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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Planes, Pathogens, and Passengers: Infection Risk During Commercial Air Travel

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: Although air travel has been linked to transmission of respiratory infections, the actual risk of becoming infected during air travel is low. The risk is greatest, though, when seated within about two seats/rows of a contagious individual. Walking around the cabin increases risk.

SOURCE: Hertzberg VS, Weiss H, Elon L, et al; FlyHealthy Research Team. Behaviors, movements, and transmission of droplet-mediated respiratory diseases during transcontinental airline flights. *Proc Natl Acad Sci U S A* 2018;115:3623-3627.

Commercial airline passengers take billions of trips each year, and it is well-documented that air travel can serve as a conduit for the spread of infections. Researchers have studied pathogens and aircraft to better understand the risks for infection, but the actual behaviors of crew members and airline passengers had not been carefully observed previously. Thus, Hertzberg and colleagues documented careful observations of the behaviors during flight that potentially could enhance the spread of infection.

The researchers made observations on 10 separate transcontinental flights in the United States involving single-aisle aircraft (with three seats on each side of the aisle). Flight durations varied between 211 and 313 minutes. Seven of the 10 flights were full, and the others had two, three, and 17 empty seats. Observations involved 1,540 passengers and 41 crew members in the economy class seating area.

Overall, 38% of passengers remained in their seats for the entire flight, another 38% left their seats once, 13% left their seats twice, and 11% left their

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seats more than twice. For those who left their seats, they were up for a median of 5.4 minutes. Seat location was linked to movement away from the seat, with 80% of people seated at the aisle moving, 62% of those in middle seats moving, and only 43% of those in window seats getting up to move around. Only half the passengers used a lavatory during the flight. The average crew member spent about one-third of the flight in contact with passengers and two-thirds of the flight in the galley area.

Moving around the aircraft increased contact with other passengers. Passengers who left their seats had a median of 44 other contacts with people and a total of 47 person-minutes of contact with someone not seated near them. Crew members had 206 person-minutes of contact with other crew members and 1,149 person-minutes of contact with passengers. Passengers in aisle seats had much more contact with other passengers (64 contacts with other people) than did passengers seated in window seats (12 contacts with other people).

Based on this information about passenger and crew behavior and knowing that respiratory pathogens are transmitted via droplets over distances less than one meter by cough, sneeze, and breathing, Hertzberg and coworkers then constructed a dynamic network model simulating transmission of influenza. Assuming a high rate of influenza transmission and an index case seated mid-plane in an aisle seat, up to 11 passengers likely would become infected, with the rest of the passengers having less than a 3% chance of having close contact with the index case. An infected coughing crew member likely would share the infection with four or five passengers.

Finally, the investigators gathered 228 air and surface (such as seat belt buckle) samples during the flights they studied. Eight of the 10 studied flights occurred during influenza season, and samples were tested by polymerase chain reaction (PCR) for 18 common respiratory viruses. No sample had evidence of harboring a respiratory pathogen.

The authors pointed out the extremely low risk of infection being transmitted on the 10 flights they happened to observe. By their modeling, even with a highly contagious individual moving around from an aisle seat in the middle of the plane, less than 10% of fellow passengers would risk becoming infected.

However, there are reports of higher infection rates with air travel. Astutely, the authors pointed out that transmission of infection also can occur in waiting areas and during the boarding and deplaning processes. In addition, pathogens that spread via aerosol might reach passengers more than a meter away from an infected index case. And, some of the reported outbreaks were associated with flights of longer duration than the three- to six-hour flights in this study.

■ COMMENTARY

These new data remind us that passenger behaviors influence the risk of becoming infected during air travel. Although most infections don't extend more than two seats beyond an infected index passenger, movement around the aircraft can expand the risk of spread.

[Although most infections don't extend more than two seats beyond an infected index passenger, movement around the aircraft can expand the risk of spread.]

Anecdotally, I reviewed this paper during a trans-Atlantic flight; I did not notice anyone coughing or sneezing within two seats or two rows of me. However, standing 6'4", I tend to move from my aisle seat much more than the typical passenger reported by Hertzberg's group, and I tend to spend more time out of my seat stretching my legs than did the average studied passenger. These new data offer clues as to how my mobility exposed me to more potentially infected co-travelers and might explain why I

developed a viral upper respiratory infection shortly after arriving at my destination.

Passenger movement during flight increases contact with different passengers. Modeling data also suggest that passenger movement alters the displacement of aerosolized particles in ways that might increase the spread of aerosolized pathogens.[1]

Beyond passenger behavior, other factors also influence whether a passenger will become infected during a long flight. Cabin ventilation systems on commercial aircraft use particulate filters and fully exchange cabin air approximately 15 times per hour.[2] This is effective in decreasing the risk of transmission of infection and explains why most cases are from passengers sitting in close proximity to contagious individuals or related to passenger movement around the cabin. However, ventilation systems are not always activated during flight delays prior to take-off, and spread of influenza has been reported with a three-hour on-ground delay when a plane's ventilation system was not activated.[3]

Hertzberg's data suggest that it is relatively uncommon for sick people to travel. However, with approximately 3 billion air passengers each year (averaging one flight for each two people on the planet each year), there will be times when germs are flying with airplane passengers. What should be done when someone with a respiratory infection is traveling? "Cover the cough" is always good advice, and the use of surgical-type face masks is relatively more common in Asia than elsewhere, for protection against both air pollution and infection.

As noted by Hertzberg, aircraft cabin hard surfaces are disinfected at least daily; it is not clear that wiping down seats and trays by passengers alters the transmission of infection. Since most transmission occurs within a meter of an infected person, asymptomatic passengers might try to move away from coughing travelers when other seats are available. ■

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ABSTRACT & COMMENTARY

Dealing With Multidrug-resistant Organisms on a National Level: CDC Successes and Problems on the Horizon

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

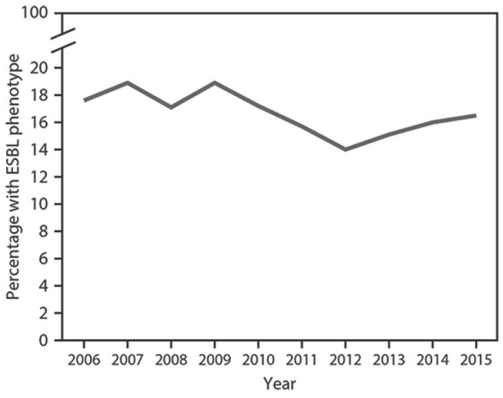
SYNOPSIS: CDC efforts, implemented at the local level, have been associated with a modest reduction in the incidences of *Escherichia coli* and *Klebsiella pneumoniae* with an ESBL phenotype and a more dramatic reduction in carbapenem-resistant *Enterobacteriaceae*.

SOURCE: Woodworth KR, Walters MS, Weiner LM, et al. Vital Signs: Containment of novel multidrug-resistant organisms and resistance mechanisms — United States, 2006-2017. *MMWR Morb Mortal Wkly Rep* 2018;67:396-401.

Woodworth and colleagues examined the trend in incidence of isolation of *Enterobacteriaceae* (focusing on *Escherichia coli* and *Klebsiella pneumoniae*) with an ESBL phenotype as evidenced by resistance to an extended spectrum ("third generation") cephalosporin, or of *Enterobacteriaceae* resistant to an anti-pseudomonal carbapenem (CRE). They used data from the National Healthcare Safety Network from 2006-2015.

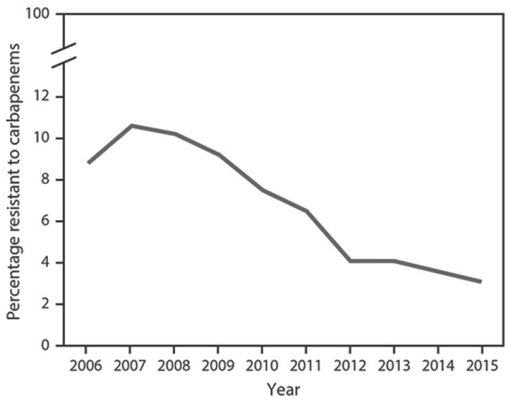
During that time, the proportion of *Enterobacteriaceae* with an ESBL phenotype decreased by approximately 2% each year, although in short-term acute care hospitals, the proportion remained stable among *E. coli* and *K. pneumoniae*, starting at 16.7% in 2006 and ending at 18.9% in 2015. (*See Figure 1.*) In contrast, the proportion of those with a CRE phenotype decreased by 15% annually during the same period. (*See Figure 2.*)

Figure 1: Percentage of ESBL-phenotype *Escherichia coli* and *Klebsiella pneumoniae* Causing Central Line-associated Bloodstream and Catheter-associated Urinary Tract Infections



Source: Centers for Disease Control and Prevention

Figure 2: Percentage of CRE *Escherichia coli* and *Klebsiella pneumoniae* Causing Central Line-associated Bloodstream and Catheter-associated Urinary Tract Infections



Source: Centers for Disease Control and Prevention

Testing for the presence of five carbapenemases was performed on 4,442 CRE isolates from January 2017 to September 2017 as well as 1,334 carbapenem-resistant *Pseudomonas aeruginosa* (CRPA). A carbapenemase was detected in 32% of CRE (65% of CRE *K. pneumoniae*) and in 1.9% of CRPA. KPC accounted for 88% of carbapenemases in CRE, while among the 25 CRPA, VIM was present in 72%.

A study of a median of 10.5 contacts in the healthcare setting of patients with CRE found that 11% of the contacts were colonized with a CRE carrying one of five carbapenemases; this proportion was higher in post-acute care facility contacts (14%) than in short-stay acute care hospitals (5.8%).

■ COMMENTARY

These results provide clear evidence of a decreased incidence of CRE from 2006-2015 but a much lesser improvement in incidence of ESBL phenotype *Enterobacteriaceae*. Woodworth and colleagues suggested that these differing results are the consequence of the more extensive control efforts directed at CRE than ESBL-producing organisms. Thus, the CDC developed CRE-specific guidance in 2009 (and subsequently updated them twice and also published an extensive report on the subject) for healthcare facilities that identified the presence of CRE with recommendations that included laboratory surveillance and targeted screening for asymptomatic colonization. Finally, in 2017, the CDC outlined a rapid reaction approach to the detection of even a single isolate of an emerging antibiotic-resistant pathogen. This approach, as summarized by Woodworth et al, rests upon the following:

- Rapid detection of targeted organisms and determination of their resistance mechanisms;
- On-site assessment to identify gaps in infection prevention;
- Identification of asymptomatic colonization by contact screening;
- Coordination of response among relevant facilities;
- Continuation with these interventions until any transmission is controlled.

These efforts are now also CDC-supported by establishment of the Antibiotic Resistance Laboratory Network, which provides testing for carbapenemases in CRE and CRPA at 56 state and local public health laboratories as well as screening for colonization at seven regional laboratories.

[These results provide clear evidence of a decreased incidence of CRE from 2006-2015 but a much lesser improvement in incidence of ESBL phenotype *Enterobacteriaceae*.]

Of the carbapenemase-positive isolates, 65% of which were *K. pneumoniae*, 221 expressed a carbapenemase other than KPC, and these included the metallo-β-lactamases NDM, VIM, and IMP. The presence of even small numbers of metallo-β-lactamases (VIM, NDM) is of concern, given their resistance to the currently commercially available β-lactamase inhibitors, including avibactam.

Despite this, the report reviewed here provides evidence that directed attention to an emerging problem of antibiotic resistance can provide significant improvement. Now we need even more of such efforts. ■

ABSTRACT & COMMENTARY

Extended-pulsed Dosing of Fidaxomicin vs. Standard-dose Vancomycin for *Clostridium difficile* Infection

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

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

SYNOPSIS: A randomized, controlled, open-label clinical trial conducted at 86 European hospitals that included adults aged 60 years or older found that extended-pulsed dosing of fidaxomicin was superior to standard-dose vancomycin for sustained cure of *Clostridium difficile* infection and resulted in fewer disease recurrences.

SOURCE: Guery B, Menichetti F, Anttila VJ, et al. Extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients 60 years and older (EXTEND): A randomised, controlled, open-label, phase 3b/4 trial. *Lancet Infect Dis* 2018;18:296-307.

Clostridium difficile infection (CDI) recurs in approximately 25% of patients treated with a standard 10- to 14-day course of oral vancomycin. Previous studies have shown that a 10-day course of fidaxomicin is non-inferior to vancomycin in achieving initial clinical cure.

Fidaxomicin is thought to cause less collateral damage to the gut microbiota than vancomycin, and extending the dosing of fidaxomicin may cause sustained suppression of *C. difficile*, leading to better microbiota recovery. Therefore, Guery and colleagues sought to assess whether extended-pulsed fidaxomicin would lead to more sustained clinical cures of CDI compared to vancomycin.

The study was a phase 3b/4, randomized, controlled, superiority, open-label trial conducted at 86 hospitals in 21 European countries (the EXTEND study). Patients eligible for the study were hospitalized, 60 years of age or older, and with clinically confirmed CDI, defined as having three or more unformed bowel movements in the 24 hours before randomization with a positive test for *C. difficile* toxin A or B.

Patients were excluded who received therapy for CDI for more than one day within the past 48 hours or who had three or more episodes of CDI within three months of enrollment. The participants were randomized in a 1:1 fashion to receive either fidaxomicin 200 mg twice daily for five days, followed by 200 mg every other day for 20 days, or vancomycin 125 mg four times a day for 10 days. The primary outcome was sustained clinical cure of CDI at 30 days at the end of treatment (day 40 for vancomycin and day 55 for fidaxomicin).

There were 177 patients randomized to the extended-pulsed fidaxomicin group and 179 to the vancomycin group. For the primary endpoint, 124 of 177 (70%) patients in the group that received extended-pulsed fidaxomicin had sustained clinical cure at 30 days compared to 106 of 179 (59%) patients in the vancomycin group (odds ratio [OR], 1.62; 95% confidence interval [CI], 1.04-2.54; $P = 0.030$). For the patients who demonstrated clinical response to treatment at the test of cure visit (day 12 for vancomycin and day 27 for fidaxomicin), fewer who received fidaxomicin had a recurrence of CDI at days 40, 55, and 90 compared to those who received vancomycin.

At day 90, only 11 (6%) of the patients who received fidaxomicin had a recurrence of CDI, compared with 34 (19%) who received vancomycin. Furthermore, bacterial diversity increased in stool samples to a higher extent in the fidaxomicin-treated patients compared to the vancomycin group. The rate of

serious drug-related adverse events was low in both groups.

■ COMMENTARY

The EXTEND study demonstrated the superiority of extended-pulsed fidaxomicin compared to standard-dose vancomycin for sustained clinical cure of CDI in patients 60 years of age and older. It also had the lowest rate of recurrent CDI at day 90 (6%) of any reported randomized clinical trial using metronidazole, vancomycin, or fidaxomicin.

Previously, studies with fidaxomicin showed a recurrence rate of 8-26%, depending on the number of recurrent CDIs. Thus, it seems probable that the dosing regimen in the present study accounted for the observed improved outcomes. As the authors hypothesized, this likely is due to the less harmful effects on the gut microbiota with the extended-pulsed fidaxomicin than oral vancomycin, the latter of which is known to deplete many beneficial types of gut bacteria, such as the Bacteroidetes.

One limitation of the study was the lack of an arm that used a tapering dosage of vancomycin, which the authors attributed to cost. Another was the exclusion of patients with three or more episodes of CDI. These patients are challenging to manage in clinical practice, and it needs to be determined how extended-pulsed fidaxomicin compares to fecal microbiota transplant in this patient population.

EXTEND is unusual because of its robust study design: a superiority antibiotic randomized clinical trial. Yet, one of the downsides of fidaxomicin has been its high cost, especially compared to generic vancomycin. The authors argued that because the extended-pulsed fidaxomicin uses the same number of tablets as the standard regimen, there is no additional increase in treatment cost with this approach. Additional studies of pulsed dosing of fidaxomicin for CDI in other scenarios, for example in patients with multiple disease recurrences or in those receiving antibiotics for another concurrent infection, along with more pharmacoeconomic analyses, are especially warranted. ■

ABSTRACT & COMMENTARY

Tuberculosis in the United States in 2017

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: While the incidence of tuberculosis in the United States in 2017 was the lowest ever recorded, the current rate of decline would be required to almost double to reach the goal of elimination of the disease in this country by the year 2100.

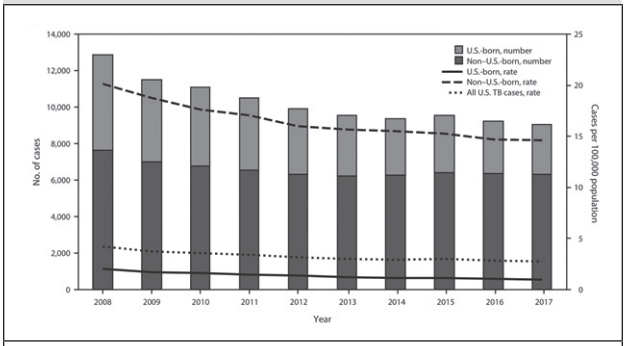
SOURCE: Stewart RJ, Tsang CA, Pratt RH, et al. Tuberculosis — United States, 2017. *MMWR Morb Mortal Wkly Rep* 2018;67:317-323.

The incidence of tuberculosis in the United States in 2017 was 2.8 cases per 100,000 persons, the lowest rate on record. However, the rate of reduction in incidence has slowed and is insufficient to reach the goal of elimination by the year 2100.

Based on provisional data, the CDC reports that 9,093 new cases of tuberculosis were reported in the United States, for an incidence of 2.8 cases per 100,000 population, a 2.5% decrease from the previous year — and the lowest incidence ever recorded. Among U.S.-born persons with new onset of tuberculosis in 2017, African Americans and whites accounted for 37.1% and 29.5% of cases, respectively, with a 55% decrease in case counts for each group over the past 10 years. The incidence ranged from 0.3 cases per 100,000 in Montana to 8.1 in Hawaii; it was 4.1 in New York state and 5.2 in California. The highest incidences among the U.S.-born were recorded for Native Hawaiians and other Pacific Islanders (6.5 per 100,000) and American Indians and Alaska Natives (3.7), followed by African Americans (2.8), Asians (2.0), Hispanics (1.5), and whites (0.4).

The decrease in the absolute number of new cases of tuberculosis in U.S.-born individuals was accompanied by an increasing proportion of cases attributed in non-U.S.-born individuals, who accounted for 69.8% of the total and whose incidence of tuberculosis was now 15 times greater than in U.S.-born persons. (*See Figure.*) The highest rate among these was in

Figure: Number of Tuberculosis (TB) Cases and Rate, by National Origin — United States, 2008-2017



Source: Centers for Disease Control and Prevention

Asians (27.0 per 100,000), followed by non-Hispanic blacks (22.0). The countries of origin of these cases in absolute numbers was highest for Mexico, followed by the Philippines, India, Vietnam, and China. The rate in non-U.S.-born decreased by only 0.9% from 2016 to 2017 (compared to a decline of 7.0% in U.S.-born individuals). Although not probative, but consistent with evidence that the majority of cases of tuberculosis in the United States result from activation of latent infection (LTBI), 45.0% of all cases in non-U.S. individuals occurred among those who had been in the United States for ≥ 10 years.

Overall, 4.6% of cases occurred in individuals who had experienced homelessness in the previous year, while 1.6% were in residents of long-term care facilities and 3.0% were confined to a correctional facility.

Only 1.0% of infections were caused by multidrug-resistant (MDR) *Mycobacterium tuberculosis* and there was only a single isolate of extensively drug-resistant (XDR) *M. tuberculosis*.

■ COMMENTARY

Although the United States experienced the lowest recorded incidence of tuberculosis in 2017, the rate of decrease has slowed from 5.3% in 2010-2013 to 2.0% in 2014-2017. (*See Figure.*) As pointed out by the authors, the 2017 rate is 28 times higher than the threshold of tuberculosis elimination in the United States, which is < 1 per 1 million persons. Achieving elimination of tuberculosis by 2100 would require a sustained annual decrease of 3.9% — almost twice the current rate of decrease.

As Stewart et al indicated, any hope of approaching such a rate of improvement requires maintaining efforts to reduce transmission of tuberculosis and enhanced efforts to detect and treat patients with LTBI. Testing for detection of LTBI should be focused on high-risk individuals, including individuals born in countries with a high prevalence of tuberculosis (no matter how long they have resided in the United States) and in persons in high-risk congregate situations, such as correctional facilities and homeless shelters. ■

ABSTRACT & COMMENTARY

HANDOC: Some Guidance on When to Order Echocardiograms in Patients With Streptococcal Bacteremia

By Dean L. Winslow, MD, FACP, FIDSA

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

SYNOPSIS: Non-β-hemolytic streptococci (NBHS) are the most common cause of infective endocarditis. In this retrospective study of 399 patients with NBHS bacteremia, 26 patients had endocarditis. HANDOC score (heart murmur, aetiology by specific species of NBHS, number of positive blood cultures, duration of symptoms, only one species in blood culture, and community-acquired infection) was predictive of endocarditis vs. non-endocarditis bacteremia.

SOURCE: Sunnerhagen T, Tornell A, Vikbrant M, et al. HANDOC: A handy score to determine the need for echocardiography in non-β-hemolytic streptococcal bacteremia. *Clin Infect Dis* 2018;66:693-698.

Researchers reviewed medical records from 399 patients with NBHS bacteremia in southern Sweden as part of an initial cohort. Of these 399, 26 patients ultimately were deemed to have infective endocarditis (IE). The following factors were identified that correlated with diagnosis of endocarditis: presence of heart murmur or valve disease; etiology with *Streptococcus mutans*, *S. bovis*, *S. sanguinis*, or *S. anginosus*; number of positive blood cultures ≥ 2; duration of symptoms ≥ 7 days; only one species growing in blood culture; and community-acquired infection. Using a cutoff between 2 and 3 points, HANDOC had a sensitivity of 100% and specificity of 73% in the first cohort. When these criteria were applied to a second validation cohort of 399 patients, the sensitivity was 100% and the specificity was 76%.

■ COMMENTARY

While NBHS and *Staphylococcus aureus* cause most cases of native valve endocarditis, the majority of patients who have bacteremia with either of these pathogens do not have IE. The Infectious Diseases Society of America currently has a panel of experts who are developing new guidelines to help clinicians manage *S. aureus* bacteremia, including when to order echocardiography. However, we do not have official guidelines in development to provide similar guidance for when to order echocardiography in the setting NBHS bacteremia. This is important since NBHS not only commonly cause IE, but also are seen commonly in neutropenic sepsis and are secondary only to coagulase-negative staphylococci as common contaminants seen in blood cultures.

I believe that for experienced clinicians, using the HANDOC criteria is something most of us have been doing all along (although we didn't have that spiffy acronym). However, this retrospective study should provide important guidance for hospitalists and other doctors who commonly manage patients with NBHS bacteremia in the hospital setting.

[This retrospective study should provide important guidance for hospitalists and other doctors who commonly manage patients with NBHS bacteremia in the hospital setting.]

Applying the criteria that came from this nice retrospective study should significantly reduce the inappropriate ordering of both transthoracic echocardiograms, which are expensive, and transesophageal echocardiograms, which are both expensive and can be associated with complications due the requirement for sedation as well as potential adverse consequences of passing a transducer into the esophagus, in patients with NBHS bacteremia. ■

ABSTRACT & COMMENTARY

Prosthetic Valve Endocarditis Due to *Candida*

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: Prosthetic valve endocarditis due to *Candida* spp. is associated with high mortality, but is curable — or at least controllable.

SOURCE: Rivoisy C, Vena A, Schaeffer L, et al; French Mycoses Study Group and Grupo de Apoyo al Manejo de las Endocarditis en España (GAMES). Prosthetic valve *Candida* spp. endocarditis: New insights into long-term prognosis — The ESCAPE Study. *Clin Infect Dis* 2018;66:825-832.

Rivoisy and colleagues reviewed the prospectively collected records of 46 patients from 41 centers in France and Spain with prosthetic valve endocarditis (PVE) due to *Candida* spp. Ten cases were judged by the Duke criteria to be possible endocarditis and 36 were proven endocarditis. *Candida* PVE, 60% involving a bioprosthesis, occurred 4-27.2 months (median, 8.9 months) after native valve replacement surgery. Almost half (48%), including all nine intravenous drug users, had experienced a previous episode of endocarditis after a median interval of 338 days. In five of these 22 patients, the initial episode had been due to *Candida* of the same species as was isolated subsequently

during the second episode of valve infection, and each had involved a native valve.

Presentation with one or more embolic complications occurred in 21 (46%) patients. Among these, pulmonary emboli occurred in four (36%) of 11 with right-sided endocarditis, while cerebral emboli occurred in 10 (21.7%) patients, and seven (15.2%) had splenic emboli.

Infection was due to *Candida parapsilosis* in 19 (41%) patients, followed by *Candida albicans* in 16 (35%), *Candida tropicalis* in five (10.9%), *Candida glabrata* in four (8.7%), and *Candida guilliermondii* in two (4.3%). None were found to be resistant to standard antifungals, including amphotericin B (although there are no official breakpoints for this drug), flucytosine, fluconazole, voriconazole, and caspofungin.

All patients received antifungal therapy, with 19 (41%) also undergoing surgical intervention; 27 patients received antifungal therapy alone. Twelve (71%) and 19 (66%) patients, respectively, survived. A contraindication was present in 15 of the 27 who did not undergo surgery, while three refused surgery and, in the remaining nine, surgery was deemed not necessary by their physicians.

Combination antifungal therapy, most often liposomal amphotericin B (L-amB) plus 5-flucytosine, was administered to 31 (67%) patients. The duration of induction antifungal therapy ranged from 24 to 69 days (median 40 days). In univariate analysis, survival was associated with younger age, L-amB-based treatment, long-term receipt of fluconazole, and being an intravenous drug user. Patients who received monotherapy with L-amB had better survival at six months than those who received caspofungin monotherapy (adjusted odds ratio [aOR], 13.52; 95% confidence interval [CI], 1.03-838.10).

The overall in-hospital mortality was 30%, but increased to 56% during the entire period of follow-up, with 18 (69%) deaths due to *Candida* PVE. Of the 31 patients who were alive at the end of induction therapy, 21 (68%) received maintenance fluconazole therapy and four (19%) of these had a relapse of their infection, as did five (50%) of the 10 who did not receive maintenance therapy.

■ COMMENTARY

The 2016 Infectious Diseases Society of America (IDSA) guidelines recommend initial treatment of *Candida* PVE with L-amB with or without flucytosine or an echinocandin given in high dose (e.g., caspofungin at 150 mg daily) together with valve replacement with continued induction antifungal therapy for a minimum of six weeks post-operatively.[1] This is to be transitioned to chronic administration of 400 to 800 mg (6-12 mg/kg) fluconazole daily.[1] However, it should be noted that all the IDSA recommendations are graded as strong, but based on low-quality evidence.

Although the IDSA guideline indicates that echinocandin and L-amB are each first-line treatment choices, the study reviewed here found that treatment with L-amB was statistically marginally superior to treatment with caspofungin. However, no information is provided regarding the doses administered, and it is possible that the higher-than-usual caspofungin doses recommended by IDSA were not used in these patients.

Somewhat surprisingly, Rivoisy and colleagues found outcomes of *Candida* PVE to be similar to those reported for *Candida* native valve endocarditis. However, they did confirm that the relapse rate is higher with the former infection. Of note is that the relapse rate was higher in those who received only 200 mg fluconazole daily — lower than recommended.

[Rivoisy and colleagues found outcomes of *Candida* PVE to be similar to those reported for *Candida* native valve endocarditis.]

Mortality was similar in patients with possible and probable endocarditis. The finding of similar outcomes for patients with and without surgical intervention seems surprising to me and raises the question of whether some of the latter group did not, in fact, have *Candida* PVE. I would think twice about recommending against valve replacement for a patient with this infection. ■

REFERENCE

1. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016;62:e1-50.

Updates

By Carol A. Kemper, MD, FACP

Probiotics and Lactobacillemia

SOURCE: Boumis E, Capone A, Galati V, et al. Probiotics and infective endocarditis in patients with hereditary hemorrhagic telangiectasia: A clinical case and review of the literature. *BMC Infect Dis* 2018;18:65.

Probiotics are consumed widely, including generalized use in many acute care medical facilities, as well as by health foodies worried about their fecal microbiota. And yet, whenever I speak with patients about their use, they seldom remember the name of the product, nor do they know the ingredients. Many are surprised to learn the contents often simply are no more than lactobacilli or various yeasts.

The risk of these kinds of products (other than to your pocketbook) generally is low, and such products seldom are pathogenic, mostly in those at risk, e.g., immunocompromised patients.

The authors of this study reported a case of an older patient with hereditary hemorrhagic telangiectasia (HHT) and a bioprosthetic aortic heart valve who presented with lactobacillemia. The patient had been diagnosed with HHT about seven years earlier, and experienced repeated episodes of epistaxis requiring laser coagulation and nasal packing. The patient had a history of recurrent *Streptococcus mutans* and *S. aureus* bacteremia, possibly related to these procedures and/or the packing, and had received multiple courses of antibiotics. As a result, the patient developed intermittent diarrhea and was self-medicating with up to seven different probiotic products, three of which contained *Lactobacillus rhamnosus*.

In 2017, the patient was hospitalized for fever of unknown origin, and multiple blood cultures grew *L. rhamnosus*. A transesophageal echocardiogram demonstrated a 1.1 cm vegetation on the aortic valve. The patient responded to a six-week course of amoxicillin-clavulanate and gentamicin.

A systematic review of the literature found only 10 cases of infective endocarditis associated with probiotic ingestion, six of whom had HHT. Most patients with lactobacillus bacteremia have had a recent dental extraction or disruption of intestinal mucosa that would increase the risk for gut translocation (e.g., colonoscopy). Surprisingly, immune compromise does not appear to be a significant predisposing factor for lactobacillus bacteremia. In a survey of 89 episodes of lactobacillus bacteremia, 47 (53%) of which were due to *L. rhamnosus*, more than two-thirds of patients (69%) were found to have gastrointestinal or hepatic neoplasm within 12 months.

Endocarditis from lactobacillus is rare. In one series of 73 cases of endocarditis from *Lactobacillus* species, 63% had predisposing valvular disease and 12% had a prior history of endocarditis. A dental procedure was identified as a likely risk factor in 47% of cases, but only three cases were linked to probiotic use.

It has been surmised that patients with HHT have disruption in nasal and gastrointestinal mucosa, predisposing them to bacteremia and endocarditis. As a result, patients with HHT undergoing nasal procedures involving disruption of mucosa and nasal packing should be considered candidates for pre-emptive antibiotics.

Probiotic strains of *L. rhamnosus* may appear identical to clinical strains, although they can be differentiated using pulsed-field gel electrophoresis (although this was not done for this case).

The Last Poliovirus Challenge

SOURCES: Collett MS, Hincks JR, Benschop K, et al. Antiviral activity of pocapavir in a randomized, blinded, placebo-controlled human oral poliovirus vaccine challenge model. *J Infect Dis* 2017;215:335; Sutter RW, Modlin JF, Zaffran M. Completing polio eradication: The case for antiviral drugs. *J Infect Dis* 2017;215:333; McNeil DG Jr. The war on polio, from the boots on the ground. *The New York Times*, Oct. 24, 2017: D4.

The Global Commission for the Certification of the Eradication of Poliomyelitis, which was launched in 1996-1997, is zeroing in on its final goals. At that time, poliovirus was still in circulation in many parts of the non-Western world, and thousands of children still were paralyzed every year. Since then, wild poliovirus type 2 has been officially eradicated from the world (although it still exists in the laboratory) and wild poliovirus type 3 has not been seen causing naturally occurring infection since 2012. At present, only pockets of circulating wild poliovirus type 3 continue to infect fewer than 100 children per year, mostly in remote, hard-to-reach areas of Afghanistan, Pakistan, and, to a lesser degree, Nigeria and neighboring countries.

Another goal of the global commission was the removal of Sabin type 2 strain from oral polio vaccine (OPV), which was accomplished in 2016, with the aim of diminishing the circulation of vaccine-derived virus. Immunocompromised individuals infected with OPV-derived strains of virus can excrete virus for years, and ultimately will remain the last "natural" reservoir of poliovirus — remaining a threat to those who are non-immune or unvaccinated.

This means that in addition to the final push to eradicate wildtype virus, there must be a renewed focus on the eradication of vaccine-strain virus still found circulating in some communities around the world. This can be done only by continued surveillance of sewage samples, identification of such individuals, and antiviral treatment aimed at eradicating their chronic infection. Currently, there is no effective treatment for immune deficiency-associated vaccine-derived infection.

In a randomized, placebo-controlled, blinded study, researchers examined the efficacy of a new enterovirus capsid inhibitor called pocapavir (V-073) (similar to another capsid inhibitor, pleconaril) in a group of adults aged 18 to 50 years, who received a single dose of monovalent OPV1. Participants previously had received four doses of childhood poliovirus vaccine, and had normal levels of total IgA immunoglobulin and evident PV-specific immunity. Study participants were randomized to active treatment or placebo in a 2:1 ratio. The treatment group was assigned one of four different dosing schemes of pocapavir: 1,600 mg daily for 14 days, started at either 24 hours or 72 hours post-mOPV1 challenge, with or without a fatty meal.

Participants entered the study facility in eight groups of 18 patients. They remained in isolation for 14 days, were assigned to one of three different bedrooms (six people per bedroom), and shared common dining, entertainment, and bathroom facilities. Cumulative and daily excretion of virus was measured in stool samples for 28 days. Neutralizing antibodies were measured at baseline and on the final study day.

Upon OPV oral challenge, 98% of individuals became infected and had virus-positive stools. Fecal virus was cleared within a median of 10 days in the treatment group vs. 13 days in the placebo group ($P = 0.0019$). Virus susceptibility was measured from the beginning to the end of study — and initially, 138 of 141 participants had pocapavir-sensitive virus. Three of the subjects were found to have pocapavir-resistant virus at baseline before the administration of study drug. Of those who initially excreted pocapavir-sensitive virus, 31%, including five patients in the placebo group, were resistant to pocapavir by the last positive stool.

Drug-resistant virus began to appear as early as day 2 to day 13, and the duration of excretion of drug-resistant virus ranged from 2 to 27 days (mean, 13 days). Drug levels measured for all 96 participants in the treatment group for each of the four different dosing regimens were well above the recognized in vitro antiviral inhibitory concentration for OPV1.

In the subgroup of 52 individuals treated with pocapavir with no evidence of resistant virus during the study course, virus was cleared more quickly from stools within a median of 5.5 days (range, 2-18 days).

These data indicate that transmission of OPV-derived virus and secondary infection within the facility were common. This is consistent with known data on the high frequency of secondary infection in the household setting — but serves as a stark reminder of just how infectious excretion of virus in stool may be — even in a controlled setting such as this. ■

ABIM CME MOC ACCREDITED

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
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CME QUESTIONS

1. Risk factors for becoming infected by a respiratory pathogen during air travel include which of the following?

a. Sitting within 3 m of a coughing passenger

b. Remaining seated throughout the flight

c. Failing to sanitize tray tables

d. Sitting in the plane during pre-take-off delays

2. In the CDC report on containment of multidrug-resistant bacteria, which of the following is correct?

a. Ninety-nine percent of carbapenem-resistant *Enterobacteriaceae* (CRE) were due to the presence of KPC.

b. A carbapenemase was found in only 1.9% of carbapenem-resistant *Pseudomonas aeruginosa*.

c. Metallo-β-lactamases were not detected.

d. The reduction of the incidence of *Enterobacteriaceae* with an ESBL phenotype has been much greater than the reduction of CRE.

3. Which of the following is correct regarding tuberculosis in the United States in 2017?

a. The incidence in 2017 was the lowest rate on record.

b. A decreasing proportion of cases occurred in non-U.S.-born persons.

c. The occurrence of active tuberculosis among non-U.S.-born persons after they have been in the United States for ≥ 10 years accounts for only 5% of cases among all non-U.S.-born individuals.

d. A total of 106 cases of XDR tuberculosis were identified.

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.