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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Extreme Weather and Infectious Diseases: What Will Follow Hurricanes Harvey and Irma?

By Stan Deresinski, MD, FACP, FIDSA

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

Among the dangers faced after a severe weather event is an increased risk various of infections.[1] After Hurricane Katrina, the main types of infections seen were gastrointestinal, wound, respiratory, and skin.[2] CDC has listed a panoply of post-disaster infections. (*See Table 1.*)

Waterborne infections resulting from exposure to flood waters or contamination of water supplies are of major concern. A systematic literature review of global waterborne outbreaks involving water-related weather events identified 93 reports dealing with 87 individual outbreaks in 29 countries.[3] The most frequent causes were *Vibrio spp.* (most in Asia) and *Leptospira spp.* (most in North America and Asia). The water supply was confirmed as the apparent source of infection in 54.8% of instances in which testing was performed. The weather events consisted of heavy rainfall and flooding, each often resulting from hurricanes, in just over one-half. Contact with water most commonly occurred while wading or performing cleaning activities.

Among the identified problems were overwhelmed water treatment facilities and sewage systems. Among the cases in which the type of contaminated water source was stated, the main water supply was implicated in two-thirds and well water in one-third. The former source often was associated with outbreaks due to *Campylobacter* and *Cryptosporidium*. Pathogens associated with environmental water exposure, rather than water

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Infectious Disease [ALERT]

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supply contamination, were *Leptospira spp*., *Cryptosporidium spp*., norovirus, and *Vibrio vulnificus*.

After Katrina the notable causes of diarrhea/gastroenteritis were norovirus, non-toxigenic *Vibrio cholerae*, and non-typhoidal *Salmonella*. An outbreak of norovirus is believed to have affected at least 1,000 individuals in a large evacuation center in Houston.[4] *Vibrio* infections acquired in the United States almost always are caused by species such as *Vibrio parahaemolyticus*, *V. vulnificus*, and non-O1, non-O139 *V. cholerae* that are noncholeragenic, and no cholera epidemic was identified after Katrina. However, two cases of infection with toxigenic *V. cholerae* that appeared to be the result of eating undercooked or contaminated shrimp occurred in a Louisiana couple after Hurricane Rita (which occurred approximately one month after Katrina).[5]

Leptospirosis, not a cause of diarrhea, often results from exposure to environmental water and may be an important cause of febrile illness after flooding. As an example, after Hurricane Hortense in Puerto Rico, 17 of 70 (24%) febrile patients with a negative serological screen for dengue virus infection had evidence of leptospirosis.[6]

Wound infections also are of concern. After Katrina, 14 cases due to *V. vulnificus*, three of which were fatal, were recorded, as were three wound infections, with two deaths due to *V. parahaemolyticus*.[2] More common causes of wound infection, of course, also occur.

Skin/mucosal infections identified after Katrina included MRSA infection, tinea corporis, folliculitis, and presumed viral conjunctivitis. Others observed were scabies, head lice, and immersion foot. Arthropod bites, which may mimic infection, also were observed. Varicella infection often is diagnosed first as the result of its skin manifestations.

Respiratory illnesses noted by CDC after Katrina included pertussis, respiratory syncytial virus infection, and streptococcal pharyngitis, with the apparent increased frequency likely the result of crowding in evacuation centers. Exposure to communicable diseases, including respiratory infections in these centers, is of concern and perhaps none more so than tuberculosis. CDC reported that after Katrina, evaluation of evacuees with suspected tuberculosis resulted in confirmation of this infection in two of nine. An associated problem for public health departments was assuring maintenance of patients on therapy for tuberculosis.

Crowding in shelters leads to exposure to additional communicable diseases. Among illnesses identified in Louisiana shelters after Katrina was "flu-like symptoms or pneumonia," which occurred in 26.3/1,000 residents and was more common than all other infections (15.6/1,000).[2] Among these "other infections" were tuberculosis, hepatitis, pertussis, varicella, encephalitis, meningitis, and "other serious communicable illness of outbreak concern." Diarrhea occurred in 12.8/1,000 sheltered evacuees.

Also of concern after fresh water flooding, whether after a hurricane or not, is an increase of arbovirus infections as a result of proliferation of mosquito populations. An apparent increase in cases of West Nile virus infection was observed in Mississippi after Katrina. The recent introduction of Zika may prove to be of concern. Finally, after recession of the flood waters, molds will take over.[7]

The strain placed on public health by extreme weather events is enormous. Posid has listed some of the issues that must be faced.[2] (*See Table 2*.) Dean Winslow provided a fascinating narrative insider review of the elements of the critical military response to Katrina, for which he was tasked with assessing and managing public health issues and force protection issues for the National Guard and active duty forces involved in rescue, recovery, and relief operations.[8] Events such as those discussed here will only continue to increase in frequency and ferocity as climate change progresses. ■

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Table 1. Infectious Diseases After a Disaster

Cryptosporidiosis	Shigellosis
Enteroviruses	Skin infections
Escherichia coli (gastrointestinal)	Tetanus
Giardiasis	Toxoplasmosis
Hepatitis B, C, and HIV	Trench foot or immersion foot
Leptospirosis	Tuberculosis
Legionnaires' disease	Varicella
MRSA	*Vibrio cholerae*
Norovirus	*Vibrio vulnificus*
Rotavirus	West Nile virus

Source: Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/disasters/disease/infectious.html. Accessed Sept. 18, 2017.

Table 2. Public Health Issues Associated With Natural Disasters

Water quality
Wounds
Solid waste disposal
General sanitation (debris removal)
Vector control
Immunizations (workers and population)
Close-quarter, densely populated living conditions
Disruption of access to medical services
Also — maintenance of continuity of care (HIV, TB)

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ABSTRACT & COMMENTARY

Chagas Seroprevalence in Military Personnel in Texas

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 cross-sectional study of military trainees and instructors who spend significant time in field conditions was performed at Joint Base San Antonio to determine the prevalence of *Trypanosoma cruzi* infection. None tested positive by polymerase chain reaction nor by enzyme-linked immunosorbent assay or indirect immunofluorescent antibody.

SOURCE: Webber BJ, Pawlak MT, Valtier S, et al. Prevalence and seroprevalence of *Trypanosoma cruzi* infection in a military population in Texas. *Am J Trop Med Hyg* 2017. [Epub ahead of print.]

Investigators studied 1,033 military trainees and instructors (most of whom were enrolled in the Security Forces Apprentice course) during a 16-month period (April-November 2015, April-November 2016). Fifteen to thirty percent of students and instructors participated in the study. This population was chosen since they spend more time in field conditions than basic military trainees do. Study participant demographics were consistent with current active duty United States Air Force (USAF) members: 77% male, 55% white/non-Hispanic, with a mean age of 21.6 years. Five subjects reported a triatomine bite and 131 reported a bite from an unidentified insect during the study period. Instructors had more time in field conditions than students did. All polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (EIA), and indirect immunofluorescent antibody (IFA) tests were negative, with the exception of one equivocal EIA result (in a student who was born and lived in Central America before immigrating to the United States and enlisting in the U.S. Armed Forces).

■ COMMENTARY

This was an incredibly important study, which was performed in a rigorous manner by the USAF and

U.S. Army Military Public Health teams in San Antonio. The findings from this seroprevalence study are reassuring in view of the alarming biosurveillance findings at Joint Base San Antonio (JBSA) and elsewhere in South Texas. These recent biosurveillance findings included: 1) 8% seroprevalence of *T. cruzi* in military working dogs and a large number of cases of acute Chagasic cardiomyopathy in dogs were observed. 2) Forty-three percent of adult triatomines and 22% of nymphs tested positive for *T. cruzi* by PCR, and 33% of these triatomines tested positive for human blood in their mid-gut. (Among adult triatomines, *Triatoma sanguisuga* [66%] and *Triatoma gerstaeckeri* [30%] were trapped most commonly.) 3) Cases of autochthonous transmission/acquisition of human infection with *T. cruzi* have been documented in South Texas.

A number of factors may have contributed to the fact that no military trainees or instructors acquired infection with *T. cruzi* during the relatively short study period. In my opinion, the major reason no new infections were seen may have been because the biosurveillance findings (noted above) were acted upon promptly by the USAF Military Public Health team led by Dr. Leo Cropper (senior author on this paper). This included removal of cotton rat nests from the vicinity of the field tents, application of insecticide inside and outside the tents, and use of DEET as well as permethrin-treated uniforms by all military personnel. Biological reasons for low transmission observed in humans may include the fact that the sylvatic triatomine vectors in the southern United States are less likely to defecate while taking a blood meal. Lastly, it is known that older individuals, those of Hispanic ancestry, and those living in rural or poverty stricken areas are more susceptible to infection with *T. cruzi*. The subjects in this study population were largely non-Hispanic whites and were young (21.6 years of age), so they may have had high resistance to acquisition of infection.

In the interest of full disclosure, I had the pleasure of working closely with Dr. Cropper and his team (including most of the authors listed on this paper) during one of my last assignments before retiring from the military in late 2015. I was incredibly impressed with the scientific rigor that went into their approach to this and several other health and safety issues they addressed during the time I was assigned to JBSA and the 59th Medical Wing. The excellent but often under-recognized scientific work being conducted by U.S. military scientists and epidemiologists follows in the proud tradition of Walter Reed and other giants of military medicine. ■

ABSTRACT & COMMENTARY

Rheumatic Heart Disease — The Global Situation

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: With advances in access to good medical care, the global burden of rheumatic heart disease is declining. However, there still is significant disease in resource-limited regions of the world.

SOURCE: Watkins DA, Johnson CO, Colquhoun SM, et al. Global, regional, and national burden of rheumatic heart disease, 1990-2015. *N Engl J Med* 2017;377:713-722.

As part of the 2015 Global Burden of Disease study, Watkins and colleagues systematically reviewed data about non-fatal and fatal rheumatic heart disease over the course of 25 years, ending in 2015. The researchers determined estimates of prevalence and mortality.

Data indicate that there were approximately 33.4 million cases of rheumatic heart disease in 2015, with a cumulative total of 10.5 million disability-associated life-years due to rheumatic heart disease.

Rheumatic fever, the instigator of rheumatic heart disease, is considered to be a disease of poverty. Indeed, India, China, Pakistan, Indonesia, and the Democratic Republic of Congo account for three-fourths of the world's new cases of rheumatic heart disease. With many people living with rheumatic heart disease, it is estimated that 1% of the people of

South Asia and central Sub-Saharan Africa and 1.5% of those in Oceania are living with rheumatic heart disease.

From 1990 to 2015, the global mortality of rheumatic heart disease decreased by 48%, but this still represented 319,400 deaths in 2015. The highest mortality rates were found in Oceania, South Asia, and Central Africa. Pacific Island nations accounted for very high death rates, with more than 10 deaths per 100,000 population per year reported in the Solomon Islands, Papua New Guinea, Kiribati, Vanuatu, Fiji, the Federated States of Micronesia, and the Marshall Islands.

■ COMMENTARY

In the 1980s, the conventional teaching was that penicillin treatment for group A streptococcal pharyngitis reduced the risk of developing rheumatic fever but did not otherwise alter the clinical course of the illness. With rheumatic fever almost eradicated from the United States, there was legitimate academic discussion about whether it was even necessary to treat children with strep throat.[1]

Then, two things happened. First, in 1984, John Nelson finally published data from a study he had done in the 1950s.[2] Randomized and placebo-controlled, the results showed clearly that penicillin treatment was associated with reductions in pharyngeal injection and cervical lymph node tenderness two days after initial evaluation, with improved resolution of fever, and with more rapid family assessment that the child had recovered. Second, there was a resurgence in the number of clinical cases of rheumatic fever in the western United States.[3]

Appropriate evaluation of febrile children with pharyngitis and early antibiotic treatment of those with positive streptococcal tests have continued in the United States, and rheumatic fever continues to be uncommon in the United States. However, rheumatic heart disease remains common in parts of the world where children are less likely to get care for acute illnesses.

An editorial accompanying Watkins' paper was titled "Rheumatic Heart Disease — an Iceberg in Tropical Waters."[4] The editorialists pointed out that Watkins only included clinically evident cases of patients suffering from rheumatic heart disease and that echocardiographic screening usually finds three to 10 cases of subclinical rheumatic heart disease (the "submerged and hidden" part of the "iceberg") for each clinical case. In one area of Kenya, for instance, local screening has demonstrated that 8% of schoolchildren have rheumatic heart disease.

What Can Be Done?

Multifaceted changes in healthcare infrastructure could help, and cardiac surgery could be made more available in resource-limited areas. There is already exploration in these directions in Kenya.[5] At the same time, efforts are needed to stop the spread of streptococcal infections and to treat active infections prior to the onset of cardiac disease.[6] The *New England Journal of Medicine* editorialists certainly agree with continuing to focus efforts on major diseases like tuberculosis, HIV, and malaria that each cause three to five times as many deaths as rheumatic heart disease. However, they cleverly point out that more than 500 times as much money is spent on research and development related to those diseases as for rheumatic heart disease. Maybe, as the authors suggest, now would be a good time for renewed scientific investigation and funding.[4]

In addition, other acquired cardiac conditions still plague children in resource-limited regions of the world, including tuberculous carditis and HIV cardiomyopathy.[7] As prevention and management of streptococcal pharyngitis improves and cardiac care expands, there also would be benefit for children with other acquired cardiac conditions in settings where there is no cardiac surgery available.[7] ■

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ABSTRACT & COMMENTARY

Fungal Endophthalmitis: Another Risk Associated With Intravenous Drug Use

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 retrospective cohort study found that endogenous fungal endophthalmitis is associated with intravenous drug use and frequently results in poor visual outcomes despite appropriate surgical and antifungal therapy.

SOURCE: Tirpack AR, Duker JS, Baumal CR. An outbreak of endogenous fungal endophthalmitis among intravenous drug abusers in New England. *JAMA Ophthalmol* 2017;135:534-540.

Intravenous drug users (IVDUs) have an increased risk for a number of serious infectious disease complications, including infective endocarditis, osteomyelitis, HIV, and HCV. Less frequently, IVDUs can develop endogenous fungal endophthalmitis (EFE) through transient fungemia with dissemination to the eye. Tirpack and colleagues noticed an increase in cases of EFE at their institution (New England Eye Center, Boston) in IVDUs and sought to determine patient characteristics, management, and outcomes currently associated with EFE.

The study was retrospective and included IVDUs who had fundus findings characteristic of EFE, along with positive fungal ocular and/or blood cultures. Patients with exogenous endophthalmitis, such as post-surgical or from trauma, were excluded. The presenting visual acuity (VA) was assessed and the main outcome measured was the final best-corrected VA. All patients with EFE who presented to the investigators' institution between May 2014 and May 2016 were screened for inclusion in the study.

Ten patients were included in the study, all of whom had unilateral eye involvement. Their mean age was 34 years (range, 24-60 years), and five patients were female. Nine patients lacked systemic signs or symptoms of infection, and one reported fevers and chills. The most common presenting symptom was that of floaters in the eye (n = 8), followed by reduced vision (n = 6), eye pain (n = 5), and photophobia (n = 3). The presenting VA ranged from 20/25 to detection of hand motions only. Dilated fundus examinations showed vitreous inflammation in all the eyes, with four having the classically described "string of pearls" formation. Nine of the patients were admitted to the hospital (one refused admission) and underwent intravitreal aspiration for cultures, followed by injection of an antifungal agent, with seven receiving voriconazole and two receiving amphotericin B. All patients received systemic antifungal therapy as well, with eight prescribed intravenous voriconazole and one prescribed oral voriconazole and oral fluconazole. The reason for the oral therapy was not provided. All patients were discharged home with oral antifungal therapy for a mean duration of 55 days (range, 35-76 days). Despite this, five patients developed worsening vitreitis and/or VA and required pars plana vitrectomy (PPV). The mean time to PPV was 18 days (range, 7 to 45 days). Cultures, including vitreous fluid and blood, were positive in only four cases and included *Candida albicans* (n = 2), *Candida tropicalis* (n = 1), and *Candida dubliniensis* (n = 1). The final VA ranged from 20/40 to 20/300, with 20/70 as the median final VA in the five patients who underwent PPV and 20/300 in those who did not have the procedure. All of the patients were eventually non-adherent to follow-up.

■ COMMENTARY

The diagnosis of EFE is made by a history of acute or progressive vision loss, characteristic physical examination findings, and laboratory confirmation (i.e., culture results). However, the diagnosis can be challenging, especially in IVDUs who may present with other signs or symptoms of embolic disease such that the eye symptoms are overlooked. Moreover, patients experiencing mental status changes might not be able to communicate changes in their vision. As the study by Tirpack et al highlights, a dilated funduscopic examination is a crucial step when the diagnosis of EFE is being considered. The low diagnostic yield of the cultures (only 4/10 were positive for *Candida*) was not surprising and has been observed in previous studies. This is believed

to occur because *Candida* preferentially sequesters within inflammatory nodules and the initial vitreous tap is of low volume and from the middle of the vitreous cavity, when most of the focal inflammation is closer to the retinal surface. Moreover, even though a larger volume of fluid is available at the time of PPV, cultures obtained during the procedure often are negative because the patient already would have been started on systemic antifungal therapy.

Amphotericin B used to be the standard therapy for EFE, although it has fallen out of favor because it does not reach therapeutic intraocular levels when administered systemically and frequently causes retinal toxicity when given by intravitreal administration. Voriconazole has superseded amphotericin B because it achieves better blood-retinal barrier penetration, resulting in high intraocular concentration, and is safe for intravitreal therapy.

An area of controversy in the management of EFE pertains to the role of early vitrectomy in patients with worsening inflammation despite local and systemic antifungal therapy. Prior studies have shown improved visual outcomes when PPV is performed earlier in the course of EFE, which may be due to the procedure clearing the infecting organism, removing inflammatory mediators, and allowing increased penetration of systemic antifungal therapy. However, these benefits must be weighed carefully against the increased risk for retinal detachment when surgery is performed on an acutely inflamed eye. The final median VA was higher in the patients who had PPV, which also was associated with earlier resolution of inflammation and infectious lesions.

It is notable that none of the patients had 20/20 vision at the end of the study period, emphasizing the serious consequences of EFE. Thus, clinicians must maintain a high index of suspicion for EFE in IVDUs who present with visual changes, which might be the only clue that a serious fungal infection is present. ■

Delafloxacin (Baxdela®)

By Lina Meng, PharmD, BCPS, BCCCP

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

Delafloxacin is a new broad-spectrum fluoroquinolone with in vitro activity against Gram-positive organisms including methicillin-resistant *Staphylococcus aureus* (MRSA), Gram-negative organisms including *Pseudomonas aeruginosa,* and fluoroquinolone-resistant *Klebsiella pneumoniae*, atypical organisms, and anaerobes including *Bacteroides fragilis*. It is available both intravenously and orally. Delafloxacin was approved by the U.S. Food and Drug Administration in June 2017 for Acute Bacterial Skin and Skin Structure Infections (ABSSSI), based on two global Phase III trials for ABSSSI showing non-inferiority to vancomycin plus aztreonam for the primary endpoint of clinical response at 48-72 hours.[1,2] In a post-hoc analysis of these studies, delafloxacin achieved high microbiological response rates against levofloxacin-non-susceptible *S. aureus* isolates (80/81; 98.8%) and MRSA isolates (70/71; 98.6%).[3]

Structural modifications to delafloxacin improve its basicity, which is theorized to improve transmembrane passage and its activity in acidic environments. Delafloxacin may have a role in infections involving biofilms and low pH based on in vitro studies, but whether this translates into benefit in the clinical setting remains to be seen.[4]

In vitro studies suggest a low probability of selection of resistant mutants: Spontaneous resistance was seen in 2×10^{-9} to $< 9.5 \times 10^{-11}$ in MRSA strains.[5] Delafloxacin's activity against Gram-positive organisms may be enhanced by its inhibition of DNA gyrase (topoisomerase II) and topoisomerase IV enzymes to similar degrees, which is unlike other fluoroquinolones that have a greater affinity for topoisomerase IV in Gram-positive organisms.[5] Additionally, efflux pumps did not affect delafloxacin activity in vitro.[5]

A survey of isolates collected at U.S. and European medical centers in 2014 found that U.S. isolates of MRSA exhibited delafloxacin MIC_{50} values over 64 times lower than levofloxacin and ciprofloxacin MIC_{50} values. (*See Table 1.*) Delafloxacin was the most active fluoroquinolone against *S. pneumoniae* and *S. viridans* group streptococci, showing MIC_{90} values over 64 times lower than levofloxacin. Against *P. aeruginosa*, delafloxacin and ciprofloxacin were two-fold more active against levofloxacin. (*See Table 1.*) In a separate study, delafloxacin and ciprofloxacin

Table 1. Activities of Delafloxacin and Comparator Fluoroquinolones (U.S. Isolates, 2014 survey)[6]

Organism group	% of isolates susceptible by CLSI criteria	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	Notes
MRSA				
Delafloxacin	-	0.06	0.5	87.6% of isolates susceptible at MIC ≤ 0.25 µg/mL, the manufacturer's proposed breakpoint for susceptible[7]
Levofloxacin	30%	4	> 4	
Ciprofloxacin	0%	> 128	> 128	
S. pneumoniae				
Delafloxacin	-	0.008	0.015	
Levofloxacin	98.9%	1	1	
P. aeruginosa				
Delafloxacin	-	0.25	> 4	65% of isolates susceptible at MIC ≤ 0.5 µg/mL, the manufacturer's proposed breakpoint for susceptible[7]
Levofloxacin	72.5%	0.5	> 4	
Ciprofloxacin	75.0%	0.25	> 4	

Table 2. Dosing in Adults With ABSSSI[7]

Renal function† (mL/min/1.73 m^2)	Dosing
eGFR ≥ 30	450 mg PO q12h for 5-14 days 300 mg IV q12h for 5-14 days 300 mg IV q12h, then switch to 450 mg PO q12h for a total duration of 5 to 14 days
eGFR < 30	PO: No dosage adjustment necessary IV: 200 mg IV q12h ± switch to 450 mg PO q12h
eGFR < 15 or ESRD on hemodialysis	Use is not recommended; contains cyclodextrin
†As calculated using the Modification of Diet in Renal Disease (MDRD) eGFR equation	

Table 3. Pharmacokinetics/ Pharmacodynamics[7,8]

Absorption	• PO bioavailability (450 mg tablet) 58.8% • Time to peak: 1 hour
Distribution	$V_{d,ss}$: 30-48 L (approximates total body water)
	Plasma protein binding 84% (primarily to albumin)
Metabolism	• Unchanged parent drug is predominant component in plasma • Glucuronidation (UGT1A1, UGT1A3, and UGT2B15) accounts for ~1% of administered dose
Elimination	Renal CL: 35-45% of total clearance
	$t_{1/2}$ (h): 3.7 ± 0.7 (single IV dose); 4.2-8.5 h (multiple dose PO)
Excretion	• IV: 65% unchanged (urine), 28% unchanged (feces) • PO: 50% unchanged (urine), 48% unchanged (feces)
Pharmacodynamic target	AUC/MIC

exhibited $MIC_{50/90}$ values of 32/128 µg/mL for levofloxacin-resistant *P. aeruginosa*.[4]

ADVERSE EFFECTS/WARNINGS[7]

Delafloxacin carries similar black box warnings as other fluoroquinolones for tendinitis and tendon rupture, peripheral neuropathy, central nervous system effects, and exacerbation of myasthenia gravis. Other notable adverse effects include hypersensitivity reactions and *Clostridium difficile*-associated diarrhea.

Its effects on QTc were studied in healthy adults at doses up to 900 mg.[9] Changes in QTc interval, corrected for heart rate using Fridericia's formula, were less than 10 milliseconds compared to baseline.

DRUG INTERACTIONS[7]

Delafloxacin should be taken at least two hours before or six hours after antacids or multivitamins containing aluminum, magnesium, sucralfate, zinc, or iron due to interference with delafloxacin's absorption.

CONCLUSIONS

Delafloxacin is an orally available alternative in ABSSSI when MRSA (including fluoroquinolone-resistant strains) might be involved. Its activity against fluoroquinolone-resistant *S. pneumoniae*, *K. pneumoniae*, and *E. coli* is of interest. However, use in monomicrobial infections likely would result in employment of an antibiotic with an unnecessarily

broad spectrum. With in vitro activity against *B. fragilis*, delafloxacin may prove useful in mixed aerobic-anaerobic infections, or mixed *S. aureus* and *P. aeruginosa* infections. Its potential role in other infections where highly bioavailable oral options are needed (such as osteomyelitis or bacteremia) would need to be validated first in clinical studies. Additionally, although in vitro delafloxacin resistance to MRSA was infrequent, there is a general concern of selective pressure and the emergence of quinolone resistance, particularly in *S. aureus*.

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ABSTRACT & COMMENTARY

California and Coccidioidomycosis: Be Careful About the Air You Breathe

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

SYNOPSIS: Cases of coccidioidomycosis significantly increased in 2016.

SOURCE: Cooksey GS, Nguyen A, Knutson K, et al. Notes from the Field: Increase in coccidioidomycosis — California, 2016. *MMWR Morb Mortal Wkly Rep* 2017;66:833-834.

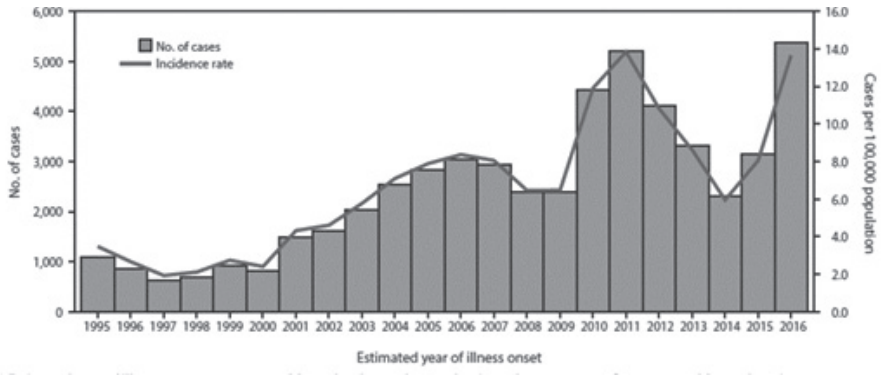
All but approximately 3% of cases of coccidioidomycosis in the United States are reported in the states of Arizona and California, and the number reported generally has increased, with some fluctuations, in both states over the last two decades. (*See Figure.*) In California during that time, a peak incidence of 13.8 per 100,000 population was reached in 2011, followed by decrease through 2014. This was followed by a small increase in 2015 and then approached the previous record peak in 2016 when the reported incidence was 3.7 per 100,000 population, with the total of 5,372 cases the highest ever.

Most cases were reported from the Central Valley and Central Coast regions, especially in counties known to be highly endemic, with Kern County, whose major city is Bakersfield, alone accounting for 42% of total cases. While the incidence rate in 2016 was highest in individuals 40 to 59 years of age, those younger than 20 years of age experienced the greatest increase in incidence relative to the previous year at 134%. Males were affected more frequently than females; there was too much missing data to allow reporting of the incidence by race or ethnicity.

■ COMMENTARY

The cause of the observed 2016 spike in reported cases of coccidioidomycosis is unknown. Most suspect, however, were the heavy rains in that year following several years of drought. Such conditions may be optimal for the proliferation of fungus in the soil, which, with disruption by wind or human activity, results in airborne dissemination of

Figure. Number of Coccidioidomycosis Cases and Incidence Rate, by Estimated Year of Illness Onset* — California, 1995-2016



*Estimated year of illness onset was extracted from the closest date to the time when symptoms first appeared for each patient.
Source: Centers for Disease Control and Prevention.

disarticulated arthroconidia, which then may be inhaled.

Currently, early steps have been taken to construct a high-speed rail system from the San Francisco Bay Area through the middle of the Central Valley to Los Angeles. It can be predicted that many of the workers constructing this system through the most highly endemic area will acquire coccidioidomycosis. ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Corporate Antibiotic Stewardship

SOURCE: Statement on Antibiotic Use — Updated 8/23/2017. McDonald's. Available at: http://news.mcdonalds.com/us/media-statements/response-to-antibiotics-in-chicken. Accessed Sept. 12, 2017.

Antibiotic stewardship is not just for hospitals and medical clinics. In an August press release, McDonald's announced that they are ahead of schedule in tightening the use of antibiotics in their broiler chicken supply. The press release states that "engaging farmers, producers and veterinarians in the responsible use of antibiotics is key to our vision of preserving antibiotic effectiveness through ethical practices." The company announced that it had attained the goal of serving broiler chicken throughout the United States that had not received certain antibiotics (as designated by the World Health Organization) earlier than expected in 2016. And they are on track to eliminate the use of antibiotic-treated broiler chicken in Europe, Brazil, Canada, and Japan by January 2018, and plan to ban the use of colistin in broiler chicken by the end of 2019. Similar restrictions are planned for beef, pork, and laying hens.

Their goals are being reached sooner than anticipated with the assistance of the U.S. Department of Agriculture and the development of more rapid screening techniques for verifying antibiotic-free meat.

But … the cat is already out of the bag.

Hypervirulence Meets Antibiotic Resistance — A Lethal Combination

SOURCE: Gu D, Dong N, Zheng Z, et al. A fatal outbreak of ST11 carbapenem-resistant hypervirulent *Klebsiella pneumoniae* in a Chinese hospital: A molecular epidemiological study. *Lancet Infect Dis* 2017; doi.org/10/1016?S1473-3099(17)30489-9.

Chinese investigators report the appearance of a new *Klebsiella* "superbug," which appears to be a convergence of hypervirulent and multidrug-resistant strains of *Klebsiella pneumoniae*. Five critically ill, mechanically ventilated trauma patients admitted to intensive care at a new branch of Zhejiang University Hospital (in Hangzhou, China) between February and April 2016 developed severe pneumonia. All of them failed to respond to antibiotics and died with multi-organ system failure and septic shock. Carbapenem-resistant *K. pneumoniae*, which were resistant to 26 different antibiotics, were recovered from blood or respiratory secretions. Since this kind of multidrug-resistant organism had not been previously found in this brand new facility, which had opened only three months earlier, an outbreak investigation was launched. Twenty-one carbapenem-resistant *K. pneumoniae* strains were recovered from various clinical specimens from the five patients. All 21 strains shared similar PFGE profiles, except for one patient who had four slightly different strains. One representative strain was selected from each patient, and all five carried blaKPC2,

blaTEM-1, and blaCTX-M-65 genes — meaning all were New Dehli metallo-beta-lactamase (NDM) strains. Pairwise SNP analysis suggested the different organisms derived from a single clone. The first patient with recognized infection had been transferred to the Zhejiang facility from an outside hospital following a car accident with multiple injuries, and ultimately was considered the source for the outbreak.

Bacterial colonies were found to be unusually viscous with a positive string test. Eighty percent of organism survived within neutrophils for one hour, and killed 100% of wax moth larvae within 24 hours, consistent with other hypervirulent *K. pneumoniae* strains. Further testing revealed they belonged to the ST11 strain type with the acquisition of a pLVPK-like virulence plasmid. In addition to containing the typical virulence genes for ST11 strains, the five outbreak strains also contained iucABCD, rmpA2, and iutA genes, which are considered additional virulence genes.

The authors retrospectively screened 387 clinical ST11 carbapenem-resistant *K. pneumoniae* strains from 25 provinces and municipalities in China from 2015. Eleven isolates (3%) from three different provinces carried the pLVPK-like virulence plasmid, similar to above, all of which also carried blaKPC-2 genes. Two isolates also carried rmpA2 and iucA, while the other nine carried rmpA and iroN genes, suggesting they could harbor the full cassette of genes observed in the five cases above. All of the isolates were recovered from blood and/or respiratory secretions, and five of the patients had died.

These results demonstrate the convergence of a highly virulent ST11 strain of *K. pneumoniae*, which has acquired a unique set of virulence genes, together with NDM-containing organism with the blaKPC-2 gene — creating a most effective, lethal, and drug-resistant superbug.

Glue Masquerading as an Aortic Root Abscess

SOURCE: Silverton N, Bull DA, Morrissey CK. Excessive surgical adhesive: A case report of aortic root abscess doppelganger. *A A Case Rep* 2017;9:57-59.

Aortic root abscess is considered a surgical emergency — especially when involving a prosthetic valve. This unfortunate 23-year-old was admitted with streptococcal aortic valve endocarditis requiring prosthetic valve replacement. His post-operative course was complicated by cardiac arrest, complete heart block requiring temporary pacing, and recurrent sepsis and hemodynamic instability. Repeat transesophageal echocardiogram (TEE) showed a new 1 × 2 cm tricuspid valve vegetation with severe TCV regurgitation, and a heterogenous echodensity at the base of the aortic valve concerning for root abscess. He was taken back to the operating room for intended tricuspid and aortic valve replacement and aortic root debridement and reconstruction.

Once the surgeons got into the chest, they discovered that the aortic valve was well seated and functioning normally with no evidence of abscess. Instead, they found an excess of surgical glue posterior to the aortic root that was removed easily with suction. The TCV was replaced, and the patient made an uneventful recovery, except for problems with his pacer.

Surgical glue often is used as an adjunct to strengthen the suture line in cardiovascular surgery. Surgical glue is made from a combination of bovine serum albumin and glutaraldehyde, and comes in a pre-filled syringe. Cardiologists should be aware that globs of surgical glue may appear on echocardiogram as a heterogenous fluid collection mimicking abscess. It would be interesting to know how long this image persists post-operatively and what magnetic resonance imaging would reveal.

Molecular Diagnostic Coup

SOURCE: Sada R, Uno S, Hosokawa N, Komiya T. Prosthetic valve endocarditis caused by *Bartonella henselae* presenting as recurrent fever and imitating granulomatosis with polyangiitis. *J Formos Med Assoc* 2017; doi: 10.1016/j.jfma.2017.04.001.

The use of 16S ribosomal RNA PCR testing for diagnostic purposes has greatly expanded our diagnostic ability in tough cases of culture-negative endocarditis that come to surgery for valve replacement. A colleague had a recent diagnostic coup using 16S RNA testing of pathologic tissue samples from a case of culture-negative endocarditis. All cultures and serologies, including serologies for *Bartonella henselae* and *B. quintana*, had been unrevealing, but PCR of valve tissue yielded *Bartonella clarridgeiae* — which allowed for appropriate antibacterial therapy in this challenging case.

These authors describe a case of a 61-year-old Japanese dairy farmer with recurrent fever of unknown origin for months, which seemed to respond transiently to various courses of antibacterial therapy. The patient had a remarkable history of prosthetic aortic valve replacement, but multiple blood cultures were negative, and echocardiography on three separate occasions was

unremarkable. Because of continued fever, his workup was extended — and he was found to have polyclonal gammopathy with anti-PR3-ANCA. He then developed nephritis with active sediment, and renal biopsy demonstrated crescentic glomerulonephritis. A tentative diagnosis of granulomatosis with polyangiitis was made. Just before corticosteroids were introduced, a fourth echocardiogram suggested a small prosthetic valve vegetation, prompting aortic valve replacement. Surgical specimens were positive for *B. henselae* by 16S ribosomal gene PCR sequencing, using specific primers, and *Bartonella henselae* IgM and IgG serologies were positive.

Infective endocarditis rarely may mimic vasculitis, and C-ANCA (especially with an atypical pattern) may be found in a number of conditions stimulating a strong immune system response, including inflammatory bowel disease, cystic fibrosis, rheumatoid arthritis, and chronic infection. In this dairy farmer with house cats and dogs, an occult zoonosis makes sense. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. Which of the following were the most frequent type of infections identified after Hurricane Katrina?

a. Gastrointestinal, wound, respiratory, and skin

b. Gastrointestinal, bone, respiratory, and skin

c. Respiratory, bone, lungs, and skin

d. Urinary, gastrointestinal wound, respiratory

2. Which of the following statements is true about rheumatic heart disease?

a. It has been all but eradicated.

b. It affects millions of people, mostly in resource-limited regions.

c. It is fatal without early cardiac surgery.

d. It is rare in Pacific Island nations.

3. Which of the following is correct regarding delafloxacin?

a. It is highly active in vitro against levofloxacin-resistant *Pseudomonas aeruginosa*.

b. It has no activity against *Bacteroides fragilis* in vitro.

c. It has potent in vitro activity against MRSA.

d. Despite in vitro activity, it was ineffective against MRSA causing acute skin and skin structure infections in clinical trials.

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.