is associated with upregulation of nonspecific intrinsic multidrug-resistant efflux and target site modifications to the 16S rRNA or 30S ribosomal proteins.[1] The C7 and C9 modification allow eravacycline to retain activity against organisms that carry certain tetracycline-specific resistance mechanisms, such as efflux mediated by *tet*(A), *tet*(B), and *tet*(K), and ribosomal protection ended by *tet*(M) and *tet*(Q).[1]

PHARMACOKINETICS/PHARMACODYNAMICS[1]

Absorption: Although not marked as an oral medication, in healthy volunteer studies, the oral bioavailability was approximately 28%.[5]

Distribution:
- Protein binding: 79-90%;
- Plasma concentration range: 100-10,000 mcg/mL;
- Steady state volume of distribution: 321 L;
- Steady state achieved in 5-7 days.

Metabolism: CYP3A4- and FMO-mediated oxidation;
Elimination: Renal elimination: 34% (20% as unchanged drug);
Feces Excretion: 47% (17% as unchanged drug).

Eravacycline is only available as an intravenous formulation. In earlier dose experimental studies, the oral bioavailability of eravacycline was approximately 28%.[5] Eravacycline is highly protein bound with a volume of distribution that is a large steady state volume of distribution. In rabbit PK studies, the mean tissue concentrations are highest in renal cortex > liver > renal medulla > gallbladder > spleen > psoas muscle > lungs > bone marrow > pancreas > heart > vena cava > brain.[6] Eravacycline is metabolized by CYP3A4- and FMO-mediated oxidation. About 34% of the dose is excreted in the urine and 47% is excreted in feces.[1]

The pharmacokinetic/pharmacodynamic parameter that best correlates with efficacy is area under the plasma concentration-time curve to the minimum inhibitory concentration (AUC:MIC).[1]

DOSAGE AND ADMINISTRATION

Adjust dosing frequency for Child-Pugh Score C hepatic impairment. Dose adjustment is not required for renal impairment.

Table 2: Renal Impairment

Estimated CrCL (mL/min)	Dosage
CrCL ≥ 90 mL/min	1 mg/kg (total body weight) every 12 hours
60-90 mL/min	No adjustment
30-60 mL/min	No adjustment
15-30 mL/min	No adjustment

Table 3: Hepatic Impairment

Child-Pugh Score	Dosage
A	No adjustment
B	No adjustment
C	1 mg/kg Q12H on day 1, then 1 mg/kg Q24H on day 2

ADVERSE EFFECTS/WARNINGS

The most common side effect of eravacycline in Phase 3 clinical trials included infusion site reactions (7.7%), nausea (6.5%), vomiting (3.7%),

and diarrhea (2.3%). The most common side effects leading to discontinuation of therapy were gastrointestinal.

The use of eravacycline should be avoided in patients who have known hypersensitivity to the tetracycline class antibacterial. Tooth discoloration and enamel hypoplasia may occur if eravacycline is administered during tooth development because this is a known adverse reaction of the tetracycline antimicrobial class. Tetracyclines also are known to form a stable calcium complex to bone-forming tissue and may result in a decrease in growth rate of the fibula. The safety and efficacy of eravacycline has not been established in pediatric patients; therefore, the same precautions for tetracycline class medications should be considered with eravacycline in the pediatric population.

DRUG INTERACTIONS

Eravacycline is metabolized primarily by CYP3A4. Concomitant use of strong CYP3A4 inducers, such as rifampin, can decrease eravacycline AUC by 35% and increase eravacycline clearance by 54%. Concomitant use of itraconazole (a strong CYP3A inhibitor) increased eravacycline Cmax by 5% and AUC by 32%, and decreased eravacycline clearance by 32%.

PREGNANCY AND LACTATION

- In animal studies, eravacycline crosses the placenta and is found in fetal plasma. Eravacycline administration during the organogenesis period was associated with decreased ossification and fetal body weight and increased post-implantation loss.[1]
- Eravacycline is excreted in milk in lactating rats; however, the extent of absorption in human infants is unknown.[1]

CONCLUSION

Eravacycline is a novel tetracycline antibiotic recently approved for the treatment of complicated intra-abdominal infections. It is unaffected by the two acquired tetracycline-specific resistance mechanisms (efflux pumps and ribosomal protection). It has broad antimicrobial activity against several MDR organisms, such as CREs, ESBLS, MRSA, VRE, and MDR *Acinetobacter*. It is unknown how eravacycline compares to tigecycline in the clinical setting, but it does appear to have a more favorable safety profile. ■

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ABSTRACT & COMMENTARY

IV to Oral Conversion of Antibiotic Therapy for Bacteremia Due to *Enterobacteriaceae*

By Stan Deresinski, MD, FIDSA, FACP

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

SYNOPSIS: Oral step-down antibiotic therapy (IV to oral conversion) is safe and effective in patients with bloodstream infection due to *Enterobacteriaceae*.

SOURCE: Tamma PD, Conley AT, Cosgrove SE, et al; Antibacterial Resistance Leadership Group. Association of 30-day mortality with oral step-down vs continued intravenous therapy in patients hospitalized with *Enterobacteriaceae* bacteremia. *JAMA Intern Med* 2019; Jan 22. doi: 10.1001/jamainternmed.2018.6226. [Epub ahead of print].

Tamma and colleagues examined the efficacy and safety of oral step-down therapy (IV to oral conversion) in patients with bacteremia due to commonly isolated *Enterobacteriaceae* in a multicenter retrospective study using propensity analysis. Only 2,161 of 4,967 bacteremic patients met entry criteria, 876 (40.5%) of whom underwent step-down of their therapy. Compared to those who received their entire course of therapy intravenously, the step-down group was less likely to be severely neutropenic or severely ill or to have received combination antibiotic therapy for at least 48 hours. In the step-down group, the urinary tract was more likely to be the source of bacteremia.

To overcome these differences in their analysis, the authors performed propensity analysis with matching yielding 739 in each study arm. The most frequently isolated pathogens, in decreasing order of frequency, were *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp., *Proteus mirabilis*, *Serratia marcescens*, and *Citrobacter* spp. Approximately two-fifths of infections arose from the urinary tract, one-fifth each from an intra-abdominal source and a venous catheter, one-seventh from the biliary tract, and the remainder from the lungs and skin or skin structure.

The patients in the IV-only group received a median of 14 days of IV therapy, while the step-down cohort received only a median of three days of therapy by that route. In comparisons of the oral step-down and IV groups, there were no significant differences in 30-day mortality (13.1% vs. 13.4%) or recurrent bacteremia (0.8% vs. 0.5%). The duration of hospitalization was two days shorter in the step-down group: five days vs. seven days.

Antibiotics considered to have high oral bioavailability (fluoroquinolones and trimethoprim-sulfamethoxazole) were administered to 83.9% of patients receiving step-down therapy, with the remaining receiving oral beta-lactams, with all considered to have low bioavailability. No significant differences in outcomes were observed in a comparison of the two groups.

■ COMMENTARY

The number of patients in this study who received step-down therapy with low bioavailability drugs was small, making the finding that they appeared to do as well as those who received high bioavailability oral antibiotics potentially suspect. However, the authors pointed out that this finding is consistent with the results of other retrospective analyses. This is not terribly surprising, especially in view of a recent randomized trial that found that seven days of IV therapy was noninferior in a randomized trial in patients with Gram-negative bacteremia.[1,2]

It seems likely to me that the median of five days of IV therapy given to step-down patients by Tamma and colleagues may have been sufficient to cure most cases of bacteremia, and the subsequent oral therapy may have been irrelevant. We have been using step-down commonly as early as day 3 of IV antibiotic therapy to complete a total of seven days of therapy in uncomplicated cases with good initial responses. ■

REFERENCES

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2. Deresinski S. Treatment of Gram-negative bacteremia: How long is long enough? *Infect Dis Alert* 2019;38:49-50.

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Jump in Cocci Cases, Winter 2017

SOURCE: Bezold CP, Khan MA, Adame G, et al. Notes from the field: Increase in coccidioidomycosis — Arizona, October 2017-March 2018. *MMWR Morb Mortal Wkly Rep* 2018;67:1246-1247.

The largest number of cases of coccidioidomycosis ever reported in the state of Arizona occurred in December 2017 (17.2 cases/100,000). Most of the reported cases of coccidioidomycosis within the United States occur in California and Arizona, with a remarkably seasonal distribution. Generally, an increasing trend in cases is observed in the late summer to fall, peaking approximately in December, and then falling off by spring, probably as the result of wind and weather patterns. Observations from Arizona in fall to winter 2017 suggested a larger than expected number of cases were occurring, with this dramatic peak in cases in December 2017.

Compared with October 2016 to March 2017, when 3,050 cases were reported in Arizona, the total number of reported cases during the same time period in 2017-2018 was 4,827 cases (a 58% increase). The median age of cases in 2017-2018 was 56 years, and there was no apparent difference between gender. Ninety percent of the 2017-2018 cases lived in Maricopa County (Phoenix), Pima County (Tucson), or Pinal County. For Maricopa County alone, a 70.5% increase in cases was reported for the month of December 2017 (87 cases/100,000) compared with December of the previous year.

Reported cases of cocci may be based on serologic data alone and/or molecular, microbiologic, or histopathology supporting the diagnosis. On the chance that this observed increase in cases occurred because of some laboratory anomaly, researchers examined the proportion of cases diagnosed solely on the basis of coccidioidomycosis IgM antibodies by EIA. From October 2017 to March 2018, the proportion of cases diagnosed based on IgM serology alone was similar to that of the same time period the previous year (13% vs. 10.6%). Thus, no apparent change in laboratory technique explained the dramatic increase in observed cases.

Many attribute this increase to an effect of global warming, with changes in wind and precipitation. A similar increase in cocci cases was observed in California last winter. Comparing the months of January 2017 and January 2018, a total of 249 cases vs. 636 cases were reported in the state, respectively (a 155% increase). The annual upward trend in cocci cases in California should raise alarm bells: The total number of cases for every year for the past three years has increased (from 5,706 in 2016 to 7,534 in 2017 to 8,187 cases in 2018).

Although weather patterns may play a role, it is important to note that the Census Bureau reported that Maricopa County was the country's fastest growing county from 2016 to 2017 (with 73,650 new arrivals). Phoenix ranked second in population growth in the United States from 2016 to 2017, now ranking as the fifth largest U.S. city.

All of those new arrivals, many of whom are older and retiring to Arizona, probably lack protective immunity to coccidioidomycosis, making them vulnerable newcomers to the state. Further, to accommodate all of these individuals, all of the construction and new housing in Phoenix and Tucson could only be kicking up more dust.

Who Knew the Ink Was Not Sterile?

SOURCE: Griffin I, Schmitz A, Oliver C, et al. Outbreak of tattoo-associated nontuberculous mycobacterial skin infections. *Clin Infect Dis* 2018; Nov 17. doi: 10.1093/cid/ciy979. [Epub ahead of print].

A diagnosis of nontuberculous mycobacterial (NTM) infection complicating new tattoos in three individuals from the same tattoo parlor in February-March 2015 prompted investigation by the Miami-Dade County Department of Public Health. As with crime scene investigations, the first step was to collect evidence at the scene. An initial interview revealed that the three tattoo artists working at the facility chose to dilute gray ink, some with distilled water or with tap water. To create more variation in shading, prediluted gray ink, in various strengths, can be ordered from the manufacturer, but apparently further gradations in shading were desired. Further, one particular bottle of diluted gray ink had been open and in use for several months (ink A).

A survey was administered to clients of the parlor during the same time period: 246 of 356 clients could be located, although 20 declined to participate. Investigators identified eight confirmed cases of NTM infection plus 30 other individuals with a suspect rash occurring at least two weeks after getting tattooed. Of these, 27 cases were male (71%), and the median age was 28 years (19 to 54 years of age). The 38 individuals reported a variety of symptoms, including (in descending order) papules/pustules at the site of infection (100%), redness (76%), itching (58%), swelling (26%), pain (26%), and fever (8%). The incubation period ranged anywhere from one to 59 days, and the duration of rash extended from 15 days to five months. When contacted later, eight people (38%) remained symptomatic six months or more later.

Only a minority of patients had sought medical care, and only four individuals reported taking medication when prescribed. More cases were identified after the tattoo parlor had stopped using ink A in April 2016. Among the eight confirmed cases, six tested positive for *Mycobacterium abscessus* or *M. abscessus-chelonae* complex (by culture and/or PCR) and one case tested positive for *Mycobacterium fortuitum* (by both PCR and culture). Interestingly, by PGFE analysis, the isolates appeared to be the same species, differing only by one or two bands.

All skin biopsies underwent histopathologic review, with special stains and PCR testing, and isolates were identified and compared using pulsed-field gel electrophoresis. In addition, environmental

samples collected from tap water, sink taps, and gray wash ink were submitted to FDA laboratories for microbiologic testing and genome analysis. The tap water yielded multiple mycobacterial species (*M. abscessus*, *M. fortuitum*, *M. mucogenicum*, and two others). The open bottle of ink A grew *M. abscessus* and *M. fortuitum*. The five unopened bottles of ink of varying dilution grew *M. chelonae* and several molds.

Investigators used shotgun whole-genome sequencing to compare isolates (five from skin biopsies, three from tap water, and nine from gray wash ink) to four isolates from an American culture collection. Phylogenetic analysis suggested similarity between the *M. fortuitum* isolates from both the clinical case and ink A, but none of the clinical isolates matched the isolates in the unopened ink bottles. This suggests that contamination of ink A, diluted on site, likely was the source for the clinical infections, and not contamination at the manufacturer (although the unopened ink was contaminated with other pathogens). Samples of gray wash ink from five other tattoo parlors in the area also yielded five unrelated *M. chelonae* organisms.

Even though it is applied intradermally, tattoo ink is classified by the FDA as a "cosmetic agent." As such, it does not need to be sterile, although regulations specify it should be free of "pathogens." Similar to nail salons and hair parlors, the responsibility for regulating tattoo parlors and suppliers falls to individual counties. However, many counties, including Miami-Dade, do not have specific regulations for the use of tattoo ink. The Miami-Dade County health code stipulates that tattoo parlors should follow manufacturers' guidelines for ink. There are none.

Somehow, with all that signage about "sterile needles" and "sterile technique," who would imagine that the ink was a problem?

Homeless Population Requires Hepatitis A Vaccination

SOURCE: Foster M, Ramachandran S, Myatt K, et al. Hepatitis A virus outbreaks associated with drug use and homelessness — California, Kentucky, Michigan, and Utah, 2017. *MMWR Morb Mortal Wkly Rep* 2018;67: 1208-1210.

A multistate outbreak of hepatitis A virus (HAV) infection in the homeless and/or drug-using population has prompted the United States Advisory Committee on Immunization Practices (ACIP) to add "homelessness" as an indication for HAV vaccination, effective Oct. 24, 2018. This indication is in addition to existing indications for HAV vaccination of men who have sex with men (MSM) and illicit drug users (with the exception of marijuana use).

During 2017, a total of 1,521 outbreak cases of acute hepatitis A infection were reported from California, Kentucky, Michigan, and Utah, mostly in the homeless and/or drug-using population. An outbreak case was defined as acute HAV infection with a viral specimen matching the outbreak strain or if the case could be linked with another identified case. Although HAV generally is transmitted by close personal or sexual contact and unsanitary conditions, this was the first time an outbreak was fueled, in part, by parenteral transmission from contaminated needles and other shared paraphernalia. This shift in the epidemiology of hepatitis A infection raised alarms for health officials.

Forty-one (3%) of the outbreak cases died and 1,073 (71%) were hospitalized. Three percent had confirmed hepatitis B co-infection and 22% had confirmed or probable hepatitis C co-infection. More than half (57%) reported homelessness and/or drug use, and 5% were MSM.

Increasingly, molecular techniques are used to identify outbreaks of HAV infection. For this investigation, serum samples submitted to the CDC were used to extract and amplify a fragment of the VP1/P2B region of the virus for genetic characterization. A total of 1,054 specimens were tested, 96% of which were positive for genotype 1b virus, which generally is an uncommon strain. Most clinical cases of HAV infection in the United States before 2017 have been due to genotype 1a virus. The genotype 1b strain circulating in California, Utah, and Kentucky was different from that found in the Michigan cases.

In California, the outbreak started in San Diego County in November 2016 and quickly spread to Los Angeles, Santa Cruz, and Monterey counties. In October 2017, Gov. Jerry Brown declared a state of emergency in order to secure a large number of doses of vaccine. Three California counties mounted an offensive, deploying vans to homeless encampments and distributing alerts to local clinics and emergency rooms. Approximately 123,000 doses of HAV vaccine were dispensed, effectively quelling the outbreak in this state.

Although aggressive public health intervention in California stopped the outbreak there, it continues in Kentucky, Michigan, and Utah and may be spreading to other states. As of October 2018, more than 7,000 cases of acute HAV infection have been reported from 12 states. ■

ABIM CME MOC ACCREDITED

CME INSTRUCTIONS

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CME QUESTIONS

1. For children with acute fever and cough in resource-limited areas of the world:

a. tachypnea is a sensitive and specific factor to determine the potential benefit of antibiotic treatment.

b. antibiotics are always indicated.

c. viral infections often are associated with tachypnea.

d. chest radiographs are essential in diagnosing bacterial pneumonia.

2. Which of the following is an FDA-approved indication for the use of eravacycline?

a. Complicated urinary tract infection including pyelonephritis

b. Complicated urinary tract infection but not including pyelonephritis

c. Complicated intra-abdominal infection

d. Community-acquired pneumonia

3. Which of the following was first added in the past year as an indication for vaccination against hepatitis A virus infection?

a. Homelessness

b. Traveling to developing countries with high or intermediate hepatitis A endemicity

c. Significant exposure to hepatitis A

d. Chronic hepatitis B or C infection

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.