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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Treatment of Gram-Negative Bacteremia: How Long Is Long Enough?

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: Antibiotic administration for seven days is sufficient in stable patients with Gram-negative bacteremia.

SOURCE: Yahav D, Franceschini E, Koppel F, et al; Bacteremia Duration Study Group. Seven versus fourteen days of antibiotic therapy for uncomplicated Gram-negative bacteremia: A non-inferiority randomized controlled trial. *Clin Infect Dis* 2018; doi: 10.1093/cid/ciy1054. [Epub ahead of print].

Yahav and colleagues examined the question of the necessary duration of antibiotic therapy in 604 patients with bacteremia due to aerobic Gram-negative bacilli in a randomized, open-label, noninferiority trial. Ninety percent of infections were due to *Enterobacteriaceae*, mostly *Escherichia coli*, while *Pseudomonas* was isolated in 7.5% of cases. The urinary tract was the source of infection in two-thirds of cases. Patients who were hemodynamically stable and afebrile for at least 48 hours were randomized to receive a total antibiotic therapy course of either seven or 14 days.

The noninferiority margin was set at 10%. The primary composite outcome, including mortality, clinical failure, and readmissions or extended hospitalization at 90 days, occurred in 140/306 (45.8%) of those who received seven days of therapy and in 144/298 (48.3%) of those who received 14 days of therapy (difference, -2.6%; 95% confidence interval [CI], -10.5% to 5.3%).

Researchers found no significant differences for any of the individual components of the composite outcome, including all-cause 90-day mortality, which was 11.8% and 10.7% in the

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short- and long-duration therapy groups, respectively. The duration of appropriate antibiotic therapy was seven days fewer in the short-duration group. Investigators observed no significant difference in the frequency of adverse events between the treatment groups.

■ COMMENTARY

The results of this trial indicate that a seven-day course of antibiotic therapy was noninferior to treatment for 14 days in patients with Gram-negative bacteremia, the majority of whom were infected with *E. coli* and for whom the source of bloodstream infection was the urinary tract.

These results are consistent with those of several mostly retrospective studies, which were briefly reviewed by the authors. Therefore, they are totally unsurprising. However, it could be argued that the results are biased by the large proportion of patients with a urinary source, which often may be cleared more readily.

[We are beginning to develop the necessary data that allow us to turn back the tide of overly prolonged antibiotic therapy and its attendant adverse consequences.]

Clinicians have long given overly prolonged courses of antibiotics for various infections. This practice often includes infectious disease specialists, whose contribution to the problem is likely disproportionate because of their influence over other clinicians. Fortunately, we are beginning to develop the necessary data that allow us to turn back the tide of overly prolonged antibiotic therapy and its attendant adverse consequences regarding microbiome alteration, selection of resistance, superinfection, allergic reactions, and direct drug toxicity. ■

ABSTRACT & COMMENTARY

A Nosocomial Outbreak at the NIH Clinical Center From *Sphingomonas koreensis*, a Rare Human Pathogen

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 genomic and epidemiologic investigation of an outbreak at the National Institutes of Health Clinical Center determined that *S. koreensis* was an opportunistic human pathogen that persisted in a reservoir in the hospital plumbing.

SOURCE: Johnson RC, Deming C, Conlan S, et al. Investigation of a cluster of *Sphingomonas koreensis* infections. *N Engl J Med* 2018;379:2529-2539.

Sphingomonas koreensis is a nonfermenting, Gram-negative bacillus that resides in aqueous reservoirs. It is a very rare human pathogen, with only two previously published cases. Johnson and colleagues reported the results of an epidemiologic investigation of an outbreak of *S. koreensis* that occurred at the National Institutes of Health (NIH) Clinical Center.

NIH opened a new inpatient hospital building in 2005. In 2016, a cluster of *Sphingomonas* infections was identified

that occurred in 37 patients starting in 2001. Between 2006 and 2016, 12 clinical isolates of *S. koreensis* were identified. The median length of stay was 44 days until a positive culture occurred. Nine of the 12 patients were stem-cell transplant recipients and eight had *S. koreensis* bacteremia. One patient had *S. koreensis* grow from a urine culture with a low colony count, which was thought to represent bacteriuria and not a true urinary tract infection. Three of the 11 patients died. Of the six *Sphingomonas* cases identified in 2016, four were *S. koreensis*. Because of the association between *Sphingomonas* and water sources, between November 2016 and December 2017 the investigators obtained samples from faucets in the rooms where patients were residing when they acquired *S. koreensis* infections, the main municipal intake pipe, smaller pipes supplying the rooms with known culture-positive sinks, ice machines, and the isolated components from three disassembled culture-positive sinks, including any visible biofilm. Investigators used whole-genome DNA sequencing and shotgun megagenomic sequencing to assess the clinical and environmental isolates.

S. koreensis grew in 22 of 56 (39%) samples from faucets and nine of 17 (53%) water samples collected from faucets in the rooms of patients who had *S. koreensis*. Nine faucets that were positive for *S. koreensis* were replaced, but six became recolonized within five to 90 days.

The environmental samples were resistant to multiple antibiotics, which matched the patient isolates. Furthermore, isolates taken from sink components and water samples had > 99.7% average nucleotide identity to the *S. koreensis* isolated from clinical samples in 2016. This is strong evidence that the sinks or water was the most likely source of the nosocomial *S. koreensis* outbreak. Interestingly, the chlorine concentration in the cold water was adequate, but it was well below the recommended value in the hot water. Also, the hot water temperature ranged from 46-49°C, which is lower than the hospital standard of 51°C or greater. In December 2016, the free concentration of chlorine was increased to 1.0 mg/L in the hot water, and the water temperature was increased from 46-49°C to 60°C. No further *S. koreensis* infections occurred after these measures were implemented. In addition, subsequent environmental cultures from sinks immersed in 71°C water baths for 20 minutes were negative.

■ COMMENTARY

The transmission of waterborne pathogens, such as *Legionella*, *Pseudomonas*, and nontuberculous mycobacteria, is a well-known risk in healthcare settings and occasionally can lead to institutional outbreaks. For such an event to occur at the NIH Clinical Center is disconcerting, but not unfathomable. Previous studies have shown that waterborne bacteria colonize pipes in newly constructed facilities not yet in use in which water has stagnated. This likely is the route by which the *S. koreensis* disseminated throughout the hospital.

[The pervasiveness of *Sphingomonas* in clean water supplies makes it a conundrum for healthcare institutions, especially for immunocompromised patients.]

The *S. koreensis* isolates were resistant to multiple antibiotics, including aminoglycosides, beta-lactams, and levofloxacin. They were susceptible to trimethoprim-sulfamethoxazole and ciprofloxacin. Other *Sphingomonas* clinical isolates were less antibiotic resistant. The pervasiveness of *Sphingomonas* in clean water supplies makes it a conundrum for healthcare institutions, especially for immunocompromised patients. It is notable that nine of the 12 clinical samples with *S. koreensis* came from stem-cell transplant patients, underscoring the risk these patients face from waterborne bacteria. The steps taken by the staff at the NIH Clinical Center to mitigate their *S. koreensis* outbreak are effective against many opportunistic waterborne pathogens and should be applicable to other healthcare settings.

One limitation to the study is the lack of metagenomic data for the isolates prior to 2016 from patients and sinks. Another is that the genomic methods used are not yet widely available, thus limiting the generalizability of the methods to other settings. It is hoped that as the cost of metagenomic analysis decreases, its use as part of epidemiologic investigations will become more commonplace.

Patients go to healthcare institutions with the goal of getting better and do not expect to acquire a nosocomial infection. Clinicians and microbiologists alike must be vigilant in recognizing unusual clusters of illnesses and ideally have access to sophisticated methods, such as whole-genome sequencing, to rapidly identify and curtail nosocomial outbreaks. ■

ABSTRACT & COMMENTARY

Duration of Intravenous Antibiotic Therapy for Late-Onset Neonatal Group B Streptococcal Bacteremia

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: Although standard treatment of late-onset neonatal group B *Streptococcus* bacteremia includes intravenous antibiotic therapy for 10 days, shorter courses seem safe and effective.

SOURCE: Coon ER, Srivastava R, Stoddard G, et al. Shortened IV antibiotic course for uncomplicated, late-onset group B streptococcal bacteremia. *Pediatrics* 2018;142:e20180345.

During the first three months of life, group B *Streptococcus* is a leading cause of serious bacterial infection. The use of intrapartum antibiotics in mothers colonized by group B *Streptococcus* has reduced the risk of neonatal infection during the first week of life, but it has not significantly altered the risk of subsequent infection. In the United States, 0.03% of newborns become ill with late-onset group B *Streptococcus* infection. Although current recommendations are that babies with uncomplicated late-onset group B *Streptococcus* infection be treated with intravenous antibiotics for 10 days, there are no actual data suggesting that this duration of treatment is better than shorter-course treatment. Anecdotally, babies treated for less than 10 days sometimes do well and sometimes experience recurrent infection. Of course, longer courses of intravenous antibiotics also are associated with increased costs and, especially with the placement of central catheters, potentially more complications.

Thus, Coon and colleagues reviewed treatment and outcomes data from the Pediatric Health Information System database, which includes patients at 49 stand-alone children's hospitals in the United States. Included patients had been dismissed from a participating hospital prior to 4 months of age with a diagnosis of group B streptococcal disease and bacteremia sometime between January 2000 and September 2015. Patients were identified as having "uncomplicated" disease by the absence of a concurrent diagnosis of meningitis, osteomyelitis, septic arthritis, or a significant co-infection and by the absence of marked prematurity (< 29 weeks of gestation), a prolonged hospital course (more than 14 days), or receipt of intensive care services. Patients who received a peripherally placed central catheter were assumed to have received longer antibiotic courses (even if post-discharge home intravenous antibiotics were not identified in the database). Only patients admitted after 7 days of age were included.

A total of 1,369 infants were identified as potential study participants. Of them, 594 were excluded based on exclusion criteria, leaving 775 babies to be evaluated. Of those, 612 (79%) had received more than eight days of antibiotic therapy, and 163 (21%) received eight or fewer days of intravenous antibiotic treatment. The infection occurred at a median age of 48 days. Shorter courses of treatment were more likely in older children, in the later years of the study, and in infants with concurrent urinary tract infection. The source of payment was not statistically significantly associated with the duration of antibiotic treatment, nor was race or ethnicity.

Among patients treated with shortened intravenous courses, 16% were discharged with an oral antibiotic. The use of shortened antibiotic courses varied by hospital, with 14 of the participating 49 hospitals never using shortened courses and five hospitals using shorter courses in more than half of their patients.

Overall, 2.2% of studied infants had subsequently repeated group B streptococcal infection, 1.8% of those with longer treatment and 2.3% of those with shortened courses of treatment (the rates were not statistically different). None of the children receiving oral antibiotics at discharge had recurrent infection. One percent of patients experienced complications of central line use.

The authors pointed out that prolonged antibiotic courses can be complicated with adverse outcomes. They summarized their novel findings about management of uncomplicated late-onset group B *Streptococcus* bacteremia by saying that shortened courses of intravenous antibiotics are prescribed, with low rates of recurrence.

■ COMMENTARY

This new study points out several features of common evidence-based medicine practice. First, the evidence for the duration of antibiotic treatment is limited to what has been studied, and there is a dearth of comparative studies on the effectiveness of shorter durations. Second, as time goes on, physicians increasingly are switching to shorter courses of treatment, even without published evidence and guidelines to support such a practice. Third, the application of evidence-based medicine varies with the habits of peers — as seen by the variation between hospitals in using shorter antibiotic courses. Fourth, despite the common adage to "do no harm," this new paper shows that longer intravenous antibiotic courses do not necessarily help outcomes and it adds concrete data about the frequency of significant complications ("harm") of intravenous lines used for antibiotic treatment.

Clearly, there has been a move over recent years to use shorter courses of antibiotics, and supportive data sometimes follow the early adaptation of practice change. Uncomplicated urinary tract infections, even in children, are treated for fewer days than when some of us were in training. More recently, serious bone and joint infections have been treated with shorter intravenous courses. Resources do affect practice (but not necessarily outcomes), and the World Health Organization was recommending five-day antibiotic courses for pneumonia when most American physicians still were treating for 10 days.

In addition, there are newer data to guide treatment decisions. In a prospective study of 29 infants with early-onset group B streptococcal bacteremia, conversion from intravenous to oral treatment (amoxicillin 200-300 mg/kg/day) after 48 hours of therapy yielded highly bactericidal concentrations (> 5 mg/L) of the antibiotic in the blood of treated babies after 48 hours of oral therapy.[1]

Recurrent infection has been used often as an adverse outcome suggesting the inadequacy of initial treatment. However, infants colonized and infected with group B *Streptococcus* often live with family members who are similarly colonized. Many mothers who are colonized with group B *Streptococcus* during pregnancy still are colonized with the same clonal strain of bacteria one year later.[2] In addition, women transmit group B *Streptococcus* in their breast milk.[3] Thus, some subsequent infection after successful treatment of the initial bout of bacteremia could be due to re-colonization and re-infection rather than to failure of the initial treatment.

[The World Health Organization was recommending five-day antibiotic courses for pneumonia when most American physicians still were treating for 10 days.]

Finally, prior to rushing to uniformly short courses of intravenous antibiotics for bacteremic babies, readers of this study should remember that these data are based on the practices of clinicians. It is possible that the clinicians judged the patients who received longer courses to be sicker and to need longer courses (and not to have decided on antibiotic duration simply based on protocol or habit). The babies who were treated with shorter courses tended to be older. It might be premature to apply shorter courses to sick, younger babies.

As we await more data, pediatricians treating newborns with bacteremia can be aware of the possibility of shorter courses and the risks of longer intravenous courses. These data can help guide thoughtful practice. ■

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ABSTRACT & COMMENTARY

Rotavirus Vaccine and Hospitalization for Seizures

By Dean L. Winslow, MD, FACP, FIDSA

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

SYNOPSIS: In an analysis of insurance claims for 1.8 million U.S. children with 2,950 recorded seizures, researchers found that the risk of hospitalization for seizures was 24% lower in rotavirus-vaccinated children.

SOURCE: Burke RM, Tate JE, Dahl RM, et al. Rotavirus vaccination is associated with reduced seizure hospitalization risk among commercially insured US children. *Clin Infect Dis* 2018;67:1614-1616.

Researchers used data for 2006-2014 abstracted from the Truven Health commercial claims and encounters database. Among the 1,773,295 children who were eligible for analysis, there were 2,950 seizures recorded (654 seizures occurred before 6 months of age and were not included in the primary analysis). Seventy-one percent of children in the cohort were fully vaccinated, 15% were partially vaccinated, and 14% were unvaccinated against rotavirus. An extended Cox regression analysis provided a crude hazard ratio for seizure hospitalization of 0.66 when fully vaccinated and unvaccinated children were compared, and 0.88 for partially vaccinated compared to unvaccinated children.

■ COMMENTARY

Febrile seizures are a common reason for pediatric emergency department treatment and hospitalization, and of course are frightening events for the parents of an affected child. The robust data presented in this paper confirm the earlier estimate of an 18-21% risk reduction in one-year seizure risk among children vaccinated against rotavirus compared to children who were not vaccinated.[1]

It behooves all of us as adult and pediatric infectious disease specialists (and often as respected leaders in our communities) to advocate strongly for immunization against infectious diseases, especially in the current "anti-science" environment. Coincidentally, New York state now is in the midst of one of the largest measles outbreaks in U.S. history. This is almost entirely related to "anti-vax" sentiment and schools' lax enforcement of immunization requirements.[2] In my opinion, this is inexcusable in the 21st century. ■

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ABSTRACT & COMMENTARY

A Rabies Death in Virginia

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: A Virginia resident who had not received pre- or post-exposure prophylaxis died of rabies resulting from a dog bite during a prolonged trip to India. Many exposed healthcare workers subsequently received post-exposure prophylaxis.

SOURCE: Murphy J, Sifri CD, Pruitt R, et al. Human rabies — Virginia, 2017. *MMWR Morb Mortal Wkly Rep* 2019;67:1410-1414.

A 65-year-old woman in Virginia developed right arm pain and paresthesias and presented to an urgent care center three days later, on May 6, 2017. Clinicians diagnosed carpal tunnel syndrome. The following day, the patient was evaluated at a hospital with complaints of shortness of breath, anxiety, insomnia, and difficulty swallowing water. She was deemed to be experiencing a panic attack and was given lorazepam.

On May 8, she was admitted to a different hospital with chest discomfort, shortness of breath, progressive paresthesia involving the right shoulder and arm, and increased anxiety. The serum troponin was elevated (as was lactic acid). Angiography revealed normal coronary arteries. That evening, the patient became progressively agitated and combative and was noted to be gasping for air when attempting to drink water. This apparently led to questioning about animal exposures. Her husband reported that she had been bitten by a puppy in India six weeks previously. The patient had been part of a yoga tour in India from Jan. 28 to April 5, 2017, that included rural areas. It was confirmed that she had been bitten outside her hotel in Rishikesh. The wound was washed with water, but no further intervention was performed.

A diagnosis of rabies was confirmed on May 11 when rabies virus RNA was detected by RT-PCR on skin biopsy and saliva specimens, as well as rabies antigen detection on the skin specimen. Typing indicated that the virus was consistent with rabies virus circulation in dogs in India.

The patient became progressively more ill, required intubation, and died on May 21 after life support was withdrawn. An extensive and exhaustive epidemiological investigation was performed that included 250 healthcare workers, 72 (29%) of whom were advised to receive post-exposure prophylaxis. The cost of the rabies immune globulin and vaccine for this treatment was estimated at $235,000.

■ COMMENTARY

There is much to be learned from this unfortunate case. The patient initially received incorrect sequential clinical diagnoses of carpal tunnel syndrome, panic attacks, and coronary artery disease. This situation was associated with the potential exposure of many healthcare workers to the rabies virus until the diagnosis was made and the patient was placed in appropriate isolation.

[An even more critical issue is that this patient had been a candidate for rabies vaccination prior to travel.]

An even more critical issue is that this patient had been a candidate for rabies vaccination prior to travel, given the prolonged visit to India, including rural areas, as recommended by CDC. After she was bitten by a dog in India (one of 122 countries in which canine rabies virus is present), the only treatment provided was washing the wound with water, rather than post-exposure prophylaxis, which would have prevented her unfortunate outcome. ■

PHARMACOLOGY UPDATE

Rifamycin Delayed-Release Tablets (Aemcolo)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a new drug for the treatment of traveler's diarrhea (TD). Rifamycin sodium is the second in the class of rifamycin antibacterials (rifamixin) to be approved for this indication. The FDA granted qualified infectious disease product, priority review, and fast track designations. Rifamycin will be marketed as Aemcolo.

INDICATIONS

Rifamycin is indicated for the treatment of TD caused by noninvasive strains of *Escherichia coli* in adults.[1]

DOSAGE

The recommended dose is 388 mg (two tablets) orally twice daily for three days.[1] It should be taken with a glass of fluid (not alcohol) and can be taken with or without food. Rifamycin is available as 194 mg of rifamycin in a delayed-release formulation.

POTENTIAL ADVANTAGES

Rifamycin is formulated using a Multi Matrix (MMX) technology. The enteric-coated, pH-dependent polymer film allows the drug to be released in the distal small bowel and colon.[2] In addition to minimal systemic absorption, this targeted release reduces the risk of disturbing the microflora in the upper gastrointestinal tract.[3]

POTENTIAL DISADVANTAGES

It is not recommended for use in patients with diarrhea complicated by fever and/or bloody stool or caused by other (e.g., invasive) bacteria.[1]

COMMENTS

The approval of rifamycin was based on two randomized, Phase III trials. The authors of one trial compared the drug to placebo. In the second trial, the authors compared rifamycin to ciprofloxacin in subjects with TD.[1,4,5,6] In trial 1, subjects were randomized to rifamycin (two tablets twice daily for three days; n = 199) or matching placebo (n = 65). The primary endpoint was time to last unformed stool (TLUS) between the first dose of the study drug and the last unformed stool passed before the start of clinical cure.[5] Clinical cure was defined as passage of two or fewer soft stools or no watery stools, no fever, and no sign or symptoms of enteric infection during a 24-hour interval or no stools or only formed stools during a 48-hour interval. The median TLUS was 46 hours for rifamycin vs. 68 hours for placebo. Percent clinical cures were 81.4% compared to 56.9%, respectively.

In trial 2, the authors compared rifamycin (n = 420) to ciprofloxacin (500 mg twice daily) for three days (n = 415).[4,6] TLUS was 44.3 hours for rifamycin compared to 40.3 hours for ciprofloxacin, demonstrating noninferiority. Clinical cure rates were 85.0% compared to 84.8%. The risk of colonization by extended spectrum beta-lactamase-producing *E. coli* was more likely with ciprofloxacin than rifamycin. Adverse reactions associated with rifamycin in these trials were constipation (3.5%) and headache (3.3%).[1]

[Traveler's diarrhea is the most common travel-related illness, affecting 10-40% of travelers.]

CLINICAL IMPLICATIONS

TD is the most common travel-related illness, affecting 10-40% of travelers.[7] High-risk areas are Asia, Africa, the Middle East, Mexico, and Central and South America. The most common bacterial pathogens are enterotoxigenic and enteroaggregative *E. coli*. Less common pathogens include mucosa-invasive *Campylobacter jejuni*, *Shigella* spp, and *Salmonella* spp.[8] The International Society of Travel Medicine recommends azithromycin, ciprofloxacin, and rifaximin as options for moderate to severe TD, with azithromycin as the preferred agent to treat severe TD.[9] A fluoroquinolone (e.g., ciprofloxacin) and rifaximin are options if fluoroquinolone-resistant *E. coli* or invasive bacteria are not suspected.[9]

Rifamycin provides another potential option for noninvasive TD due to *E. coli*. Rifamycin has been shown to be noninferior to ciprofloxacin, but comparative efficacy to rifaximin has not been published. Azithromycin and ciprofloxacin can be given as a single dose (unless symptoms have not resolved in 24 hours) compared to a three-day course for rifaximin and rifamycin.[9] Rifamycin is expected to be available the first quarter of 2019. ■

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ABSTRACT & COMMENTARY

Playing Opossum: A New Model of Antibiotic and Immune Resistance

By Joseph F. John, Jr., MD, FACP, FIDSA, FSHEA

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

SYNOPSIS: Researchers observed nongrowing cells of *Salmonella* that remained persistent, resisted antibiotics, and retained infectivity.

SOURCE: Stapels DAC, Hill PWS, Westermann AJ, et al. *Salmonella* persisters undermine host immune defenses during antibiotic treatment. *Science* 2018;362:1156-1160.

Microbiologists in England, Germany, and the Netherlands recently have been studying the population of bacterial pathogens that lie dormant and metabolically inactive, as though dead. In her London lab, Sophie Helaine, senior author on this paper, showed in 2014 that nongrowing forms of one particular bacterial pathogen, *Salmonella enterica*, can enter macrophages and assume a nongrowing state — known as persisters — that does not respond to antibiotics. Earlier observations established that certain bacteria grown in vitro will have some cells that remains dormant, but these new observations about *Salmonella* were unique because the microbes could reassume pathogenicity.

Stapels and colleagues set out understand the metabolism of *Salmonella* persisters. Through the following set of experiments, they showed that antibiotic treatment of persisters after they infect bone-marrow macrophages selects an active set of persisters that can regrow and retain infectivity. Active persisters survive by expressing what is called a pathogenicity island that in *Salmonella* contains those genes that evade immune destruction.

In an elegant set of experiments using new molecular methods to detect gene expression even in single cells, researchers found that transcription and translation were retained in active persisters. Furthermore, they performed what is known as dual RNA sequencing of both bacterial and host cells. In so doing, the group demonstrated that genes translocated from the *Salmonella* pathogenicity island to host cells resulted in dampening of the immune response to the infecting *Salmonella*. Additional experiments on the type of macrophage altered to reduce immune reactivity allowed support of the hypothesis that downregulation of specific macrophages (M2 rather than M1 macrophages) by active persisters allows certain persisters to survive and reignite infection.

Taken together, this work on mechanisms of survival for a classic, major human pathogen highlights the cross talk between the bacterium and the host cell. In this case, active but nongrowing *Salmonella* retained the ability to make proteins that would depress the immune response, allowing *Salmonella* to resist antibiotic destruction and immune alteration.

■ COMMENTARY

Clinicians are familiar with some forms of bacterial trickery, such as spore formation to insure bacterial survival. Clinicians also know that certain bacteria, like *Salmonella* and *Listeria*, require an intracellular

sanctuary not only to survive but also to produce disease. The work of these scientists seems momentous to me. It reinforces the complexity of the bacterial infection. It is only with newer molecular methods that the complexity of cross talk between host and pathogen could be culled. Some parts of the bacteria are crucial to promote survival vs. destruction, either through antibiosis or immune attack. Pathogenicity islands are a good example of a kind of secret bullet within the bacterial genome that fires with initial infection and alters the host response so that the dormant persister remains nonresponsive to antibiotics but also has sensitized the host genome to alter its immune response.

The implications of this work are profound. First, this new type of antimicrobial resistance, the nonresponsiveness of the persister, is very challenging. Therapeutics would have to be devised to turn on the persister and find a way for it to respond adversely to the antimicrobial. Second, even if the persister can be spurred to interact with the antimicrobial, there needs to be an adequate immune response to effect killing intracellularly. Perhaps interrupting specific parts of the pathogenicity island with a CRISPR insertion could allow the host cell to regain the upper hand. Finally, do these results suggest that there is even further interaction between microbial invader and host cell, other than the immune escape shown in this experimental design, that produces additional survival advantages?

Clinicians will need to adopt new terminology. In staphylococcal infection, we now have concern for another kind of persister, the small colony variant. But small colony variants, seen also in other genera, continue to metabolize. In the *Salmonella* persisters of this current work, we are facing a newly discovered entity that evades both antimicrobial attack and immune subversion. New imaging techniques will be required to help clinicians understand that certain cells remain infected even with bacterial cellular forms that only seem dead and really are just playing opossum. ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

The Great Leveler

SOURCE: Zuckerman NS, Mor Z, Bucris E, et al. Sexual intermingling of Arab and Jewish MSM in Israel: Results of a molecular epidemiology study. *AIDS* 2019;33:339-344.

It has been said that sex is the great leveler. In this epidemiological and molecular study, researchers examined interethnical/religious connections of HIV-1 virus between Arab and Jewish men who have sex with men (MSM) in Israel, suggesting a high degree of shared mutations. In 2016, there were ~7,500 HIV-positive individuals living in Israel, including about 3,349 HIV-positive males. Using a National Civil Registry, the researchers could cross-match the religious affiliation of all of the HIV-positive MSM diagnosed between 2005 and 2016 (n = 1,143). Among these MSM, 93.6% were Jews and 6.4% were Arabs (a higher proportion of Arab HIV-positive patients was observed among non-MSM compared with MSM [19% vs. 6.4%]).

Using a stratified random selection design, researchers selected ~40% of the HIV in each year for subtype analysis and sequencing (including 440 MSM Jews and 62 MSM Arabs). Subtype B was the most common subtype identified among Israeli-born HIV-positive MSM (80.6% of MSM Jews and 82.3% of MSM Arabs). The proportion of the various subtypes (A, B, C, and non-A/B/C) between the two groups was remarkably similar.

The overall prevalence of transmitted drug resistance mutations (TDRM) was 13.1%. The distribution of TDRM was similar between Jews and Arabs (14.1% and 9.7%, respectively; *P* = NS). The most common TDRM was K103 N/S in 9%, followed by PR-L90 in 3.2%, M184V in 1.2%, and T215S in 1%.

Phylogenetic analysis revealed multiple clusters within subtypes between Arab and Jewish MSM. In HIV subtypes A and C, the most common TDRM (K103) formed two single larger shared clusters, although a subset of patients with one base pair change (K103S) was identified in later years (2013-2014) within subtype A. In contrast, within subtype B, multiple clusters were identified, including five large clusters and 31 smaller clusters of less than four individuals. Arab and Jewish MSM sequences were intermingled within these clusters. Investigators observed two larger clusters with specific mutations, with a common ancestor in one dating back to the 1990s, and the K103N mutation appearing more than 10 years later. Such clustering is highly suggestive of a shared common TDRM with

secondary transmission, intermingled between the two groups.

Increased Cancer Risk in HIV (Even With Long-Term Suppression)

SOURCE: Park LS, Tate JP, Sigel K, et al. Association of viral suppression with lower AIDS-defining and non-AIDS-defining cancer incidence in HIV-infected veterans: A prospective cohort study. *Ann Intern Med* 2018;169:87-96.

After more than 25 years of attempting to control HIV infection and lipid levels (and treat sexually transmitted diseases), I have been faced with a number of non-AIDS-related solid tumors in my HIV-positive patients, especially in my older patients (including several lung cancers, pancreatic cancer, two patients with melanoma, and one with throat cancer). So, I found this article from the National Cancer Institute (NCI) and the Department of Veterans Affairs of particular interest.

These authors performed a large, prospective cohort study comparing rates of AIDS-defining cancers and non-AIDS-defining cancers in 42,441 HIV-positive veterans vs. 104,712 demographically matched non-HIV-positive veterans from 1999-2015. The investigators standardized the incidence rates of AIDS-defining and non-AIDS-defining malignancies by viral suppression status. The status was defined as unsuppressed; early suppression, meaning the initial two years of observation with HIV RNA levels < 500 copies/mL; and long-term suppression, allowing for only one "blip" greater than 1,000 copies/mL. Those patients who became unsuppressed after a period of early or long-term suppression and then were suppressed again were classified as early suppression, at least during the initial two years of the observation period (i.e., the clock was reset).

More than half (62%) of the HIV-positive veterans achieved long-term suppression during follow-up. Compared with HIV-negative veterans, HIV-positive persons had a higher prevalence of chronic hepatitis C virus infection (22% vs. 10%) and a lower prevalence of diabetes (21% vs. 34%).

For each cancer type, researchers calculated standardized weights based on person-time distribution by age (five-year groups) for various time intervals. They included in the analysis only those cancer types with at least 30 cases.

Compared with HIV-negative veterans, cancer incidence was highest for the unsuppressed group (relative risk [RR], 2.35; 95% confidence interval [CI], 2.19-2.51), lower among those with early suppression (RR, 1.99), and lowest among those with long-term suppression (1.52). This observation was strongest for AIDS-defining malignancies, but non-AIDS-defining malignancies followed a similar trend. Compared with HIV-negative veterans, the relative risk of non-AIDS-defining cancers was highest for the unsuppressed group (RR, 3.82; CI, 3.24-4.49), lower for those with early suppression (RR, 3.42, CI, 2.95-3.97), and lowest for those with long-term suppression (RR, 3.17; CI, 2.78-3.62).

[Even those with long-term suppression remained at significantly higher risk for non-AIDS-related cancers.]

Note that long-term suppression was associated with a 23% reduction in excess risk, but even those with long-term suppression remained at significantly higher risk for non-AIDS-related cancers. These predominately included non-HPV-cancers of the oropharynx and larynx, pancreatic and lung cancers, and melanoma. Other lymphoproliferative and hematologic malignancies, such as multiple myeloma and leukemias, also were increased, especially in the unsuppressed and early suppression groups. Only the relative risk of prostate cancer appeared unaffected by HIV status. And that is exactly what I am seeing. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. Which of the following is true regarding the treatment of uncomplicated, late-onset neonatal group B *Streptococcus* infection?

a. Intravenous antibiotics are provided uniformly for at least 10 days at children's hospitals in the United States.

b. Home intravenous antibiotic use is associated with high rates (> 5%) of readmission for complications.

c. Oral amoxicillin can lead to bactericidal concentrations in blood.

d. The standard duration of intravenous antibiotic use should be changed to seven days.

2. Which of the following is correct regarding the randomized trial evaluating the duration of treatment of patients with Gram-negative bacteremia by Yahav and colleagues?

a. Approximately two-thirds of infections arose from the urinary tract.
b. Fourteen days of therapy was superior to seven days.

c. The majority of infections were due to *Pseudomonas aeruginosa*.

d. The all-cause 90-day mortality was twice as high in those treated for seven days compared to those treated for 14 days.

3. Which of the following is correct regarding rifamycin (Aemcolo)?

a. It is approved for treatment of all types of traveler's diarrhea.

b. It was superior to ciprofloxacin in the treatment of traveler's diarrhea due to noninvasive strains of *E. coli* in adults.

c. The risk of colonization with extended spectrum beta-lactamase-producing *E. coli* is lower after treatment of traveler's diarrhea with rifamycin than with ciprofloxacin.

d. It is recommended that it not be used in patients whose traveler's diarrhea is accompanied by fever.

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.