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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Healthcare Personnel Hospitalizations and COVID-19 — with Possible Implications for Vaccine Prioritization

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: During the period of study, 5.9% of individuals hospitalized for COVID-19-related reasons were healthcare providers (HCP), with approximately one-third involving HCP who were not expected to have direct patient contact in the course of their work.

SOURCE: Kambhampati AK, O'Halloran AC, Whitaker M, et al. COVID-19-associated hospitalizations among health care personnel — COVID-NET, 13 States, March 1-May 31, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1576-1583.

Kambhampati and colleagues used data collected by the COVID-NET population-based survey to evaluate the proportion and characteristics of healthcare personnel (HCP) who had COVID-19-associated hospitalizations in 98 counties of 13 states during March 1 to May 31, 2020. HCP were broadly defined to include anyone in a healthcare occupation with potential exposure to patients or infectious materials. In-depth medical chart abstractions were performed on a subset, and 438 (5.9%) of the 6,760 for whom documentation was available were HCP. (*See Figure.*)

The median age of the HCP hospitalized with COVID-19 was 49 years and 71.9% were female. Approximately one-half were categorized as non-Hispanic Black, one-fourth as non-Hispanic white, and one-tenth as Hispanic or Latino. Just more than two-thirds (67.4%) had occupations for which direct patient contact was expected to occur, with 36.3%

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[INSIDE]

Infectious Disease [ALERT]

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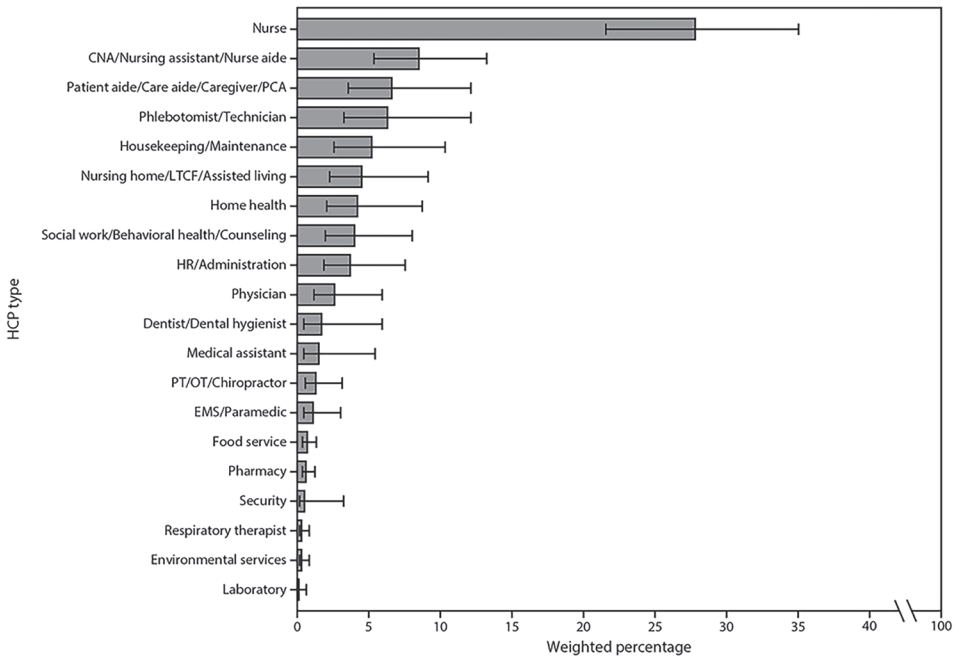
Figure 1: Weighted Percentage of Personnel Types*,† Among Reported Health Care Personnel (HCP) with COVID-19-Associated Hospitalizations (N = 438) — COVID-NET, 13 States,§ March 1-May 31, 2020



Abbreviations: CNA = certified nursing assistant; COVID-19 = coronavirus disease 2019; COVID-NET = COVID-19-Associated Hospitalization Surveillance Network; EMS = emergency medical services; HR = human resources; LTCF = long-term care facility; OT = occupational therapist; PCA = patient care assistant; PT = physical therapist.
* HCP categorized as "unspecified" or "other" have not been included in the figure but are included in the denominator.
† Error bars represent 95% confidence intervals.
§ Sites located in the following 13 states: California, Colorado, Connecticut, Georgia, Maryland, Michigan, Minnesota, New Mexico, New York, Ohio, Oregon, Tennessee, and Utah.
Source: Kambhampati AK, O'Halloran AC, Whitaker M, et al. COVID-19-associated hospitalizations among health care personnel — COVID-NET, 13 States, March 1-May 31, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69: 1576-1583.

of the total in nursing-related categories. Almost nine in 10 had an underlying condition: obesity (72.5%), hypertension (40.6%), or diabetes mellitus (30.9%). Among the women who were 18-49 years of age, 9.6% were pregnant. Intensive care unit care was required for 27.5%, 15.9% received mechanical ventilation, and 4.2% died.

■ COMMENTARY

Kambhampati et al provide useful information regarding the burden of COVID-19 on HCP. However, the study examines data from relatively early in the U.S. pandemic and some of the results may be different currently because of changing and improved approaches to the disease. During the time studied, some institutions may have had limited supplies of personal protective equipment.

Although nursing occupations make up the largest single proportion of cases, no denominator data were presented. Thus, it must be recognized, e.g., that registered nurses are reported to account for one-third of U.S. healthcare practitioners. The broad range of occupational categories presented in the figure provides an overall picture across all types of HCP.

The picture presented in this study provides some useful input into initial strategies for COVID-19 vaccination which will be constrained by limited availability at the outset. Although national recommendations for vaccine prioritization have been published, these will have to be adapted to circumstances at the level of healthcare organizations, including hospitals, something which has been addressed, to an extent, by the

Society for Healthcare Epidemiology of America.[1]

The difficulties of vaccination prioritization will be dictated by the extent of vaccine availability. Many recommendations suggest that the first target should be individuals who provide direct care to COVID-19 patients on a regular basis. However, the study reviewed here found that approximately one-third of the hospitalized HCP had occupations in which direct patient contact was not expected to occur. Other data from serosurveys suggest that direct care givers are not the HPC at greatest risk for infection. Thus, a recent survey at our institution found low levels of seropositivity overall, and the highest rates were not in HCP but in, e.g., environmental and food workers. Others have reported that the seroprevalence was not significantly different among direct-care providers when compared to others.[2,3]

These data, as well as those of Kambhampati et al, do not address the issue of where the infections occur. It is almost certain that the most infections occur in the community, rather than in the healthcare setting. Although different arguments can be made, I believe the data indicate that HCP such as environmental and food workers should be, at a minimum, at the same priority level as those providing direct care to COVID-19 patients.

A last note: the finding that three-fourths of HCP hospitalized for COVID-19-related reasons are obese suggests that healthcare institutions should be directly addressing this problem among their employees. ■

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ABSTRACT & COMMENTARY

Virtual Visits and Antibiotic Prescribing

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: Compared to in-person visits, virtual visits were associated with improved antibiotic prescribing practices for women with uncomplicated urinary tract infections.

SOURCE: Johnson KL, Dumkow LE, Salvati LA, et al. Comparison of diagnosis and prescribing practices between virtual visits and office visits for adults diagnosed with uncomplicated urinary tract infections within a primary care network. *Infect Control Hosp Epidemiol* 2020; Oct 29.:1-6. doi: 10.1017/ice.2020.1255. [Online ahead of print].

Johnson and colleagues retrospectively examined the appropriateness of outpatient treatment of uncomplicated urinary tract infections in women ages 18-65 years who were encountered either via virtual or actual visits between Jan. 1 and Dec. 31, 2018. After screening of records, a total of 350 cases (175 in each group) were selected using a random number generator.

Virtual visits to providers in this large primary care practice health system start with a patient entering information into an existing system. On electronic notification, the provider examines the information, including patient answers to a questionnaire, makes a diagnosis, and selects a treatment plan from a drop-down menu with antibiotic (dose and duration) and supportive care choices based on national recommendations.

Antibiotics were prescribed during 100% and 96.6% of virtual and in-person visits, respectively. Guideline-concordant antibiotic selection occurred significantly more frequently during virtual visits: 74.9% vs. 59.4% ($P = 0.002$). Nitrofurantoin was the most frequently prescribed antibiotic in both groups. The prescribed duration of antibiotic therapy was more likely to be guideline concordant for virtual visits (100% vs. 53.1%; $P < 0.001$).

A urinalysis was ordered during 97.1% of office visits and 0% of virtual visits, while urine cultures were ordered during 73.1% and 0%, respectively. The bacteria isolated in culture from the office visitors was susceptible to nitrofurantoin 94.8% of the time in those given this drug but was susceptible to the alternative agents administered to the others only 76.3% of the time ($P = 0.011$). An unplanned interval revisit in the following seven days occurred more frequently in those with an initial office visit: 18.9% vs. 5.1%; $P < 0.001$.

■ COMMENTARY

Increasing progress has been made in the implementation of effective antimicrobial stewardship in the outpatient setting. This has resulted in increased appropriate use of antibiotics during in-person patient visits. However, there has been a significant shift from in-person to virtual patient visits. Although the shift was, to some extent, already occurring, the emergence of the COVID-19 pandemic and the Centers for Medicare & Medicaid Services (CMS) waiver of its previously existing payment limitations has shifted telemedicine into high gear. Although the CMS waiver is planned to only be temporary, it seems clear that telemedicine will continue to be a significant part of clinical practice — and this raises the question of whether and how to implement antimicrobial stewardship practice into the management of patients during virtual visits. Now Johnson and colleagues have provided useful information in this regard.

These same investigators previously performed a very similar study in adults with acute sinusitis and found that virtual visits were associated with a significant greater likelihood of guideline-concordant diagnoses as well as a significant decrease in antibiotic prescriptions.[1]

The improved adherence to antibiotic prescribing guidelines during virtual visits may be the result of a number of factors, perhaps most importantly the use of a drop-down menu giving recommendations. Regarding the results in patients with sinusitis, it could also be speculated that it is easier for the provider to say "no" to a remote patient's request for an antibiotic prescription than it is to say "no" to a patient sitting in front of that provider. At any rate, it would appear that telemedicine may prove to be an important element in the armamentarium of antimicrobial stewardship programs. ■

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ABSTRACT & COMMENTARY

Does MRSA Nares Colonization Predict Non-Respiratory MRSA Infections?

By Ralph Tayyar, MD

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

SYNOPSIS: Nares screening for methicillin-resistant *Staphylococcus aureus* (MRSA) has a high negative predictive value to rule out MRSA infections at various sites.

SOURCE: Mergenhagen KA, Starr KE, Wattengel BA, et al. Determining the utility of methicillin-resistant *Staphylococcus aureus* nares screening in antimicrobial stewardship. *Clin Infect Dis* 2020;71:1142-1148.

Methicillin-resistant *Staphylococcus aureus* (MRSA) nares screening has been a crucial test in antimicrobial stewardship since it has become essential in deciding on de-escalating anti-MRSA coverage in respiratory infections. Mergenhagen and colleagues looked at the significance of MRSA nares testing in ruling out subsequent MRSA infections at various sites. They retrospectively collected data from patients who were screened for MRSA nares colonization between January 2007 and January 2018 across Veterans Administration (VA) medical centers nationwide.

A total of 561,325 clinical cultures were collected within seven days of nares swabs from 245,833 unique patients. Out of the MRSA nares screened, 73.7% were performed via polymerase chain reaction (PCR) and 26.3% were performed via standard

culture techniques. MRSA nares screening was positive in 22.9% of the total screened samples and MRSA was identified in 8.3% of the various clinical cultures.

The study classified clinical cultures per source as follows: blood, intraabdominal, pulmonary, renal, wound, and miscellaneous. For the whole cohort, the negative predictive value (NPV) for isolating MRSA in clinical cultures was 96.9% for MRSA nares screened by PCR and 95.5% for MRSA nares screened by culture. The NPV was lowest in graft cultures at 89.6% and highest in renal system cultures at 99.1%. However, MRSA colonization had a positive predictive value (PPV) as low as 7.6% in predicting MRSA isolation from renal cultures.

■ COMMENTARY

The study concluded that a negative MRSA nares screen is a helpful tool in ruling out MRSA infection in various clinical cultures. One could argue that clinicians might feel less comfortable discontinuing empiric MRSA coverage with NPV lower than 99%. However, the large number of samples studied by Mergenhagen and colleagues would give antimicrobial stewardship programs additional arguments for de-escalating empiric MRSA-targeted therapy when appropriate. The study results should be tailored to individualized cases, and the decision regarding screening nares for MRSA should be based on the clinical likelihood of MRSA infections at the different sites and the risk factors of the screened patient.

Moreover, this study had low PPV to the various culture sites and, hence, a positive MRSA nares colonization was not thought to predict the isolation of MRSA. Several other studies have looked at the correlation between MRSA nares testing and non-respiratory infections. One of these studies is a retrospective single-centered cohort in Colorado by Marzec et al that found a 19.89 odds of developing MRSA bacteremia in MRSA nares-colonized patients compared to non-colonizers.[1] ■

REFERENCE

1. Marzec NS, Bessesen MT. Risk and outcomes of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia among patients admitted with and without MRSA nares colonization. *Am J Infect Control* 2016;44:405-408.

ABSTRACT & COMMENTARY

Voriconazole vs. Itraconazole for Treatment of Histoplasmosis

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

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

SYNOPSIS: A retrospective cohort study found that patients treated with voriconazole had increased mortality during the first 42 days after the start of treatment compared to patients who received itraconazole.

SOURCE: Hendrix MJ, Larson L, Rauseo AM, et al. Voriconazole versus itraconazole for the initial and step-down treatment of histoplasmosis: A retrospective cohort. *Clin Infect Dis* 2020; Oct 18:ciaa1555. doi: 10.1093/cid/ciaa1555. [Online ahead of print].

Currently, the Infectious Diseases Society of America (IDSA) guidelines for the management of histoplasmosis recommend itraconazole for mild disease or as step-down therapy following amphotericin B. Voriconazole has emerged as an attractive alternative agent given its in vitro activity against *Histoplasma capsulatum* and better tolerability than itraconazole. Because no comparative data had been published, Hendrix and colleagues sought to determine whether there was any difference in mortality between voriconazole and itraconazole in the treatment of histoplasmosis.

The study was a single-center retrospective cohort of adults 18 years of age or older diagnosed with histoplasmosis at Barnes-Jewish Hospital in St. Louis between Jan. 1, 2002, and Dec. 31, 2017. Patients were included in the study if they had either a positive *Histoplasma* antigen, microbiological isolation of *H. capsulatum* from any source, coding for International Classification of Diseases (ICD) codes for *Histoplasma* infection, or a positive *Histoplasma* antibody. Patients were classified in two groups based on the azole initially prescribed for treatment, either voriconazole or itraconazole. Those who received amphotericin B

before starting an azole were classified based on the first azole that was given as step-down therapy.

There were 194 patients included in the study. Of these, 175 (90.2%) received itraconazole and 19 (9.8%) received voriconazole. The median age was 48 years, the majority were white (74.7%), and most (60%) were immunocompromised. Also, 106 (54.6%) patients had disseminated disease, 133 (68.6%) had constitutional symptoms, 13 (70.6%) had respiratory symptoms, 81 (41.8%) had gastrointestinal symptoms, and 26 (13.4%) had skin manifestations. Immunocompromised patients were distributed equally between the two groups. There was no difference in mortality for patients started on amphotericin B before they switched to either voriconazole or itraconazole (27.3% vs. 24.4%, respectively; odds ratio [OR] 1.16; 95% confidence interval [CI], 0.28-4.83; $P = 0.83$). Furthermore, there was no statistical difference in the need for amphotericin B re-initiation within three to 90 days of beginning voriconazole or itraconazole (15.8% vs. 6.8%, respectively; OR 1.46 [95% CI, 0.38-5.69]; $P = 0.58$).

Forty-seven (24.2%) patients died within 180 days after the start of azole therapy, with 41 (23.4%) in the itraconazole group and six (31.6%) in the voriconazole group. After controlling for disseminated disease, the survival analysis found a significant association between voriconazole and an increase in mortality early in the treatment course (0 to 42 days) (hazard ratio [HR] 4.3 [95% CI, 1.3-13.9]; $P = 0.015$) that was not found later in the course of therapy (43 to 180 days) (HR 0.0 [95% CI, 0.0-99.0]; $P = 0.89$). Disseminated disease was an independent predictor of mortality (HR 3.1 [95% CI, 1.1-8.4]; $P = 0.026$). Finally, the year of diagnosis had no impact on any of the primary outcomes.

■ COMMENTARY

This is the first published study to compare itraconazole and voriconazole for the treatment of histoplasmosis. Itraconazole has been the standard therapy for most cases of histoplasmosis for many years. However, voriconazole has been gaining interest recently because of its better absorption and tolerability, especially with long-term use, compared to itraconazole. But the study by Hendrix and colleagues should raise concern about using voriconazole to treat histoplasmosis. Notably, the mortality rate for the patients who received voriconazole as the initial azole treatment was 4.3 times higher during the first 42 days. This suggests that voriconazole might be inferior to itraconazole for histoplasmosis. The mortality rate was similar between the two groups after 42 days. However, there were very few events between days 42 and 180, such that the cohort was not powered to be able to detect a large difference.

These findings should be viewed as preliminary and, ideally, should be replicated in a randomized controlled trial that compares the two drugs head-to-head. Until such data are available, itraconazole should remain the preferred azole. Similar data would be useful for the newer azoles (e.g., posaconazole and isavuconazole) as well. The authors hypothesized that the poorer outcome with voriconazole was due to the induction of the Y136F mutation, which leads to a four-fold increase in voriconazole minimum inhibitory concentrations (MICs).

The study had a few limitations. Most importantly, the size of the voriconazole group was small, thus lowering the overall power of the study. It was conducted at a single academic medical center in the midwestern United States, so the results might not be generalizable to other settings and populations. Finally, the findings may have been influenced by unmeasured confounding factors as a result of the retrospective design.

Hendrix and colleagues have provided some useful information for clinicians deciding about oral therapy for histoplasmosis. Other questions, such as whether voriconazole is a safe option after 42 days and whether the newer azoles, which are better tolerated than itraconazole, are just as effective, remain to be answered. ■

ABSTRACT & COMMENTARY

Flying Fox Hemolytic Fever

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: A novel mycoplasma causes a systemic infection characterized by fever, hemolytic anemia, and other cytopenias, sometimes with hemophagocytic lymphohistiocytosis, painful splenomegaly with risk of rupture, and response to doxycycline.

SOURCE: Descloux E, Mediannikov O, Gourinat AC, et al. Flying fox haemolytic fever, description of a new zoonosis caused by "*Candidatus* Mycoplasma haemohominis." *Clin Infect Dis* 2020 Oct 29:ciaa1648. doi: 10.1093/cid/ciaa1648. [Online ahead of print.]

Descloux and colleagues previously detected DNA of a novel hemotropic mycoplasma they called *Candidatus* Mycoplasma haemohominis in the blood of a patient in New Caledonia with fever, hemolytic anemia, and hemophagocytosis in 2017. They have since tested, both retrospectively and prospectively, a series of patients in New Caledonia with similar clinical pictures for the presence of this organism and identified a total of 15 cases. Those selected for study had fever, splenomegaly, and hemolytic anemia with or without evidence of hemophagocytosis.

The median age of the 15 patients, all of whom were previously healthy, identified was 48 years (range, 36-72 years), and 11 were male. The incubation period ranged from three weeks to three months. All patients had splenomegaly (often painful) and persistent fever, and 80% had experienced weight loss.

Three patients, two of whom died, had splenic rupture. Fourteen had autoimmune hemolytic anemia, 13 had thrombocytopenia, 10 were leukopenic, and 13 had evidence of hemophagocytic lymphohistiocytosis (HLH). *Candidatus* Mycoplasma haemohominis DNA was detected in the blood of all 15 patients and was recovered in culture from one.

Thirteen of the patients had a history of contact with the blood of flying foxes in the process of hunting and/or cooking, and 13 also regularly ate them. DNA of the organism was detected in the blood of 16 (40%) of 40 flying foxes (genus *Pteropus*) as well as in nine of nine of hemophagoous "bat flies."

Ten patients were treated with doxycycline for at least three weeks, and all had favorable outcomes. Treatment of three patients with a macrolide or ofloxacin was not successful. However, one patient treated with piperacillin-tazobactam and amikacin recovered. Four (27%) patients died.

■ COMMENTARY

Hemotropic mycoplasmas are known to cause infections, mostly asymptomatic, in a broad range of vertebrate animals, including bats, but some cause species-specific hemolytic anemia. In addition, scattered cases have been reported in humans from a number of countries, including in Europe, Asia, North and South America, and Africa. These cases, caused by various species, were associated with underlying immunocompromise and/or exposure to farm animals and suggest that although previously healthy individuals who become infected develop pauci-symptomatic bacteremia, those who have underlying immunocompromise experience hemolytic anemia.

Descloux et al provide strong evidence of a serious clinical illness in previously healthy individuals with a characteristic pattern caused by a novel hemotropic mycoplasma, *Candidatus* Mycoplasma haemohominis. After an incubation period of weeks to months, usually after exposure to the frugiferous bats commonly called flying foxes, patients develop persistent but fluctuating fever, splenomegaly that may be painful, autoimmune hemolytic anemia often with other cytopenias, and, in some cases, HLH.

Among the unusual features of the illness was the occurrence of splenic rupture in three patients. Patients responded to therapy with doxycycline.

Although this case series originated in the South Pacific islands of New Caledonia, the reports of human infections caused by other hemotropic mycoplasma on a number of continents makes it likely that cases will be encountered elsewhere, but the diagnosis will require effective molecular methods. ■

ABSTRACT & COMMENTARY

Antibiotics for Traveler's Diarrhea

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: International travel carries a risk of colonization by antimicrobial-resistant intestinal flora. The use of a quinolone, but not a macrolide, during travel further increases the risk of acquisition of extended-spectrum beta-lactamase-producing *Enterobacteriaceae*.

SOURCE: Wuerz TC, Kassim SS, Atkins KE. Acquisition of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE) carriage after exposure to systemic antimicrobials during travel: Systematic review and meta-analysis. *Travel Med Infect Dis* 2020;37:101823.

International travel prompts changes in the intestinal flora, and colonization by extended-spectrum beta-lactamase producing-*Enterobacteriaceae* (ESBL-PE) is associated with travel alone. The use of antibiotics during travel is thought to further increase the risk of becoming colonized by these resistant microbes. ESBL-PE-colonized individuals usually have no symptoms but are at some risk of developing symptomatic illness that carries financial costs as well as risks of morbidity and mortality.

Using standard systematic review techniques, Wuerz and colleagues identified 15 prospective cohort studies published from 2010 to 2017 that evaluated ESBL-PE acquisition associated with international travel and noted whether the traveler had been exposed to antibiotics during the trip. A total of 5,283 travelers were included in the 15 studies.

Asia was the most common destination continent, followed by Africa. Diarrhea was reported in 38% of travelers, and 10% received antibiotics. The antibiotics received were beta-lactams (30%), fluoroquinolones (25%), doxycycline (20%), and macrolides (8%). Overall, 31% of travelers acquired ESBL-PE during their travel.

As determined by meta-analysis, antibiotic use increased the risk of ESBL-PE acquisition 2.37-fold. Fluoroquinolones, as compared to no antibiotic use, increased ESBL-PE acquisition 4.68-fold. Tetracyclines (which are used for malaria prevention as well as for diarrhea treatment) increased ESBL-PE acquisition 1.68-fold. Beta-lactams and macrolides did not increase the risk of acquisition of these organisms.

■ COMMENTARY

We and our patients imagine, anticipate, and dream of the opportunity to travel internationally again. Eventually, we again will confront the possibility of providing presumptive antibiotic therapy for travelers who might develop bothersome traveler's diarrhea. Even during the pandemic, though, science is advancing. The helpful systematic review by Wuerz and colleagues provides clear evidence that the use of antibiotics for healthy travelers with mild diarrhea should be questioned and, likely, avoided.

Traveler's diarrhea is common, affecting one-third or more of short-term visitors to less-resourced countries in tropical regions. In fact, a recent study showed that 46% of medical students on overseas rotations developed traveler's diarrhea.[1] Typically, the diarrhea is self-limited, resolving within a few days. Nonetheless, the illness can be uncomfortable, inconvenient, and, rarely, severe. Bacteria, often enterotoxigenic *Escherichia coli*, are the usual cause of diarrhea in travelers from more-resourced to less-resourced countries, and antibiotics such as azithromycin and quinolones significantly shorten the duration of illness.[2]

Thus, it has been common practice to provide travelers with a course of oral antibiotics to use in the event that they develop diarrhea. The cost and side effects (rare allergic reactions) seemed minimal compared to the benefit of salvaging a day or two of lost activity and altered travel plans. It was assumed that the number of treated travelers would be small compared to the total population numbers and that a few days of antibiotic use would not contribute significantly to population-level alterations in antimicrobial resistance. However, as previously reported in *Infectious Disease Alert* (2015;34:67-69) and proposed by an expert panel of the International Society of Travel Medicine,[2] there has been growing concern that antibiotic use can increase the acquisition of resistant germs significantly, with resultant spread of these germs in new regions following the return from travel. Now, there are enough data on specific risks related to extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE) to warrant the systematic review provided by Wuerz and colleagues.

Wuerz's review is extremely useful. Clearly, ESBL-PE acquisition is common with international travel, with about one-third of travelers from North America and Europe to Asia or Africa becoming colonized. And, antibiotics increase the risk. However, as this meta-analysis clearly shows, it is not just any antibiotic that increases the risk; fluoroquinolones are problematic, and macrolides are not.

Of course, the data from Wuerz et al are not new, even if the systematic review and meta-analysis are new uses of previously published data. The prescribing patterns of experts at 20 United States travel clinics were followed from 2009-2018 as they provided care to more than 100,000 travelers prior to trip departure.[3] As new data and expert guidelines and governmental concerns about antimicrobial use were published, antibiotic use dropped significantly, and quinolones, in particular, became used much less frequently.[2,3]

Overuse of antibiotics likely also relates to the changing resistance patterns of more serious infections such as typhoid fever. A recent report of international travelers who acquired typhoid during their trips

showed quinolone resistance in 78% of South Asian *S. typhi* isolates and in 60% of isolates from sub-Saharan Africa.[4]

In terms of avoiding increases in both general antimicrobial resistance and ESBL-PE acquisition, antibiotics should not be used to treat uncomplicated traveler's diarrhea in most healthy patients.[2] Rather, oral hydration and, perhaps, an anti-motility agent such as loperamide (except in young children) can be effective in facilitating recovery and reducing poor outcomes. For immunocompromised patients, travelers with bloody diarrhea, and, possibly, those with very tight travel itineraries, an antibiotic could be considered, with preference for a macrolide over a quinolone. ■

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ABSTRACT & COMMENTARY

Predictors of Therapy Outcomes for Cryptococcal Meningitis: Failure of In Vitro Susceptibility Testing, Success of Early Fungicidal Activity

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SYNOPSIS: Although in vitro susceptibility testing failed to have value in predicting therapeutic outcome in patients with cryptococcal meningitis, detection of a rapid decline in fungal density in cerebrospinal fluid was associated with improved outcomes in a separate study.

SOURCES: O'Connor L, Van Anh D, Chau TTH, et al. Antifungal susceptibility does not correlate with fungal clearance or survival in AIDS-associated cryptococcal meningitis. *Clin Infect Dis* 2020; Oct. 14:ciaa1544. doi: 10.1093/cid/ciaa1544. [Online ahead of print.]

Pullen MF, Hullsiek KH, Rhein J, et al. Cerebrospinal fluid early fungicidal activity as a surrogate endpoint for cryptococcal meningitis survival in clinical trials. *Clin Infect Dis* 2020;71:e45-e49.

O'Connor and colleagues examined the ability of in vitro susceptibility testing to predict the outcome of treatment of cryptococcal meningitis using data from a previously reported open-label, randomized clinical trial.[1] In that trial, patients with acquired immunodeficiency syndrome (AIDS) were randomized to initially receive amphotericin B alone for four weeks, amphotericin B plus flucytosine for two weeks, or amphotericin B plus fluconazole for two weeks — each followed by fluconazole alone to complete 10 weeks of therapy. The combination of amphotericin B and flucytosine was associated with a survival benefit relative to the other regimens, and fluconazole did not significantly add to that seen with amphotericin B alone. The amphotericin B plus flucytosine combination also was associated with more rapid cryptococcal clearance from cerebrospinal fluid (CSF).

Two hundred sixty-nine patients were included in the study. The Sensititre YeastOne minimum inhibitory concentration (MIC) breakpoints used for the analysis were: amphotericin B, ≤ 0.512 mcg/mL; flucytosine, ≤ 4 mcg/mL; fluconazole, ≤ 8 mcg/mL. An examination of the hazard ratios found no consistent trend of individual MICs in relation to 70-day survival. Similarly, there was no apparent relationship between mortality and categorization of isolates as either susceptible or non-susceptible. This was true

even when limiting the evaluation to patients with high baseline fungal loads: > 6×10^6 colony forming units/mL of CSF. There also was no association between MICs and a reduction in fungal CSF load after 14 days of therapy.

Separately, Pullen and colleagues examined data from three Phase II clinical trials of treatment of 738 AIDS patients with cryptococcal meningitis, all of whom received induction therapy with amphotericin B plus fluconazole. Their purpose was to examine the predictive value of early fungicidal activity (EFA) with regard to mortality. EFA was determined by serial examination of CSF with determination of the reduction in cryptococcal density over the first 10 days of therapy. In vitro susceptibility testing was not reported. Patients with a decrease in CSF of < 0.20 $\log_{10}$ CFU/ day had an 18-week mortality rate of 50% compared to 37% in those with greater decreases in CFU density. The hazard ratio for mortality associated with an EFA < 0.20 was 1.60 (95% confidence interval [CI], 1.25-2.04; $P = 0.002$). However, this group had confounding factors with lower CD4 counts and lesser CSF pleocytosis.

■ COMMENTARY

The question of the ability of in vitro susceptibility results to predict the response to chemotherapy of cryptococcal meningitis has been addressed previously, but no definitive answer has been forthcoming. One likely reason for this failure has been the use of a variety of non-standard susceptibility testing methods. Both Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommend broth microdilution as the standard method for testing *Cryptococcus* spp., but the results obtained with Sensititre YeastOne, which was used by O'Connor et al, correlates well with the standard method and was used in this study.

The lack of predictive value of in vitro susceptibility testing may be the result of a variety of factors, such as the complexity of the host response and complications of meningitis such as CSF obstruction that may be more the result of the inflammatory response than to organism replication. In addition, the potent activity and limited MIC range of amphotericin B, which was received by all the patients, may have primarily dictated the outcomes.

In contrast, Pullen et al found that EFA, a measure that could be considered an in vivo susceptibility test, had predictive value regarding the therapeutic outcome and also validated the use of EFA as a surrogate marker in clinical trials, although host factors may have affected the outcomes. It should be noted that O'Connor and colleagues had failed to find a correlation between MIC and EFA, a finding, which taken together with the results of Pullen and colleagues, further indicates the lack of value of MIC determinations in cryptococcal meningitis. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Fatal ESBL Infection from Fecal Microbiota Transplant

SOURCES: DeFilipp Z, Bloom PP, Torres Soto M, et al. Drug-resistant *E. coli* bacteremia transmitted by fecal microbiota transplant. *N Engl J Med* 2019;381:2043-2050.

Blaser MJ. Fecal microbiota transplantation for dysbiosis – predictable risks. *N Engl J Med* 2019;381:2064-2066.

Fecal microbiota transplant (FMT) has become an accepted treatment for severe and refractory *Clostridioides difficile* infection (CDI). There has also been significant interest in the use of FMT for replacement of fecal flora in patients with intestinal dysbiosis, as a way to prevent pathogenic organisms from flourishing in such compromised patients. These authors described two patients who received FMT in the context of clinical studies for the treatment of non-CDI-related conditions, both of whom developed extended spectrum beta-lactamase (ESBL)-containing *Escherichia coli* with a donor strain. One patient died of severe sepsis.

The first patient had severe hepatic encephalopathy and received 15 FMT capsules five times over a three-week period, in addition to rifaximin. Seventeen days after his final FMT dose, he developed cough and pneumonia, and blood cultures grew ESBL-containing *E. coli*. He recovered with carbapenem treatment, and peritoneal fluid and stool samples (on selective media) were negative for ESBL. The second patient had myelodysplasia and was enrolled in a Phase II trial to administer FMT oral capsules before and after allogeneic stem cell transplant. He received 15

FMT capsules on the third and fourth days before his transplant. Eight days after his last FMT dose, and five days after his stem-cell infusion, he developed sepsis and quickly died. Blood cultures grew ESBL-containing *E. coli*. Frozen stool samples obtained from both patients before their FMT treatment were negative for ESBL.

The FMT product given to both patients was derived from the same donor. A sample of this product proved to contain ESBL *E. coli* — and whole-genome sequencing demonstrated a match between this isolate and the two clinical isolates (≤ 1 single nucleotide polymorphism [SNP] difference). Twenty-two patients also received FMT from this donor in the context of these two clinical trials, and another 16 for the treatment of CDI. None of the stool samples from patients in the clinical trial were positive for ESBL; however, five of 12 patients treated for CDI also were positive for ESBL *E. coli*. Stored capsules from 32 other FMT samples from 10 other donors also were cultured on exclusion media, none of which were positive for ESBL. This suggests the frequency of ESBL-positive stool specimens found in patients with CDI receiving this donor's stool was significant.

Extensive systematic screening of FMT donors is performed according to Food and Drug Administration (FDA) requirements. Donors are healthy, asymptomatic, and between the ages of 18 and 50 years; all donations are frozen and unused for four weeks in case of subsequent illness. Donated stool is processed, concentrated, placed in capsules, and stored frozen at -80°C. The frozen capsules these patients received had been stored for nine months in accordance with approved procedures. FDA regulatory requirements were amended in January 2019 to include screening for ESBL-containing organisms, after this product was manufactured.

Screening for ESBL-containing organisms is increasingly useful for hospital epidemiology, especially as we battle hospital-acquired infections. Our facility has been performing perirectal swabs to rule out ESBL and carbapenem-resistant *Enterobacteriaceae* (CRE) in high-risk admissions (e.g., skilled-nursing facility [SNF] patients and travelers from other countries) for several years (using exclusion media), although the process is disliked by patients and it is rather expensive as a surveillance tool. In 2017, the frequency of ESBL colonization in our SNF population was ~17%. We also see an increased frequency of ESBL and CRE colonization in patients from India and Southeast Asia, and in travelers to developing countries. Based on the cost (and the lack of reimbursement for surveillance testing from Medicare), we have had to abandon ESBL screening and now just perform CRE screening in select high-risk admissions. But the problem has always been the reduced sensitivity of the perirectal screening, even using exclusion media. Several patients with clinical ESBL infection of urine and blood initially had negative stool or perirectal screening, only to have positive results weeks or months later. Only after the selective pressure of broad-spectrum antibiotics may the fecal ESBL or CRE appear in some patients. Undoubtedly, the two patients discussed earlier had intestinal colonization with ESBL from their ingested FMT with translocation to the bloodstream — not detected by stool cultures.

The point is, even if the FDA has adopted measures to screen donated stool for resistant gram-negative organisms, the sensitivity of this surveillance is not known — and may not be adequate to the task. At a minimum, FMT probably should not be used in immune-compromised patients — but I am not sure we want to be giving ESBL or other resistant bacteria to anyone (there is no good evidence that, once colonized, you can become "uncolonized"). Perhaps we should consider using donor stool from a spouse. As I have told patients, if you have exchanged other bodily fluids for years, and raised children, and your donor stool is free from any obvious pathogens, maybe it is better to use your sexual partner's stool (if you are lucky to have one) — or an appropriately screened close family/household member.

Second Joint Infection When One Prosthetic Gets Infected?

SOURCE: Wourthuyzen-Bakker M, Sebillotte M, Arviewx C, et al. How to handle concomitant asymptomatic prosthetic joints during an episode of hematogenous PJI, a multicenter analysis. *Clin Infect Dis* 2020; Aug. 18;ciaa1222. [Online ahead of print].

Prosthetic joint infection (PJI) as a consequence of bloodstream infection is a devastating event, frequently resulting in weeks of antibacterial therapy, surgical debridement, and, often, explantation of the joint. The overall risk of PJI is ~0.07% per year of life of the prosthesis, with knee joints at the highest risk. Since many modern patients may have more than one PJ, should a PJ become infected with complicating bacteremia, what is the risk to their other PJs?

These authors examined the risk of infection to a concomitant PJ as a consequence of bacteremia with an acute hematogenous PJI. A total of 91 patients with hematogenous PJI who also had 108 other PJs were assessed (including 56 knees, 44 hips, three shoulders, and five others). Infection of the first PJ was caused by *Staphylococcus aureus* (43%), streptococci (26%), and gram negatives (18%), with bacteremia in all cases. Thirteen patients experienced symptoms

of possible concurrent PJI in an additional joint, including seven patients with acute joint pain (54%), two patients with acute on chronic pain (15%), and four patients with chronic pain (31%). All 13 had clinical signs of infection on examination. However, only 10 of these additional joints proved to be infected, and symptoms in the other three were attributed to mechanical reasons. One additional PJI became apparent in subsequent weeks, giving a total of 11/108 (10.2%) concomitant joint infection in these patients. In patients with both prosthetic hips and knees, the knee joint was more likely to be infected than the hip (78% vs. 22%). None of the other PJs were infected. Interestingly, infected joints were younger than uninfected joints (4.5 vs. 6.7 years; $P = 0.04$). The risk that a concurrent joint infection occurred as the result of a first hematogenous joint infection with *S. aureus* was 2.7% to 5.6%, depending on the joint.

This work complements the study summarized by Stan Deresinski in the January 2020 issue of *Infectious Disease Alert*, wherein the risk of PJI during an episode of bacteremia largely depends on the organism.[1] Honkanen and colleagues observed that PJI occurred with 46/643 (7%) episodes of bacteremia in 45/542 (8%) patients (one patient had two episodes). The median time interval from the first positive blood culture to identification of PJI ranged from 0-522 days, with a median interval of two days. While 1.3% of *E. coli* and 1.4% of other gram-negative bacteremias resulted in PJI, 20% of bloodstream infections from *S. aureus* caused PJI.

The present study extends this work to examine the risk to a concurrent joint during an episode of PJI and complicating bacteremia. Of course, often it is difficult to appreciate whether the bacteremia was first and the joint infection second, or whether the joint infection gave rise to the bacteremia. Presumably, many of these infections are hematogenous in origin, unless related to the original surgery. The risk of prosthetic joint infection is significantly higher with *S. aureus* bacteremia, which generally causes higher grade endovascular infection. Nonetheless, it was surprising to see that *S. aureus* infection in one PJ with bacteremia had a 2.7% to 5.6% chance of involving a second prosthetic joint. ■

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CME QUESTIONS

1. Which of the following is correct regarding COVID-19-associated hospitalizations in healthcare personnel (HCP)?

a. In contrast to the general population, it occurs mostly in HCP who have no underlying conditions.

b. HCP involved in nursing-related activities account for the largest proportion.

c. Phlebotomists/technicians make up the lowest proportion.

d. Housekeeping/maintenance personnel constitute the second lowest proportion.

2. Which of the following is true regarding colonization by extended-spectrum beta-lactamase-producing *Enterobacteriaceae*?

a. It is unrelated to international travel.

b. It is increased by the use of azithromycin.

c. It is prevented by treating traveler's diarrhea with doxycycline.

d. It is related to fluoroquinolone use as treatment of traveler's diarrhea.

3. Which of the following is correct regarding flying fox hemolytic fever?

a. The pathogen is carried by bats.

b. The cause is an unusual virus.

c. Its incubation period is two to five days.

d. There appears to be no effective treatment.