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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Biologic Warfare: A Game-Changer in the Battle Against Malaria?

By Philip R. Fischer, MD, DTM&H

Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN

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

SYNOPSIS: A non-pathogenic microsporidian organism can infect *Anopheles* mosquitoes and block the transmission of malaria parasites, without negatively altering the life of the mosquito. This organism potentially could be used for widespread malaria control.

SOURCE: Herren JK, Mbaisi L, Mararo E, et al. A microsporidian impairs *Plasmodium falciparum* transmission in *Anopheles arabiensis* mosquitoes. *Nat Commun* 2020;11:2187.

Widespread use of insecticide-treated bed nets earlier this century was associated with a marked reduction in malaria mortality. Over the past few years, though, the decline in the number of malaria cases has stalled. Current malaria control efforts are insufficient.

Some symbiotic microorganisms, living within mosquitoes, can alter the transmission of viral pathogens to humans. So far, no such organism had been identified that could alter malaria transmission significantly and sustainably. So, Herren and colleagues pursued a series of studies of a non-pathogenic microsporidian to see if it could reduce transmission of *Plasmodium falciparum*.

First, *Microsporidia MB* was found in up to 9% of *Anopheles arabiensis* mosquitoes in areas of Kenya. These organisms are of a different clade than (and, therefore, are distinct from) the previous microsporidians found in mosquitoes. *Microsporidia MB* followed seasonal patterns and was most prevalent after times of heavy rain. The organisms are transmitted vertically from mother to offspring through the ovaries.

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Infectious Disease [ALERT]

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Second, Herren and colleagues found that *Microsporidia MB*-infected mosquitoes could ingest *Plasmodium* parasites with blood meals, but that the parasites then would not progress through necessary stages of development and migration to reach the salivary glands of the mosquitoes.

Third, the researchers noted that *Microsporidia MB* did not alter the survival or reproductive potential of the infected mosquitoes. Thus, infection by the symbiotic microsporidian would not be a "dead end," but is associated with the production of subsequent generations of infected mosquitoes that also would be able to block the development and transmission of malaria parasites.

Fourth, the genetic effects of *Microsporidia MB* infection were evaluated. The symbiont promoted increased transcription of genes related to digestion, immunity, and salivary gland activity. Thus, the mechanism by which *Microsporidia MB* acts on the mosquito not only blocks malaria transmission but also might enhance the health of the mosquito.

Herren and colleagues concluded that *Microsporidia MB* could be a realistic candidate to infect mosquito populations and facilitate development of a stable vector that could replace current mosquito populations. The blockage of malaria transmission coupled with the passage of microsporidia from one generation to the next with no adverse health effects on the mosquito could make *Microsporidia MB* an attractive option for the control of malaria.

■ COMMENTARY

Through all the tragedy and politicization of the current COVID-19 pandemic, most everyone agrees that society was not adequately prepared to deal with widespread transmission of such a devastating virus. With heavy expenditures of human and material resources, there is rapid progress against SARS-CoV-2 infection.

Unlike COVID-19, malaria is neither new nor novel; it has been around for millennia. At the time of this writing, nearly 4 million people have been infected by COVID-19. Malaria infects 200 million per year. COVID-19 already is responsible for nearly 300,000 deaths; malaria kills one and a half times that many people every year. Despite the extensive resources put into malaria control efforts, malaria is not yet under control.

Widespread use of insecticides, such as dichlorodiphenyltrichloroethane (DDT), held promise of eradicating malaria, but resistance of mosquitoes to DDT and environmental toxicity limited the usefulness of those efforts. Preventive medication was sensible, but delivery systems and access to care limited those interventions. Improved medications became available as resistance developed, but medications alone were not able to stop malaria's devastation. Insecticide-treated bed nets led to huge gains, and mortality from malaria plummeted, but then plateaued.

Biologic warfare, using commensal organisms living within mosquitoes, has long been postulated as a possible weapon in the fight against malaria, but the limited reduction in *Plasmodium* transmission and/or the resulting weakness of the infected mosquitoes limited the value of those efforts.

Now, *Microsporidia* might be a game-changer. This organism appears to be extremely effective in prompting an essentially complete blockage of the transmission of malaria parasites through the mosquito, and the germs are effectively transmitted trans-ovarially to the next generation of mosquitoes, prolonging the effect.

Further studies will be needed to confirm these findings and to evaluate the feasibility of introducing these infected vectors into the population in ways that would allow them to increase to well beyond the current 9% prevalence of infection in Kenyan mosquitoes. At the same time, other species of *Anopheles* also could be evaluated as potential malaria-blocking vectors. ■

ABSTRACT & COMMENTARY

Inappropriately Broad Empiric Antibiotics Are Associated with Higher Mortality in Community-Onset Sepsis

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

Professor of Internal Medicine, Northeast Ohio Medical University; Division of Infectious Diseases, Cleveland Clinic Akron General, Akron, OH

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

SYNOPSIS: A retrospective cohort study found that broad-spectrum antibiotics were unnecessarily prescribed to patients with community-onset sepsis and was associated with worse outcomes and higher mortality.

SOURCE: Rhee C, Kadri SS, Dekker JP, et al. Prevalence of antibiotic-resistant pathogens in culture-proven sepsis and outcomes associated with inadequate and broad-spectrum empiric antibiotic use. *JAMA Netw Open* 2020;3:e202899.

In the management of sepsis, early administration of empiric antibiotic therapy is a critical step. However, overtreatment (i.e., unnecessarily broad-spectrum therapy) can have downsides, such as adverse reactions, potential selection for antibiotic-resistant bacteria, *Clostridioides difficile* infection (CDI), and higher costs. Inappropriately narrow therapy can lead to higher mortality. Therefore, Rhee and colleagues sought to determine the outcomes associated with overtreatment and undertreatment in patients with culture-positive community-onset sepsis.

The study was a retrospective cohort analysis that used a data set from a diverse group of U.S. hospitals. Patients were included who were 20 years of age or older, had a diagnosis of community-acquired sepsis, and had positive cultures for potentially pathogenic organisms by hospital day 2. They were excluded if they had hospital-acquired sepsis or were transferred from long-term care or rehabilitation facilities, hospice, or other hospitals. The diagnosis of sepsis was made using ICD-9-CM discharge codes. The investigators considered patients to have received inadequate empiric therapy if at least one pathogen isolated from any clinical culture was not susceptible to all antibiotics administered during the initial two days of admission. They considered patients to have received unnecessarily broad empiric therapy if they were prescribed anti-methicillin-resistant *Staphylococcus aureus* (MRSA) antibiotics, anti-vancomycin-resistant enterococci (VRE) antibiotics, anti-*Pseudomonas* β-lactams or carbapenems but none of the organisms targeted by these antibiotics were recovered. The primary outcome was in-hospital mortality.

The cohort included 17,430 patients. They had a median age of 69 years, and 55.9% were women. Urinary tract infection was the most common source of sepsis (48.9%), followed by pulmonary (32.9%), intra-abdominal (13.6%), and skin and soft tissue (10.3%) infections. The most frequently identified pathogens were *Escherichia coli* (33.7%), *Staphylococcus aureus* (21.3%), *Streptococcus* spp. (13.5%), *Klebsiella* spp. (12.9%), and *Enterococcus* spp. (11.1%). Antibiotic-resistant organisms included MRSA (11.7%) and ceftriaxone-resistant gram-negative organisms (CTX-RO) (13.1%). Of these, 66.3% had *P. aeruginosa*, VRE (2.1%), extended spectrum beta-lactamases (ESBLs) (0.8%), and carbapenem-resistant *Enterobacteriaceae* (CRE) (0.5%). The prevalence of at least one resistant gram-positive organism (MRSA or VRE) was 13.6%, while 13.2% of the cohort had at least one resistant gram-negative organism. Patients with resistant organisms were more likely to have a great number of comorbidities, have a pulmonary infection, require vasopressors or mechanical ventilation, be admitted to the intensive care unit (ICU), and die in the hospital.

The most commonly prescribed antibiotic was vancomycin, received by 41.7% of the patients, followed by a fluoroquinolone (40.1%), piperacillin-tazobactam (33.9%), and ceftriaxone (29.8%). Overall, 11,797 (67.7%) patients received antibiotic therapy directed against antimicrobial-resistant (AMR) pathogens listed earlier, and of these patients 3,447 (29.9%) had at least one of these organisms isolated in culture. Empiric antibiotics were active in 12,398 out of 15,183 (81.6%) cases of sepsis in which antibiotic-pathogen susceptibility

combinations could be examined. Multivariable analysis determined that inadequate therapy was significantly associated with higher mortality (adjusted odds ratio [OR], 1.19; 95% confidence interval [CI], 1.03-1.37; *P* = 0.02). This held true after adjusting for baseline characteristics, severity of illness, and adequacy of therapy. Unnecessarily broad antibiotic therapy was associated with higher mortality in patients without shock (adjusted OR, 1.22; 95% CI, 1.06-1.49; *P* = 0.007), as well as a greater risk for CDI (adjusted OR, 1.26; 95% CI, 1.01-1.57; *P* = 0.04). There also was a trend toward more acute kidney injury that did not reach statistical significance. Vital sign data during the first two days of hospitalization was reported to be missing in 47.8% of cases, while lactic acid levels (an important marker for sepsis and septic shock) were missing in 40.9%.

■ COMMENTARY

Clinicians are well aware of the mantra to recognize and treat sepsis early. But pragmatically, it is very challenging to estimate accurately which patients might have an infection due to an AMR organism. Although risk factors (e.g., prior AMR infection, recent antibiotic use, recent hospitalization, and underlying comorbidities) may be helpful, they are certainly not fool-proof. Thus, a trade-off exists between choosing empiric antibiotics with a spectrum that is too broad vs. one that is too narrow. The large cohort study by Rhee and colleagues provides some useful information for dealing with this common clinical scenario, yet highlights limitations in the diagnostic process.

Most patients with community-onset sepsis do not have AMR pathogens, so treating them with broad-spectrum antibiotics is inappropriate. That said, identifying the small fraction who do is limited by the widespread lack of rapid diagnostic testing. Better prediction models to determine the risk of an AMR infection that is assessed in a large number of patients with sepsis also could help inform empiric antibiotic decisions.

A major limitation of the study is that in approximately 30% to 50% of sepsis cases, cultures are negative or the exact source of sepsis is not clearly determined. The reliance on culture data in this study almost certainly led to an overestimate of resistant pathogens in the cohort.

Another limitation is related to the observation that more severely ill patients received broad-spectrum antibiotics, which, in fact, may have been due to residual confounding in this group related to the wide range of organ dysfunction. Finally, limitations in the data set mean the investigators did not have information on patient allergies, potential complications of antibiotics, or whether patients were hospitalized recently.

The main take-home points from this study are that most patients with community-acquired sepsis do not have resistant organisms, but inadequate therapy in those who do leads to higher mortality. Thus, it serves as yet another reminder that we need faster and more accurate diagnostic tests to optimize the management of patients with sepsis. ■

ABSTRACT & COMMENTARY

Clostridioides difficile: Risk Factors for Disease

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Approximately one-tenth of asymptomatic patients with *Clostridioides difficile* colonization went on to develop disease. A wide range of antibiotic exposures represent a significant risk.

SOURCES: Poirier D, Gervais P, Fuchs M, et al. Predictors of *Clostridioides difficile* infection among asymptomatic, colonized patients: A retrospective cohort study. *Clin Infect Dis* 2020;70:2103-2210.

Webb BJ, Subramanian A, Lopansri B, et al. Antibiotic exposure and risk for hospital-associated *Clostridioides difficile* infection. *Antimicrob Agents Chemother* 2020;64(4). pii: e02169-19.

A retrospective examination by Webb et al of patients with *Clostridioides difficile* infection (CDI) in InterMountain Healthcare Hospitals from 2006 to 2012 identified multiple risk factors by multivariate analysis. These factors included prior exposure to each of a wide range (approximately 20) of antibiotics. The antibiotics posing the greatest risk were cephalosporins (beyond first-generation), carbapenems, fluoroquinolones, and clindamycin. The odds ratios for daptomycin and doxycycline were < 1.0, suggesting a possibly protective effect. Perhaps the most interesting result in the study was the finding that antibiotics received in the 60 days prior to hospital admission (often during a prior hospitalization) posed a greater risk than antibiotics administered during the index hospitalization, with the risk increasing by 12.8% for every day of prior antibiotic exposure.

The recognition of asymptomatic colonization of new hospital admissions by *Clostridioides difficile* has raised important questions regarding the risk of disease development. Beginning in November 2013, the Quebec Heart and Lung Institute began screening all admissions for evidence of asymptomatic colonization with *Clostridioides difficile* by detection of the *tcdB* gene by polymerase chain reaction (PCR), with isolation of all who had a positive test. By January 2017, they identified colonization in 960 (5%) of 19,112 admissions. Sixty-three percent received at least one dose of a systemically administered antibiotic, with a median duration of receipt of seven days.

Of the 513 colonized individuals who met criteria for inclusion in their study, 39 (7.6%) developed hospital-onset CDI at a median of four days after admission, although in one-fifth the diagnosis was based on new diarrhea and a positive admission test without repeat testing. The attributable mortality was 15%. Another 17 patients were deemed to have developed CDI after discharge, bringing the total proportion of colonized individuals who developed disease to 56 (10.9%).

Exposures to β-lactam/β-lactamase inhibitors (BL/BLI), second-generation cephalosporins, and carbapenems, as well as exposures to multiple antibiotic classes, were associated with an increased risk of CDI. Additional risk factors were cirrhosis, use of opioids, and increased length of stay. Of note is that the use of proton pump inhibitors was not found to be a risk factor, nor was the administration of antibiotics aimed to prevent the development of CDI, although the number of patients in this group was small.

■ COMMENTARY

All studies of risk factors for CDI have several limitations, beginning with the variable means of diagnosis. That is true regarding the two papers reviewed here. In the study by Poirier and colleagues, the range of intervals from admission testing to onset of CDI was apparently 1-27 days, meaning that some cases with "hospital-onset" disease likely were incubating the illness at the time of hospital entry. Poirier et al also do not provide information regarding antibiotic exposure prior to hospitalization.

In fact, antibiotic exposure in the 60 days prior to the hospitalization under examination was identified as an important risk factor in unscreened admissions by Webb and colleagues. As many others have, Poirier et al identified exposure to BL/BLI, cephalosporins, and carbapenems as risk factors, while Webb's group found that almost any antibiotic (with the exceptions of daptomycin and doxycycline) potentially was implicated. The lesson is that a focus on reducing the use of individual antibiotics is an inadequate approach, and that all unnecessary antibiotic use must be targeted. In patients admitted to hospitals where screening for colonization is performed, special antibiotic stewardship attention could be directed at those whose tests are positive. ■

ABSTRACT & COMMENTARY

Carbapenem-Resistant Enterobacterales (CRE) in the USA — A Molecular and Clinical Analysis

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Patient mortality rates were high among patients from whom carbapenem-resistant Enterobacterales (CRE) were cultured, regardless of whether the organism was causing infection or was a only a colonizer. In addition, mortality was similar regardless of whether a carbapenemase gene was present. Finally, not all "CRE" were truly CRE.

SOURCE: van Duin D, Arias CA, Komarow L, et al; Multi-Drug Resistant Organism Network Investigators. Molecular and clinical epidemiology of carbapenem-resistant Enterobacterales in the USA (CRACKLE-2): A prospective cohort study. *Lancet Infect Dis* 2020 Mar 6. doi: 10.1016/S1473-3099(19)30755-8. [Epub ahead of print].

Van Duin and colleagues in the Multi-Drug Resistant Organism Network Investigators group examined the clinical and molecular aspects of carbapenem-resistant Enterobacterales (CRE) in the CRACKLE-2 study. They prospectively examined CRE isolates from 1,040 patients from 49 hospitals in 15 states between April 2016 and August 2017. They used the 2015 Centers for Disease Control and Prevention (CDC) definition of CRE, which includes isolates with resistance to any carbapenem, including ertapenem. The rate of hospital admissions with CDC-defined CRE was 57 per 100,000. Urine isolates accounted for 39% of the total, followed by respiratory, blood, and wound isolates in 26%, 13%, and 13%, respectively. Forty-three percent were the cause of infection, while 57% were colonizers.

The investigators classified the Enterobacterales isolates into three groups: 618 (59%) that proved to have carbapenemase genes (CPE); 194 (19%) confirmed as CRE but without a carbapenemase gene; and 228 (22%) that had been identified as CRE at local laboratories but that did not contain such a gene and that could not be confirmed as carbapenem-resistant in two central laboratories (unconfirmed CRE). Of the 593 *Klebsiella pneumoniae* isolates identified by local laboratories as CRE, 493 (83%) were CPE, while this was true for 46 (24%) of 192 *Enterobacter* species, and 38 (31%) of 122 *Escherichia coli*. The most frequently identified carbapenemase genes were $bla_{\text{KPC-3}}$, bla_{NDM}, and $bla_{\text{OXA-48-like}}$, which were detected in 51%, 41%, and 3%, respectively. In addition, extended-spectrum β-lactamase (ESBL) genes also were detected frequently in CPE: bla_{SHV} in 35% and $bla_{\text{CTX-M}}$ in 20%; the latter was detected more frequently in CRE without a carbapenemase (30%). Carriage of bla_{AmpC} was detected in 58% of non-CPE CRE and in 62% of unconfirmed CRE, while mutations of outer membrane porin (OmpK35, OMPk36) protein genes were present in 62% and 21% of these, respectively.

Among those with infection due to CDC-defined CRE, the 30-day mortality did not differ significantly by organism classification, ranging from 22% to 25%, while the 30-day mortality in those who were colonized was only 19%. Ninety-day readmission rates for those discharged were 46% for those infected and 40% for those only colonized.

■ COMMENTARY

Resistance of Enterobacterales to carbapenems generally is the result of either the production of carbapenemase or a combination of alterations of outer membrane proteins resulting in impaired ingress of the antibiotic together with hyperproduction of an ESBL or ampC cephalosporinase.

This study provides an important overview of CRE in the United States. Some of the results are of particular interest. Thus, although the mortality rates were high, there was no significant difference between infections due to CRE with or without a detectable carbapenemase — a result that differs from the one previously reported in a small, single-center study.

Also of interest was that infections for which the CDC definition of CRE could not be confirmed by two central laboratories also were not associated with a significant comparative difference in mortality. Finally, there was little difference in mortality or readmission rates in patients who were infected or only colonized with CRE. The latter indicates that the detection of CRE is an indicator of the fact that a patient is at high risk of a poor outcome for reasons over and above the presence of the organism.

One in five isolates labeled as carbapenem-resistant by local laboratories could not be confirmed to be resistant to any of the carbapenems, including ertapenem. This has important implications regarding the use of in-hospital isolation as well as of appropriate antibiotic therapy. ■

ABSTRACT & COMMENTARY

Antibiotic Therapy to Reduce the Incidence of Ventilator-Associated Pneumonia After Cardiac Arrest

By Vibhu Sharma, MD

Assistant Professor of Medicine, University of Colorado, Denver

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

SYNOPSIS: In this prospective, randomized trial, intravenous amoxicillin-clavulanate (dosed three times daily and given for two days) administered to patients admitted with out-of-hospital cardiac arrest due to a shockable rhythm reduced the incidence of early ventilator-associated pneumonia.

SOURCE: François B, Cariou A, Clere-Jehl R, et al; CRICS-TRIGGERSEP Network and the ANTHARTIC Study Group. Prevention of early ventilator-associated pneumonia after cardiac arrest. *N Engl J Med* 2019;381:1831-1842.

This prospective, randomized controlled trial assessed whether prophylactic antibiotic therapy with intravenous amoxicillin-clavulanate (IVAC) administered to adult patients undergoing targeted temperature management (TTM) to 32-34°C after out-of-hospital cardiac arrest due to a shockable rhythm would reduce the incidence of ventilator-associated pneumonia (VAP). A total of 1,116 patients were assessed for eligibility, and 198 underwent randomization. Most exclusions were because of either a non-shockable rhythm (30%) or in-hospital cardiac arrest (20%). Other reasons for exclusion included preexisting pneumonia, abnormal chest X-ray at presentation, ongoing antibiotic therapy, witnessed aspiration during initial intubation, moribund status, or ≥ 6 hours between return of spontaneous circulation and randomization. The method of TTM was not standardized, but rapid achievement of hypothermia was required. All patients received a bundle of interventions to prevent VAP (e.g., head of the bed elevation, daily spontaneous awake trial [SAT], and daily spontaneous breathing trial [SBT]). Patients were randomized to IVAC 1 g or intravenous (IV) placebo three times daily for two days.

The primary endpoint was the incidence of VAP and required clinical criteria, imaging, and microbiological criteria. The Clinical Pulmonary Infection Score (CPIS) was calculated to determine whether VAP was present, with a score > 6 implying a higher probability of VAP. This score incorporates several criteria with points assigned for each: tracheal secretions characterized as rare/abundant/abundant and purulent, chest X-ray findings, fever or hypothermia, white blood cell count, PaO_2/FiO_2 ratio, radiographic progression, and exclusion of congestive heart failure (CHF) and acute respiratory distress syndrome (ARDS). A CPIS > 6 was required based on these criteria. In addition, two or more of the following were required: auscultatory findings of pneumonia or consolidation, ventilator changes reflecting worsening ventilation/perfusion (V/Q) mismatch, or worsening PaO_2/FiO_2 ratio. Radiographic criteria included new or worsening consolidation, and microbiologic criteria included a positive respiratory culture at prespecified thresholds of 10^6 colony forming units (CFU) for endotracheal aspirates and 10^4 CFU for bronchoalveolar lavage (BAL) specimens. The specific sampling technique of the lower respiratory tract was "at the discretion of the attending physician." Blood cultures were obtained upon suspicion for VAP as well. VAP was defined as early if the occurrence was noted within seven days and late if it occurred after seven days of arrest. A final diagnosis of VAP was based on the clinical, radiologic, and microbiologic criteria, with all information available to a committee composed of two experienced intensivists. In the event of disagreement with respect to the diagnosis, a third intensivist arbitrated the final diagnosis.

The investigators reported 80 cases of VAP; however, the adjudicating committee only reported cases with pathogen documentation (60 of the 80). The initial rate of agreement on a VAP diagnosis among these 60 patients was 78%, requiring an adjudicator in the remaining 22%. Among patients receiving the antibiotic intervention, 33% of the sampled lower respiratory tract secretions grew bacterial pathogens, whereas among those receiving placebo, 62% of the sampled secretions grew pathogenic

bacteria. Cases deemed to be "colonization" based on culture results were excluded for analysis by the adjudication committee. IVAC reduced the risk of early VAP but not late VAP, with a hazard ratio (HR) of 0.53 (95% confidence interval [CI], 0.31 to 0.92; $P = 0.03$). There was no difference in ICU length of stay, nonpulmonary secondary infections, or the development of multidrug-resistant organisms out to seven days after treatment with IVAC. Mortality was unaffected by treatment with IVAC.

■ COMMENTARY

Patients undergoing TTM are at increased risk for infections, particularly pneumonia. This is hypothesized to be because of the prolonged activation of NF-κβ and augmented generation of cytokines in the setting of hypothermia.[1] An impaired immune response to gram-negative bacteria after cardiac arrest also has been hypothesized to play a role regardless of body temperature.[2] The patients in this study were a relatively young (median age approximately 60 years), majority male, and presumably community-dwelling group (although this is not specified).

This study demonstrates the difficulty of diagnosing a simple condition for the purposes of a clinical trial. Confirmation of VAP required multiple clinical criteria as detailed earlier, some of which have a questionable interrater reliability (e.g., auscultation). The CPIS is cumbersome to compute and is based on several criteria, some of which are observer-dependent, and, therefore, subjective. Tracheal secretion characteristics and progression of pulmonary opacities are examples. One study found that the specificity of a CPIS > 6 for diagnosing VAP on day 3 was only 47%, with a sensitivity of 89%.[3] The authors of the ANTHARTIC study accepted that, "The diagnosis of VAP remains complex owing to considerable heterogeneity in its definition." A total of 80 patients were reported by the investigators to have VAP based on several criteria; however, only 60 were diagnosed with VAP by the adjudication committee. The initial rate of agreement by the two adjudicators for these 60 patients was 78%, implying that for 33 of the original 80 patients (41%) diagnosed as VAP by the investigators, the diagnosis was uncertain at best.

This study assumes that all VAP is diagnosed only if microbiologic cultures are positive and at a certain clinical threshold. The microbiologic thresholds as described are not used routinely in clinical practice, and the panel making updated recommendations for hospital-acquired pneumonia (HAP)/VAP in 2016 recommended against using them.[4] Arguably, from a practical perspective, VAP may be diagnosed and treated in the absence of clearly positive microbiological cultures if multiple other clinical criteria point to the diagnosis. Cases with culture results deemed to be "colonization" were excluded from the analysis and were not reported. The flow diagram for the trial documented only one case with colonization excluded prior to randomization, but the number excluded after randomization due to "colonization" was not reported.

With respect to the bacterial pathogens reported, the majority were susceptible to IVAC and, while this may be true of the pathogens in intensive care units (ICUs) in Europe, this may not be true of ICU settings in other parts of the world. About one-third (35%) of all bacteria isolated were those that colonize the upper respiratory tract and included *Haemophilus influenzae*, *Streptococcus pneumoniae*, streptococcal species, *Neisseria* species, and *Moraxella*, suggesting that at least some of these events were simply due to aspiration of upper airway secretions that had not been apparent at the time of enrollment. Most of these pathogens were sensitive to the antibiotic being tested. The authors did not report on the number of events (i.e., VAP) diagnosed within the first two days of intubation; these would be classified more typically as community-acquired pneumonia (CAP). The authors also did not report on the proportion of *Staphylococcus aureus* species isolated that were resistant to methicillin. While staphylococci were overrepresented in the control group (14% vs. 9% in the intervention group), the relative proportions of methicillin-resistant *S. aureus* (MRSA) would be important for purposes of determining antibiotic efficacy. Finally, the investigators did not define what the diagnoses were in the 20% of cases deemed not to be VAP.

In summary, while the authors made a valiant attempt to diagnose VAP with high certainty, there were shortcomings. A more pragmatic trial may have been to randomize all 80 patients initially diagnosed with VAP. Until more outcome data are available, it may be prudent to prophylactically treat only those post-arrest comatose patients who are younger and community-dwelling (such as those enrolled in this study) and those with hypothermia targeted to 33° C rather than targeted normothermia, given some evidence of immunoplegia in the setting of hypothermia. IVAC is not available for use in the United States. Intravenous ampicillin/sulbactam may be a reasonable alternative once consideration has been given to institution/community-specific antibiograms. ■

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PHARMACOLOGY UPDATE

Lefamulin: Formulary Considerations

By Samit Patel, PharmD

Clinical Pharmacist, Hematology/Oncology, Stanford Health Care

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

The Food and Drug Administration (FDA) recently approved lefamulin for the treatment of adults with community-acquired bacterial pneumonia (CABP) caused by the following organisms: *Streptococcus pneumoniae*, *Staphylococcus aureus* (methicillin-susceptible isolates), *Haemophilus influenzae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*. It does not have activity against *Enterobacteriaceae* and *Pseudomonas aeruginosa*. Lefamulin is a pleuromutilin antibacterial that inhibits bacterial protein synthesis. Because pleuromutilin drugs have a unique mechanism, they have low cross-resistance with other classes of antibiotics.[1,2]

DOSAGE

Lefamulin can be administered orally or intravenously (IV). For IV administration, the lefamulin dose is 150 mg every 12 hours (infused over 60 minutes). Oral lefamulin is given at 600 mg every 12 hours. The medication should be administered at least one hour before a meal or two hours after a meal. The duration of therapy is a minimum of five days and varies based on disease severity and response to therapy.

There is no dose adjustment for renal impairment. For hepatic impairment, oral therapy is not recommended for moderate to severe hepatic impairment (Child-Pugh class B or C). For IV therapy, dose adjustment (to 150 mg every 24 hours) is needed for severe hepatic impairment (Child-Pugh class C). Patients with severe hepatic impairment receiving IV therapy had prolonged half-lives of the drug compared to those with normal hepatic function (17.5 h vs. 11.5 h), and reduced lefamulin protein binding. On average, unbound lefamulin plasma AUC0-inf was increased threefold in subjects with severe hepatic impairment compared to those with normal hepatic function.[1]

ADVERSE EFFECTS

The most common adverse effects were diarrhea (12%), administration site reaction (7%), nausea (3-5%) and vomiting (3%), hepatic enzyme elevation (2-3%), hypokalemia (2%), and headache (2%).[1,3,4]

DRUG INTERACTIONS

Lefamulin is metabolized primarily by CYP3A4. Concomitant use of lefamulin injection and lefamulin tablets should be avoided with strong and moderate CYP3A4 inducers or P-gp inducers. Concomitant use of lefamulin tablets should be avoided with strong CYP3A inhibitors or P-gp inhibitors. Patients should be monitored carefully for adverse reactions with concomitant use of lefamulin and another CPY3A substrate.[1]

Concomitant administration of oral lefamulin with CYP3A4 substrates is contraindicated because it may result in increased plasma concentrations of these medications, leading to QT prolongation and cases of torsades de pointes.

CONTRAINDICATIONS/WARNINGS/ PRECAUTIONS

Use of lefamulin should be avoided in patients who have known QT prolongation, ventricular arrhythmias including torsades de pointes, and in those who are receiving drugs that prolong the QT interval, such as antiarrhythmic medications.[1]

Based on animal studies, lefamulin may cause harm to a fetus, including fetal mortality, decreased fetal body weight, and developmental delays. Females of reproductive potential should be advised about the potential risk to a fetus and to use effective contraception during use of lefamulin and up to two days after the last dose of the medication.[1]

Studies in animals indicate that lefamulin was concentrated in the milk of lactating rats. Because of the potential for serious adverse effects, including QT prolongation, women who are lactating should pump and discard human breast milk for the duration of treatment with lefamulin and for two days after the last dose.[1] *Clostridium difficile*-associated diarrhea has been reported with lefamulin.[1]

CLINICAL TRIALS/EVIDENCE SUMMARY

Lefamulin's safety and efficacy were based on two Phase III trials, LEAP Trial 1 and 2.[3,4]

In the LEAP Trial 1, 276 patients were randomized to IV lefamulin and 275 patients were randomized to IV moxifloxacin with or without linezolid (both groups had the option to switch to oral therapy after at least three days). IV lefamulin demonstrated noninferiority with the end point of early clinical response at three to five days after the first dose in the intent-to-treat analysis, 87.3% with lefamulin vs. 90.2% moxifloxacin with or without linezolid.[3]

The LEAP Trial 2 compared oral therapy, randomizing 370 patients to lefamulin and 368 patients to moxifloxacin. Oral lefamulin demonstrated noninferiority with the end of point of early clinical response after the first dose in the intent-to-treat analysis, 90.8% in both groups.[4]

COMPARATIVE COST

The cost of a five-day course of lefamulin oral therapy is $1,650 (based on a 600 mg tablet average wholesale price of $165) and IV therapy is $1,230 (based on a 150 mg vial average wholesale price of $123).

CLINICAL IMPLICATIONS

Lefamulin is a novel agent indicated for CABP. Patients can be treated with oral or IV therapy, allowing for avoidance of hospitalization or expediting discharge from the hospital. Its unique mechanism of action also may help in lowering the development of resistance. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Complications of Typhoid Fever

SOURCE: Cruz Espinoza LM, McCreedy E, Holm M, et al. Occurrence of typhoid fever complications and their relation to duration of illness preceding hospitalization: A systemic literature review and meta-analysis. *Clin Infect Dis* 2019;69(Suppl 6):S435-S448.

These authors performed a meta-analysis of published reports of typhoid fever treatment to determine whether complications occur more frequently in children vs. adults, and the degree to which delay in diagnosis and treatment increases the risk for complications. Only studies with culture-confirmed disease were included in the analysis (stool, blood, bone marrow). The authors reviewed eight published studies from seven different countries that included sufficient descriptive data for use in meta-analysis. Six of these included persons of all ages, five focused only on treatment in adults, and two only on treatment in children. Originally it was believed that patients presenting more than two to four weeks into their illness would be at increased risk for complications. However, examination of pooled data found that patients presenting 10 days or more after symptom onset were at increased risk for severe disease, and this was used as a cut point for data analysis.

The pooled prevalence of complications in hospitalized patients with positive blood cultures for *Salmonella* typhi was 27% (95% confidence interval [CI], 21-32%), although there was significant variability in the frequency of reported complications between the 13 studies. Examination of pooled data revealed that patients presenting ≥ 10 days after the onset of symptoms were at greater risk for complications and hospitalization compared with those presenting with < 10 days of symptoms (36% vs. 16%), and were at three times greater risk of severe disease (odds ratio [OR], 3.0; $P < 0.0001$). Pooled prevalence data

also showed that complications in children were significantly higher than in adults (27% vs. 17%), although, again, there was significant variability between the studies.

The most frequent complications observed in pooled data were encephalopathy (7.3%), gastrointestinal bleeding (5.2%), and nephritis (4.8%). However, the most frequent complications in those presenting for care < 10 days after symptom onset were hepatitis (5.1%) and gastrointestinal bleeding (4.0%). In contrast, complications in those presenting ≥ 10 days into their course included encephalopathy (18%) and gastrointestinal bleeding (14%). Less frequent complications, occurring ≥ 10 days after symptom onset, and which were unusual in those presenting earlier in their course, included myocarditis (3.9%), cholecystitis (3.4%), osteomyelitis (2.2%), and intestinal perforation (1.1%).

Complications of typhoid fever in bacteremic patients requiring hospitalization are much more frequent than previously estimated, based on pooled prevalence data. Risks for more severe disease are much greater in children than adults, and in those presenting with 10 or more days of symptoms before diagnosis and treatment is begun.

Do I Smell a Rat? Or Is the Rat Smelling Me?

SOURCE: Fiebig L, Beyene N, Burny R, et al. From pests to tests: Training rats to diagnose tuberculosis. *Eur Respir J* 2020;55:1902243.

Researchers have spent years training giant Gambian rats to sniff out tuberculosis (TB) in sub-Saharan Africa. Preliminary data from this work were presented in this column in 2003 and 2010. By 2010, researchers reported that trained technicians detected positive acid-fast bacilli (AFB) smears by light microscopy in 10,523 specimens, but the rats performed slightly better, detecting an additional 600 specimens missed by the technicians. Overall, Gambian rat sniffing was 89% sensitive for detection of TB in expectorated specimens, compared with culture results.

Since then, the rats have continued to improve, detecting more than 16,000 cases of TB in three different African countries, with a sensitivity of > 90% and a specificity of > 70%. This is better than World Health Organization requirements for laboratory methods for detection of TB. But there was one major hurdle: getting the "rat test kit" to the clinical site. Previously, the rats were sniffing heat inactivated samples at a central research laboratory, which, since 2018, was performing confirmatory molecular testing also. Significant delays were occurring in getting specimens to the lab — and the results back to the communities — by which time many patients were lost to follow-up. By moving the lab closer to the communities being tested, and using a network of motorbike couriers, samples have been processed more quickly. (No, the rats did not get to ride the motorbikes.)

But an interesting question remained. What were the rats actually smelling in the specimens? Analytical chemistry provided a surprising answer. Like many active infections, different bacteria exude a pattern of specific volatile compounds. It turned out that the rats were indeed smelling TB infection. While TB may share certain volatile chemicals with other bacteria or non-tuberculous bacteria, it was a complex pattern of volatiles specific to TB that the rats were detecting. It is odor pattern recognition — much like waking up in the morning and smelling the coffee.

Cloth Masks — Just for Looks?

SOURCE: MacIntyre CR, Seale H, Dung TC, et al. A cluster randomised trial of cloth masks compared with medical masks in healthcare workers. *BMJ Open* 2015;5:e006577.

Friends and family are busy sewing charming face masks with sunflowers and kitties. My sister had not had her sewing machine out for 20 years until forced to shelter at home with little to do, and made beautiful masks for her family.

But how effective are these fabric masks? This randomized clinical trial evaluated the effectiveness of cloth vs. regular procedural masks in 1,607 healthcare workers (HCWs), recruited for study at 14 different hospitals in Hanoi, Vietnam, in 2011. The HCWs worked full-time in 74 high-risk units of the hospital, including the emergency departments, intensive care, and infectious disease units. The HCWs were randomized to wear a regular procedural mask, cloth mask, or no mask throughout an eight-hour shift for four weeks. Then they were followed for an additional one week for signs of respiratory illness. Either two procedural masks were provided to each worker per shift, or five cloth masks were provided per month, which were to be washed and rotated throughout the four-week study period. HCWs also were asked to wear their masks throughout their shifts, except for tea, meal, and bathroom breaks. Each HCW maintained a diary of the number of patient contacts per shift and their activities, including suctioning, sputum induction, intubation, bronchoscopy, etc. At the first onset of symptoms, HCWs reported for evaluation and respiratory polymerase chain reaction (PCR) panel testing.

HCWs had an average of 36 patient contacts per day. Those with cloth masks reported that they washed their masks 23 of 25 days (97%), either at home (80%), using the hospital laundry (4%), or both (16%).

Despite the fact that workers reported better compliance with cloth masks, an intent to treat analysis showed that rates of clinical respiratory illness, influenza-like illness (ILI), and laboratory-confirmed respiratory infection were significantly higher in the cloth mask group compared with the procedural mask group. Laboratory confirmation of respiratory viral infection was detected in 31/659 (5.5%) of cloth mask users vs. 19/580 (3.3%) of the medical mask users. The relative risk of ILI in the cloth mask group, compared with the other groups, was 13.25. Surprisingly, no significant difference was observed in the rates of infection between those wearing medical masks and those without masks. The reported frequency of hand washing was found to be significantly protective against clinical respiratory illness.

In the laboratory, the penetration of particles through cloth masks was significantly higher (97%) than with either medical masks (44%) or N95s (< 0.01%).

In addition to barrier protection, it is conceivable that other factors may be responsible for this observed difference in the risk of respiratory illness. Workers may re-adjust cloth masks more often than medical masks. Certain types of cloth used for cloth masks may be better at "acquiring" viral particles as workers move through their day, or the warm moisture from breathing may allow improved virus survival on masks. ■

CME QUESTIONS

1. Which statement is true based on the study by Herren et al?

a. More people have died of COVID-19 than of malaria in the past year.

b. Insecticide-treated bed nets did no good in reducing malaria mortality.

c. Mosquitoes infected with a microsporidian will not ingest *Plasmodium* parasites.

d. Infection of a mosquito with a microsporidian can block the transmission of malaria parasites.

2. Which of the following is correct regarding lefamulin?

a. It is a pleuromutilin and inhibits bacterial protein synthesis.

b. It has no effect on QTc interval.

c. It has no drug-drug interactions.

d. It is active in vitro against most isolates of *Pseudomonas aeruginosa*.

3. Which of the following is correct regarding carbapenem-resistant Enterobacterales (CRE) as found in the study by van Duin et al?

a. A frequent cause for their resistance is a mutation in a penicillin binding protein.

b. The presence of a carbapenemase in CRE was associated with increased mortality when compared to isolates lacking this enzyme.

c. Patients with CRE infections were more likely to die than those who were only colonized with CRE.

d. The most frequently encountered carbapenemase was bla_{KPC}.

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.