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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Prolonged vs. Short Duration Infusion of Beta-lactam Antibiotics: The Verdict Is In

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: When compared to shorter infusion duration, prolonged infusion of anti-pseudomonal β-lactam antibiotics was associated with reduced mortality.

SOURCE: Vardakas KZ, Voulgaris GL, Maliaros A, et al. Prolonged versus short-term intravenous infusion of antipseudomonal β-lactams for patients with sepsis: A systematic review and meta-analysis of randomised trials. *Lancet Infect Dis* 2018;18:108-120.

Vardakas and colleagues examined 22 clinical trials involving 1,876 patients prescribed intravenous anti-pseudomonal β-lactam antibiotics and who were randomized to receive them either as a brief (over ≤ 60 minutes) or prolonged (≥ 3 hours, including continuous) infusion. Almost all enrolled patients were receiving intensive care and were severely ill as indicated by a mean or median APACHE II score ≥ 20. The total daily antibiotic dose varied, but in 13 of the 22 trials, patients assigned to prolonged administration received 50-67% of the total daily dose received by those in the comparator arm.

Clinical cure or improvement (reported in 18 of the trials) did not significantly differ between the groups. However, a statistically significant all-cause mortality difference was observed in the 17 studies reporting this endpoint, with the results favoring prolonged infusion (relative risk [RR] 0.70; 95% confidence interval [CI], 0.56-0.87). When analyzed separately, both a penicillin with a β-lactamase inhibitor and carbapenems were each associated with significantly reduced mortality, while cephalosporins were not, possibly related to the smaller sample size and the possibility that their dosage was inadequate in both treatment arms.

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■ COMMENTARY

The critical pharmacodynamic parameter for antibacterial efficacy of β-lactam antibiotics is the proportion of the dosing interval for which the serum concentration of the non-protein-bound fraction of the antibiotic remains above its minimal inhibitory concentration (MIC) vis à vis the targeted pathogen. This can be expressed as $\%fT > MIC$. There is little benefit with concentrations greater than four times the MIC. The target for efficacy generally is in the range of 60% ± 20% of the dosing interval. The common use of short infusion times (often 30 minutes) is inferior to more prolonged infusion times with regard to pharmacodynamic target attainment (PTA) at these levels.

However, the clinical benefit of prolonged infusion has been difficult to demonstrate, and the reported results have been mixed. Among other obstacles, this is likely to depend to a significant degree on the actual MIC of the infecting pathogen. Thus, the duration of infusion probably has little potential effect when the MIC is at the extremes. If it is extraordinarily low, PTA is likely to be achieved readily regardless of the duration of beta-lactam infusion. If it is extraordinarily high, the duration of infusion is likely to be irrelevant — the antibiotic has little chance of efficacy. Thus, the greatest clinical benefit resides in the treatment of infections due to pathogens with MICs clustering around the breakpoint, both just below and just above it, and this limits the ability to detect treatment outcome differences when the overall study population is undifferentiated with regard to actual MIC.

A number of caveats must be considered in evaluating the results of this meta-analysis. There was no information on antimicrobial susceptibility, microbiological eradication, or the frequency of significant immunocompromise in the study populations. Importantly, patients with renal insufficiency were excluded from the majority of studies included in the analysis. Several of the studies allowed administration of other antibiotics in combination with the beta-lactam. Some studies used loading doses, and this approach was not analyzed.

Another issue is that most patients studied were receiving intensive care and the majority had APACHE II scores ≥ 20, a population one would like to target in evaluating mortality as an endpoint. However, such patients are likely to exhibit a number of manifestations that affect antibiotic pharmacokinetics and pharmacodynamics. These include increased volume of distribution, hypoalbuminemia (important for highly protein-bound drugs), capillary leak, and, in the absence of renal impairment, augmented clearance. Prolonged antibiotic infusions have an improved chance of achieving PTA in these circumstances, but they may not exist in non-critically ill patients, raising the question of whether the results reviewed here have relevance in them.

[The clinical benefit of prolonged infusion has been difficult to demonstrate, and the reported results have been mixed.]

This meta-analysis, which included only randomized trials, provides strong evidence of a 30% reduction in crude mortality in patients who received prolonged anti-pseudomonal beta-lactam infusions as compared to those whose individual infusions were of short duration. We implemented this approach at Stanford approximately two years ago by making prolonged infusion the default when these drugs are ordered.

One additional issue: We should realize that we are working in the dark ages with regard to beta-lactam therapy in these patients. It is becoming increasingly apparent that to further optimize outcomes, therapeutic drug monitoring, particularly in patients receiving renal replacement therapy, will be necessary. ■

ABSTRACT & COMMENTARY

MRSA Infections May Lead to Prolonged Impairment of Lymphatic Vessel Function

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

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

SYNOPSIS: In the first study to investigate the potential interactions between bacterial infections and lymphatic function, researchers found that methicillin-resistant *Staphylococcus aureus* toxins killed muscle cells critical to the pumping of lymph fluid and led to prolonged lymphatic dysfunction months after the bacteria had been cleared.

SOURCE: Jones D, Meijer EFJ, Blatter C, et al. Methicillin-resistant *Staphylococcus aureus* causes sustained collecting lymphatic vessel dysfunction. *Sci Transl Med* 2018;10(424).

Skin and soft tissue infections (SSTIs) are a frequent occurrence in patients who have impaired lymphatic vessel function, such as chronic lymphedema. SSTIs also can lead to secondary lymphedema, thus serving as both a cause and effect of lymphatic dysfunction. Jones and colleagues investigated the effects of methicillin-resistant *Staphylococcus aureus* (MRSA) infections on lymphatic vessel function and the underlying molecular mechanisms involved.

Using a mouse hind limb model, the researchers found that infection with the USA300 strain of CA-MRSA increased lymphatic vessel diameter and led to weaker, less frequent contractions that were present up to 120 days after inoculation. Only 50% of the infected mice had observable lymph flow following MRSA clearance (35 days after inoculation) compared to 90% of mice in an uninfected control group. The number of lymphatic muscle cells (LMCs) surrounding the lymphatic vessels remained depleted as late as 260 days following MRSA infection. LMCs are responsible for pumping lymphatic fluid and, thus, are crucial for modulating an effective host immune response to an SSTI.

Next, the researchers cultured LMCs in vitro and incubated them with a MRSA-conditioned supernatant. After six hours, substantial numbers of LMCs were killed. This effect was found to be caused by toxins expressed in the supernatant. Because expression of many MRSA toxins is controlled by the accessory gene regulator (*agr*) operon, the researchers tested a mutant form of MRSA lacking *agr* against several types of cultured cells and in the mouse model. The *agr*-mutant MRSA did not produce the LMC-killing toxins. Moreover, lymphatic function, including the strength and frequency of vessel contraction, was significantly better in mice that were infected with the mutant strain than in those infected with a nonmutant strain. Other types of vascular cells also were killed by the MRSA toxins, including smooth muscle cells in the posterior tibial artery.

These data suggest that *agr*-dependent MRSA toxins cause long-term inhibition of lymphatic vessel function. Finally, nitric oxide is a vasodilator that causes lymphatic vessels to contract under certain conditions. When MRSA-derived lipoteichoic acid was injected into the mouse hind limb, lymphatic contraction decreased in a dose-dependent manner. Moreover, inducible nitric oxide synthase (iNOS) knockout mice infected with MRSA had a significant reduction in lymphatic contraction, and iNOS remained undetectable in hind limb tissue 60 days after the infection.

■ COMMENTARY

This study is the first to investigate the association between a specific bacterial pathogen, in this case MRSA, and lymphatic function. The researchers found a novel mechanism of lymphatic impairment: MRSA infection leads to the death of LMCs due to the activity of *agr*-dependent toxins. This can explain how the function of collecting lymphatic vessels can be impaired long after the MRSA infection has resolved and the toxins are no longer active. If true, then the combination of slow LMC regeneration post-infection with recurrent MRSA can account for the cycle of lymphatic deterioration and reinfection in some patients with SSTIs. Therefore, novel therapies that regenerate LMCs may be able to restore lymphatic function, thus reducing lymphedema and the risk for recurrent SSTIs.

Another interesting therapeutic strategy the investigators proposed is to block *agr* signaling using specific chemical inhibitors. Several of these inhibitors are in the developmental stages and represent an antibiotic-sparing option for SSTIs. Further efforts at targeting MRSA toxins, both in animals and humans, should be a research priority. Also, the role of nitric oxide in lymphatic vessel function during and after MRSA infection needs further clarification.

The study had a few limitations. First, the murine model is not a model of recurrent infection. Second, mice do not develop chronic lymphedema. Third, the authors did not investigate the effect of other common pathogens that cause SSTIs, such as *Streptococci* and methicillin-susceptible *Staphylococcus aureus* (MSSA), on lymphatic function. However, since *agr*-mediated toxin production occurs in MSSA (albeit in lower amounts), it seems reasonable to hypothesize that the effects of infections by MSSA on lymphatic vessels would be similar to MRSA.

Additional studies in humans are needed to test the mechanistic framework proposed by Jones et al that MRSA infection leads to impaired lymphatic function, and to identify the specific MRSA toxins that cause the death of LMCs. One hopes this will lead to therapies that break the cycle of SSTI, lymph flow deterioration, lymphedema, and recurring infections. ■

ABSTRACT & COMMENTARY

Mefloquine: Still Effective and Still Safe for Malaria Chemoprophylaxis

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: Mefloquine is known as an effective agent for malaria chemoprophylaxis. However, concerns about serious adverse effects have limited its use. Now, a careful review of data suggests that fatal outcomes related to mefloquine prophylaxis are very rare.

SOURCE: Tickell-Painter M, Saunders R, Maayan N, et al. Deaths and parasuicides associated with mefloquine chemoprophylaxis: A systematic review. *Travel Med Infect Dis* 2017;20:5-14.

Mefloquine has been available for malaria chemoprophylaxis for three decades. It has been effective and is widely used. However, there is a belief that prophylactic mefloquine can prompt psychosis, suicidal ideation, and death. To better determine if data supported such a belief, an expert investigative group, in conjunction with a Cochrane review of efficacy and safety of mefloquine,[1] systematically reviewed scientific reports about death and suicidal attempts in patients using preventive mefloquine.

Using rigorous search criteria, 2,521 potentially relevant papers were identified. Of these, 71 papers mentioned mefloquine being potentially linked to death and/or suicide attempts; 17 papers reported death and suicide attempt in apparent association with prophylactic mefloquine. These papers were analyzed carefully; some papers did not actually provide data supporting death and/or suicide related to mefloquine, some dealt with treatment doses, some cited other articles which, in fact, did not corroborate the claims, and some did not provide enough information to determine any hint of a causal association between the medication and the outcome.

From this extensive literature review, two deaths were linked to what seemed to be idiosyncratic reactions "probably caused by" mefloquine (one with pulmonary fibrosis, one with an exfoliative illness with neutropenia), and there was one suicide attempt "possibly caused by" mefloquine. Using a causality framework, there were eight other reports of death deemed "unclassifiable" or "unlikely" related to mefloquine.

The investigators thought that it was "striking" that so few deaths could be causally linked to mefloquine. Despite a vigorous and rigorous search for potential cases, they found only these three cases that potentially could be linked to mefloquine. These three cases were many fewer than previously cited cases that had not been subjected to such careful scrutiny.

■ COMMENTARY

There are three main malaria chemoprophylaxis medications — mefloquine, atovaquone-proguanil, and doxycycline. No medication is perfect, and travelers can experience bothersome and life-threatening events no matter which malaria medication they are taking. Thus, it is helpful to have a good grasp of existing scientific data to sort through risks and benefits of various anti-malarial options when caring for international travelers. To that end, Tickell-Painter and colleagues have provided a good summary of published data on the possibility of mefloquine being associated with death and suicide.

Decades ago when mefloquine was introduced as a chemoprophylactic agent, caution was urged in using the medication in people with cardiac rhythm disturbances, active seizure disorders, and psychiatric difficulties. Bad psychiatric reactions seemed to be more common with larger treatment doses than with smaller weekly preventive doses. Nonetheless, there was anecdotal concern that even prophylactic dosing could trigger serious psychiatric effects in people without pre-existing psychiatric disorders. These safety concerns led to black box warnings on package inserts, a *New York Times* opinion article about "crazy pills,"[2] and a decrease in the use of mefloquine.

How large is the actual risk of serious adverse events with prophylactic mefloquine? Beyond anecdotes and case reports, Tickell-Painter and colleagues now provide a helpful systematic review of published safety data. Not surprisingly, but perhaps counter to widely held belief, mefloquine is not associated with statistically significant increased risks of either death or suicide-prone psychiatric reactions. This knowledge could help mefloquine return to a position of accepted use in the prevention of malaria in travelers.

Of course, travel itself can be associated with bad outcomes. Sleepless nights on airplanes, jetlag, and culture shock all can yield diminished psychological reserves and might provoke the emergence of symptoms related to underlying anxiety, depression, or psychosis.

Mefloquine does have some side effects, even if not life-threatening ones. Sleep disturbances (insomnia, vivid dreams) are seen in up to 20% of travelers taking prophylactic mefloquine. Cardiac rhythm disturbances, active seizure disorders, and known psychiatric disorders remain contraindications to mefloquine use. Mefloquine is readily available in pill form, but the crushed pills taste unpleasant; children don't always enjoy taking mefloquine. Despite all this, though, mefloquine still is very effective in preventing malaria. The oral dose is 5 mg/kg/dose up to an adult dose of 250 mg taken weekly starting one to two weeks prior to travel and continuing through four weeks after leaving the malarial area.

Doxycycline and atovaquone-proguanil also are reasonable chemoprophylactic options, but each requires daily use. Doxycycline can stain developing teeth, so it is not suggested for use prior to 8 years of age. Vaginal yeast infections and photosensitivity skin reactions also limit the use of doxycycline for a minority of travelers. Atovaquone-proguanil has only rare bothersome side effects. Each of these medications should be started a day prior to arrival in the malarial area and then continued until after leaving the area of risk for malaria (28 days after leaving for doxycycline, seven days after leaving for atovaquone-proguanil).

The cost of doxycycline has gone up in recent years. The cost per pill of atovaquone-proguanil is higher than that of the other agents; a trip of longer than 10 days usually makes mefloquine less costly than atovaquone-proguanil.

A recent Cochrane review, also led by Dr. Tickell-Painter of the Liverpool School of Tropical Medicine, highlighted relative risks of bothersome adverse effects of various anti-malarial prophylactic medications as determined in studies involving hundreds of thousands of subjects.[1] While mefloquine was very effective in preventing malaria, side effects were reported.[1] Compared to atovaquone-proguanil, mefloquine was associated with abnormal dreams (relative risk [RR], 2.04), insomnia (RR, 4.42), anxiety (RR, 6.12), and depressed mood (RR, 5.78). Nausea and dizziness also were more common with mefloquine. Overall, 6% of travelers opted to discontinue mefloquine use, while only 2% of atovaquone-proguanil users opted to discontinue treatment. Mefloquine and doxycycline had similar rates of discontinuation and serious adverse effects; while mefloquine was associated with more abnormal dreams, insomnia, anxiety, and depression than doxycycline, doxycycline was associated with more dyspepsia, photosensitivity, vomiting, and vaginal candidiasis.[1] Physicians providing pre-travel consultation often need to help travelers balance potential adverse reactions with the varying costs of the medications.

Emerging data suggest that primaquine is another reasonable option for chemoprophylaxis of malaria, especially in areas where *Plasmodium vivax* and *Plasmodium ovale* are common.[3] However, glucose-6-phosphate dehydrogenase deficiency

should be ruled out before initiating treatment with primaquine.[3]

The majority of travelers who are diagnosed with malaria in the United States (about 2,000 per year) were traveling to visit friends and relatives and did not take appropriate chemoprophylaxis.[4] Choosing a medication during a pre-travel consultation is important, but it is even more important to try to ensure that all travelers to areas with risk of malaria receive appropriate pre-travel counsel and interventions. Travelers visiting friends and relatives are at particular risk compared to those who travel strictly for business or tourism.[4,5,6]

There is wide variation in travel medicine practice,[7] and it behooves all physicians seeing travelers to stay current with evidence-based recommendations. There also are regional and temporal variations in the management of malaria risk in travelers. Realizing that the actual risk of malaria is very low (< 1% per month) in typical business and tourist travelers, European travel medicine specialists increasingly have used stand-by treatment (providing a curative dosing regimen to have available for use when symptoms develop and a rapid malaria test is positive) instead of providing widespread chemoprophylaxis.[8] Malaria continues to be a problem for international travelers. Travelers should seek pre-travel consultation, and physicians should choose anti-malarial chemoprophylactic regimens wisely. ■

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ABSTRACT & COMMENTARY

New Agent for Treatment of Chagas Disease Disappoints in Clinical Trial

By Dean L. Winslow, MD, FACP, FIDSA

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

SYNOPSIS: A randomized, controlled trial of E1224 (a ravuconazole prodrug) in different doses and durations was studied in adult patients with chronic indeterminate Chagas disease. Parasite clearance was observed in treated patients, but the response was transient in most patients.

SOURCE: Torrico F, Fascon J, Ortiz L, et al. Treatment of adult chronic indeterminate Chagas disease with benznidazole and three E1224 dosing regimens: A proof-of-concept, randomized, placebo-controlled trial. *Lancet Infect Dis* 2018 Jan 15: pii: S1473-3099(17)30538-8. [Epub ahead of print].

A proof-of-concept, double-blind, randomized, Phase II clinical trial was conducted in two outpatient units in Bolivia. During 2011-2012, 560 patients with chronic Chagas disease were screened and 231 were randomized. Patients were randomized 1:1:1:1:1 to oral E1224 high dose/eight weeks, low dose/eight weeks, short dose (four weeks E1224 followed by four weeks of placebo), benznidazole 5 mg/kg for 60 days, and placebo for eight weeks. The primary efficacy endpoint was parasitological clearance as assessed by polymerase chain reaction (PCR), and secondary endpoints included serologic response and changes in biomarkers.

Parasite clearance was observed with E1224 during treatment administration, but no sustained response

was seen with either the low-dose or short-course treatment regimens. Thirteen of 45 (29%) patients treated with high-dose E1224 compared with four of 47 (9%) in the placebo group had sustained responses at 12-month follow up. In contrast, benznidazole had a rapid and sustained effect on parasite clearance, with 37 of 45 (82%) at 12-month follow up as assessed by PCR. Both E1224 and benznidazole were well tolerated, with reversible dose-dependent increase in liver enzymes seen in both E1224- and benznidazole-treated patients, but only six patients in the study (3%) developed treatment-emergent serious adverse events.

■ COMMENTARY

This well-designed, randomized, placebo-controlled, proof-of-concept study demonstrated that this new imidazole prodrug had modest in vivo activity as shown by dose-dependent suppression of parasitemia as assessed by PCR. However, it was disappointing that E1224 did not appear as active as benznidazole.

This follows fairly shortly after the publication of another disappointing randomized, placebo-controlled trial in which benznidazole, while showing parasitological clearance, had no clinical efficacy in the treatment of patients with different stages of Chagas cardiomyopathy.[1] However, the fact that E1224 demonstrated trypanosomal DNA reduction activity in vivo suggests that trials of E1224 in combination with benznidazole or nifurtimox should be conducted. ■

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ABSTRACT & COMMENTARY

Does Adding Rifampin to Standard Therapy Improve Outcomes in Patients With *Staphylococcus aureus* Bacteremia?

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: The addition of rifampin to standard therapy failed to provide significant benefit to patients with bacteremia due to *Staphylococcus aureus*.

SOURCE: Thwaites GE, Scarborough M, Szubert A, et al; United Kingdom Clinical Infection Research Group (UKCIRG). Adjunctive rifampicin for *Staphylococcus aureus* bacteraemia (ARREST): A multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2017 Dec 14. pii: S0140-6736(17)32456-X. doi: 10.1016/S0140-6736(17)32456-X. [Epub ahead of print].

The ARREST trial was a randomized, double-blind, placebo-controlled trial performed at 29 hospitals in the United Kingdom that was designed to determine whether the addition of rifampin to standard therapy improved outcomes in patients with *Staphylococcus aureus* bacteremia. Patients were randomized to receive either rifampin (600 mg or 900 mg daily) or placebo for 14 days. The choice of the base antibiotic was left to the clinician, as was its duration of administration; flucloxacillin was used in 82% of patients, and many patients also received an aminoglycoside for some duration. A total of 758 patients were included in the final analysis. Sixty-four percent of infections were community acquired. Overall, 40% of bacteremias were considered to arise from a "deep" focus, but very few involved native heart valves or prosthetic devices, although almost one-fifth arose from intravenous catheters. Only 47 (6%) isolates were methicillin resistant (MRSA).

The base antibiotic was administered for a median of 29 days (IQRm 18-45 days). Treatment failure, disease recurrence, or death at 30 days occurred in 17% and 18% of rifampin and placebo recipients, respectively. There was no significant difference in composite failure rates when patients with MRSA infection were excluded from the analysis, and there also was no statistically significant difference in those with MRSA infection: 3/21 (14.3%) in placebo recipients and 9/26 (34.6%; hazard ratio [HR], 2.74; 95% confidence interval, 0.74-10.15) in those assigned rifampin. Infection recurred in 16 (4%) placebo recipients and three (1%; $P = 0.01$) rifampin recipients. There were significantly more adverse events leading to treatment modification in those assigned rifampin.

■ COMMENTARY

This is an impressive trial that goes a long way toward answering the question of when and whether adjunctive rifampin administration provides benefit in patients with *S. aureus* bacteremia. However, firm conclusions to be drawn from it must be tempered by several observations.

The circumstance in which there has been the most enthusiasm for adjunctive use of rifampin is in the treatment of retained foreign material, such as joint prostheses, but the number of such cases in this study was small. In addition, the fact that only 6% of isolated pathogens were MRSA means that application of these results to infections with that organism undoubtedly will be questioned by some. Seventeen percent of patients had infection related to central or peripheral intravenous catheters and presumably had these removed, although no data regarding source control in these or other infections were presented. On the other hand, the greater risk of adverse events or drug interactions important enough to warrant alteration of treatment in rifampin recipients suggests that the small number of patients who might have benefited from adjunctive rifampin may be insufficient to overcome this problem. It should be noted that 11% of screened patients were excluded from participation because of potential drug interactions with rifampin.

The arguments for adjunctive rifampin include its potent in vitro bactericidal activity, its intracellular penetration, and its activity against organisms growing in biofilm. However, with the exception of its use with ciprofloxacin (an antibiotic with limited antistaphylococcal activity) in orthopedic device infections, for example, evidence of its benefit is limited. In fact, many in vitro studies indicate the presence of antagonism when combined with other anti-staphylococcal agents.

Overall, it can be concluded that the available evidence does not support the use of adjunctive rifampin therapy in patients with *S. aureus* bacteremia. ■

ABSTRACT & COMMENTARY

What Do the Urinary Microbiota and Incontinence Have to Do With Each Other?

By Chiara Ghetti, MD

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

SYNOPSIS: Increased diversity of the microbiota in women is associated with urgency urinary incontinence symptoms but not with stress urinary incontinence symptoms.

SOURCE: Thomas-White KJ, Kliethermes S, Rickey L, et al; National Institute of Diabetes and Digestive and Kidney Diseases Urinary Incontinence Treatment Network. Evaluation of the urinary microbiota of women with uncomplicated stress urinary incontinence. *Am J Obstet Gynecol* 2017;216:55.e1-55.e16.

The objective of this study was to investigate the relationships between urinary microbiota and characteristics of women undergoing surgery for stress urinary incontinence. Microbiota (or synonymously microbiome) refers to a community of microorganisms. In particular, Thomas-White et al investigated the female urinary microbiota, or in other words, the microbial communities that live in women's bladders. This was a sub-study of the Value of Urodynamic Evaluation study (VALUE), a National Institutes of Health-sponsored large, multicenter, clinical trial of women with uncomplicated stress urinary incontinence planning to undergo surgery.

Adult women were eligible for the VALUE study if they reported symptoms of stress urinary incontinence for three months with stress predominant urinary incontinence as measured by the Medical, Epidemiologic and Social Aspects of Aging (MESA) questionnaire subscale score, a post-void residual < 150 mL on examination, a negative urinalysis/standard urine culture, a positive provocative stress urinary test, and a desire for stress urinary incontinence surgery. Participants in the main study consented to contributing a single baseline urine specimen to a previously established biorepository of urine samples. Demographic and clinical variables (including

stress and urgency urinary incontinence symptoms, menopausal status, and hormone use) were collected. The bacterial content of the urine was determined by sequencing the 16S ribosomal RNA gene.

Bacterial phylogenetic diversity and alpha diversity of urine samples were studied. Phylogenetic diversity refers to the evolutionary relationships between bacteria. This is described as a phylogenetic tree (a branching diagram that shows the evolutionary relationships between organisms). Alpha diversity refers to the measurement of diversity of a single sample, compared to beta diversity, which is the measurement between samples. The phylogenetic diversity and microbial alpha diversity were compared to subject demographics and urinary symptoms using generalized estimating equation models. Generalized estimating equations are a statistical methodology used to analyze correlated data (data where mutual relationships exist).

Samples from 197 of the 630 VALUE study participants were used in this analysis. Demographic and clinical characteristics of the 197 participants were similar to those of the overall trial population. The majority of samples (174) had been obtained by clean catch, with the remaining by catheterization. The majority of participants were non-Hispanic Caucasians. Forty-two percent were premenopausal, 31% postmenopausal without current exogenous hormone use, and 18% were using exogenous hormones.

Subjects reported stress predominant symptoms consistent with study eligibility, and many had concomitant urinary symptoms. The majority of urine samples (86%) had detectable bacterial DNA. Bacterial diversity was significantly associated with higher body mass index (BMI), increased urgency symptoms as measured by the MESA urge index score, and hormonal status. Hormone-positive women (premenopausal and those currently on exogenous estrogen) have predominant bacteria with a higher prevalence of *Lactobacillus* or *Gardnerella* types (66%) compared to hormone-negative women. Hormone-negative women (postmenopausal not on exogenous hormones) have a higher bacterial diversity with greater number of nondominant bacteria, which is associated with a lower frequency of *Lactobacillus* or *Gardnerella* urotypes (38%) compared to estrogen-positive women. No associations were found between bacterial diversity and stress urinary incontinence symptoms.

■ COMMENTARY

The findings reported in this study show that women undergoing stress urinary incontinence surgery have measurable urinary microbiota. The analysis suggests that increased urinary bacterial diversity is associated with urgency urinary incontinence symptoms, hormonal status, and increased body mass index and not associated with stress urinary incontinence symptoms.

Studies have shown that in a healthy human body, microbial cells outnumber human cells by 10 to one. This microbiome is thought to be an integral component in the maintaining health and proper function of the immune system.[1] Until recently, the community of microbes with which we coexist largely was unstudied. In 2008, the NIH began funding the Human Microbiome Project to help identify and characterize the microorganisms associated with humans and their role in health and disease.[2] To date, studies have focused mainly on the gut, vagina, oral cavity, and skin. New data recently have been published, reporting a large number of bacterial genomes from different body sites.[3]

Very little is still known about the urinary microbiome. In fact, before the last decade, many of us were taught that urine was sterile. The current study and several other prior studies by the authors have demonstrated by DNA analysis and microbial culture that even when urine cultures are negative, detectable bacterial communities containing mixtures of urinary and genital tract bacteria exist in the urine of some adult women.[4,5] Studies of urine from women with lower urinary tract symptoms demonstrate that large numbers of bacteria are present, often undetected by routine cultures.[6]

This study has a number of strengths, including the multicenter nature of the study, extensive characterization of participants, as well as the use of cutting-edge sequencing techniques and state-of-the art analytic approaches. Future studies will benefit from using controls matching for the significant associations found (BMI, hormone status, and lower urinary tract symptoms) and from the addition of vaginal and/or rectal samples to inform how these nearby microbiomes may affect the bladder.

The current study further highlights the diversity of the urinary microbiomes and the likely associations among microbiome characteristics, BMI and hormone status, and urinary symptoms. In particular, urinary urgency symptoms may be associated with increased bacterial diversity in the absence of a predominant bacterial type. A 2008 Cochrane review examining the use of vaginal estrogen in the treatment of women with recurrent urinary tract infections (UTIs) concluded that vaginal estrogens are effective in reducing the number of UTIs in postmenopausal women with

recurrent UTIs.[7] The current study helps bring to light a significant relationship between hormone status and urinary microbiome that may explain these findings. We are just at the beginning of an exciting new understanding of the urinary microbiome and its effect on the care of women with urinary urgency symptoms and with recurrent UTIs. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Food Tray Contamination With MRSA/VRE

SOURCE: Kwon JH, Reske KA, Hink T, et al. An evaluation of the prevalence of vancomycin-resistant Enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) in hospital food. *Infect Contr Hosp Epidemiol* 2017;38;1373-1375.

Contamination of food with various bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and ESBL-containing gram negatives, has been well documented. These researchers examined contamination of hospital food being fed to patients for the presence of MRSA and vancomycin-resistant *Enterococcus* (VRE). Samples of food from meal trays were collected by patients as they were eating, and saved in sterile cups. Homogenized specimens were cultured on sheep blood agar. A total of 910 food specimens were collected from 149 patients. Eight (5%) patients were known to be infected or colonized previously with MRSA, and seven (5%) were infected or colonized previously with VRE. A concurrent analysis assessed contamination of food samples with *Clostridium difficile*.

Food specimens from 17 (11%) patients were positive for MRSA and 17 (11%) were positive for VRE. Positive cultures were obtained from all kinds of foodstuffs, including 5% of eggs, 5% of breads or other grains, 3% of meats, and 1% of chicken. Overall, 3.2% and 2.4% of food samples were positive for MRSA and VRE, respectively. The concurrent analysis also found that only 0.2% of food samples were positive for *C. difficile*.

Foodstuffs are a recognized source for MRSA and VRE — and cultures of food eaten by 11% patients in hospital were found to be positive for MRSA and/or VRE. Some of these patients were known to be infected or colonized previously with these resistant organisms, so it's conceivable that patients themselves were the source for the contamination of some food samples. Four patients had positive clinical cultures for MRSA or VRE only after a positive food culture.

Even if some of the hospital food itself was not contaminated before reaching the patient, this study suggests two additional points:

- Having patients cleanse their hands before mealtime should be an important hospital activity. Handing patients a moist, soapy towelette for hand cleansing with their meal tray should be routine. This practice can reduce the risk of auto-infection with bacteria, especially with *C. difficile*.
- Food trays being removed from patient rooms may serve as a source for cross-contamination of mobile delivery carts and hospital foodservice personnel as trays are being carted through the hospital and back to the kitchen.

Hospital Ice Machines Contaminated With Bacteria

SOURCE: Kanwar A, et al. Hiding in plain sight: Contaminated ice machines are a potential source for dissemination of gram-negative bacteria and *Candida* species in healthcare facilities. *Infect Control Hosp Epidemiol* 2018; Jan. 31: doi: 10.1017/ice.2017.321. [Epub ahead of print].

These researchers conducted a point prevalence survey of all ice machines in five different

hospitals and two nursing homes in their area. Protocols for cleaning and disinfecting machines on either a weekly or monthly basis were in place at each facility, although none of the facilities performed surveillance cultures or molecular methods to monitor cleaning.

First, machines were inspected visually for debris, and swab cultures were obtained from both the ice and water chutes. Water samples of 100 mL were collected for culture. Swabs for culture were obtained from 64 machines (3-16 samples per facility).

Visual inspection revealed that 63 of 64 machines (98%) had stagnant water in the pan; 38% had melting ice in the pan, 34% had dripping water, even when the water spout was not in use, and 27% had visible water sprayed on the surrounding countertops or floor. Many of the machines had visible soiling, food, or slime layers.

Gram-negative bacilli and/or *Candida* organisms were cultured from 100% of the drain pans, 72% of the pan grills, and 52% of the chutes. Swab cultures from 94% of the pans yielded > 100 colonies of gram-negative bacilli, including *Enterobacteriaceae* (60%), *Pseudomonas* spp. (26%), *Serratia* spp. (6%), *Stenotrophomonas maltophilia* (4%), and *Acinetobacter* spp. (3%). Of these, 7.7% were carbapenem resistant. All cultures of water and ice were negative. Five of the machines were tested again following cleaning and disinfection with a hydrogen peroxide disinfectant, and all cultures were negative.

Hospital staff were observed using the ice machine on 20 occasions. Staff touched the ice and/or water spouts in nine of 20 episodes (45%), and falling ice touched hands (as it fell into the pan) in 10 of 20 episodes (50%). Cultures of hands frequently yielded gram negatives and yeast.

This study provides a plausible explanation for contamination of ice machines on hospital units. Even if machines are cleaned and disinfected successfully on a regular basis, they may become contaminated quickly by the hands of staff, touching either spouts or falling ice, with contamination of biofilm.

Two quick remedies may be to require staff to cleanse their hands with alcohol hand gel prior to using an ice machine, and to have housekeeping personnel perform more frequent cleaning of machines. Improvement in the design for these machines also may help. For example, deeper pans may help reduce splashes and sprays of water, and different types of spouts or chutes that cannot be touched readily by personnel would reduce cross-contamination.

Significance of *Toxocara* Serologies?

SOURCE: Liu EW, Chastain HM, Shin SH, et al. Seroprevalence of antibodies to *Toxocara* species in the United States and associated risk factors, 2011-2014. *Clin Infect Dis* 2018;66:206-212.

In May 2014, the Centers for Disease Control listed *Toxocara canis* as one of the "five neglected parasite infections in the United States." Earlier seroprevalence studies from the National Health and Nutrition Examination Survey (NHANES) from 1988–1994 found a 13.9% seroprevalence of *T. canis* antibodies in people 6 years of age or older living within the United States.

More recent data from NHANES 2011-2014 found an age-adjusted seroprevalence of *T. canis* of 5%. This amount is much less than earlier estimates, but nonetheless it suggests that up to 16 million Americans have been infected with *T. canis* at some point in their lives. This risk was not uniform, but was found to be greater in older people, people born outside the United States, African Americans, males, and those with lower educational levels, living below the poverty line, and living in more crowded households. A similar study, also published in 2017, found an almost identical seroprevalence rate of 5.1% of persons in the United States, with similar risk factors.

This classic "sandbox infection" may be associated rarely with encephalitis, seizure disorder, and blindness, especially in small children. More often it results in asymptomatic or relatively asymptomatic infection, with low-grade fever and malaise. Clinically significant illness with abdominal discomfort and cough could be missed — since those symptoms occur with many other illnesses.

However, concerns have been raised that occult *Toxocara* infection may be associated with developmental delays and learning disability, especially in lower-income children who are at greater risk for infection. Earlier case-control data from 1987 in the *American Journal of Public Health*, which examined 4,652 children in New York City, found an association of *T. canis* antibodies with higher eosinophil counts and serum IgE antibody levels. Cases also performed less well in neuropsychologic assessment, even when adjusted for lead levels, with a higher reported frequency of hyperactivity, although these differences were small and not statistically significant.

Data suggest that most pediatricians and clinicians know little about the epidemiology and treatment of *Toxocara* infection — and it seldom is considered in otherwise apparently healthy children. However,

at the moment, answers to even the most basic questions about *Toxocara* are lacking. How often does ingestion of eggs lead to clinical infection? What is the clinical significance of *T. canis* antibodies in asymptomatic persons? Should asymptomatic individuals with positive serologies be treated? Should children or adults with eosinophilia, possibly related to allergies, and positive *Toxocara* serologies be treated pre-emptively? ■

CME INSTRUCTIONS

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CME QUESTIONS

1. Malaria chemoprophylaxis with mefloquine is *not* associated with which of the following?

a. Abnormal dreams

b. Insomnia

c. Anxiety

d. Death by suicide

2. Which of the following is the critical pharmacodynamics parameter best predictive of the antibacterial effect of beta-lactam antibiotics?

a. Cmax/MIC

b. AUC/MIC

c. Both Cmax/MIC and AUC/MIC

d. % *f*T > MIC

3. Which of the following is correct regarding the treatment of bacteremia due to *Staphylococcus aureus*?

a. The addition of rifampin to standard treatment is associated with improved survival.

b. The addition of rifampin to standard treatment does not increase the incidence of adverse effects leading to changes in treatment.

c. The addition of rifampin to standard treatment is not supported by the available evidence.

d. The addition of rifampin to standard treatment is associated with overall improvement in outcome.

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.