Boonshoft School of Medicine
WRIGHT STATE UNIVERSITY

INFECTIOUS DISEASES NEWSLETTER

August 2015

T. Herchline, Editor

LOCAL NEWS

ID Fellows

Dr Shruti Patel will be at the VA Medical Center in August - September, and at Miami Valley Hospital in October. At this time, there is no 1st year fellow.

Global Health & Preventing Pandemics Presentations

Dr. Timothy Brewer, Chair, Board of Directors for Consortium of Universities for Global Health will be making a series of presentations on September 9th. At 7 AM, he will be presenting Surgery Grounds Rounds at Kettering Medical Center and at 6 PM he will addressing WSU students and faculty at the Center for Global Health (3123 Research Blvd, Kettering). There will also be informal discussions at lunchtime (contact Lynne Smith, 208-3771 or lsmith@premierhealth.com) and at the Center for Global Health from 5-6 PM. Dr. Brewer is Vice Provost for the University of California Los Angeles, and is formerly the Director of Global Health Programs for McGill University Medical School. He is also formerly the Program Director for the International Society for Infectious Diseases, whose programs include ProMED-mail.

Masquerage 2015

Masquerage 2015 will be held October 17th at the Roundhouse at the Montgomery County Fairgrounds. Since its inception, it has raised more than $1,250,000 in unrestricted funds in support of HIV/AIDS case management, education, prevention, and advocacy. Masquerage allows attendees to have a unique and entertaining experience while supporting AIDS Resource Center Ohio. Each year, guests dress up to match the evening's changing themes. The Theme Release Party will be August 17 from 6:00 to 8:00 PM at the Therapy Café on East Third Street. Tickets for the Theme Release Party are available online at: http://arcoh.convio.net/site/Calendar?id=100881&view=Detail.

Local Disease Activity

There has been a dramatic increase in cases of Legionella during the summer. For the year (through July 26), there have been 40 cases of Legionella. There were 32 cases for all of 2014, which was the highest total in the past 10 years. In the last week of June, there were 10 patients admitted with Legionella pneumonia. In July (through the 26th), there were a total of 22 patients admitted. All except one of the cases were pneumonia. Ages have ranged from 4 years to 91 years old with an average of 57.9 years; there were 24 males and 8 females. There have been no deaths reported. There have not been any geographically clustering of cases, and questionnaires have not been identified any common factors. Cases of Legionella are increased around the state of Ohio. There is some published data to suggest that there may be an increase in cases in response to increased rainfall.

A group of people became ill after attending a graduation party in Clark County in mid-June. The main symptom was diarrhea. One was an 84 year old woman who was taken to Good Samaritan Hospital subsequently passed away. It appears at least 24 people became ill out of approximately 150 attendees. Of the attendees, 41 were Montgomery County residents, with 19 reporting illness. ODH assisted Clark County in the investigation. Testing of the available food demonstrated evidence of fecal contamination, but did not confirm the presence of any pathogens.

There have been 9 reports of suspected Lyme Disease in Montgomery County this year, through July. Of these, 6 had negative Western Blots and are unlikely to have had Lyme Disease. Two were diagnosed with erythema migrans and had positive serology as well as a history of recent travel (NY, TN). The remaining report was an individual with a rash suspected to be EM; he had no travel history and was not tested for Lyme Disease.

NATIONAL NEWS

Legionella in New York City

The office of Mayor Bill de Blasio reported August 3rd that there have been 81 reported cases of Legionnaires' disease with seven deaths in a New York City outbreak. Sixty-four people have been hospitalized. All of the victims were older adults with additional underlying medical problems, according to the office of Mayor. The NYC Health Department's probe includes testing water from potential sources in the area. Of the 17 cooling towers that city health officials have inspected for Legionella, five buildings in the area of the outbreak cluster, including a hospital and a hotel, have so far tested positive for Legionella. Remediation was completed at each of the locations, all in the South Bronx. The number of cases could climb higher since the last disinfection of cooling towers tied to the outbreak took place on Monday, and the incubation period for Legionnaires' disease is 10 days. De Blasio said he would propose legislation this week to prevent future outbreaks, including regular cooling tower inspections, new recommendations for an outbreak response and sanctions for failing to comply with new standards. An estimated 8,000 to 18,000 hospitalized cases of Legionaires' disease occurs each year in the US.

Cyclospora Outbreak

The U.S. Food and Drug Administration is investigating the latest outbreak of cyclosporiasis in the United States. The Centers for Disease Control and Prevention has been notified of 358 confirmed cases of the infection through July 30. The FDA said it has not identified a "conclusive vehicle" for the latest outbreak, but preliminary investigations found that cilantro from the state of Puebla, Mexico was supplied to restaurants where some of those who have become ill ate. Fresh cilantro from Puebla has been linked by health officials to the 2013 and 2014 annual cyclosporiasis outbreaks as well. U.S. officials earlier this week implemented a partial ban on imports of the herb from the area, after human feces and toilet paper were found in growing fields and around facilities. Wal-Mart Stores Inc and Kroger Co are pulling some cilantro from stores. The 2015 outbreak has been confirmed in 26 states, with clusters of illness identified in Texas, Wisconsin and Georgia. The parasite, *Cyclospora cayetanensis*, infects the small intestine, typically causing watery diarrhea, and frequent, sometimes explosive, bowel movements. It is spread by ingesting something - such as food or water - contaminated with feces. If untreated, those infected could experience no symptoms at all, or have them come and go, or have them last from a few days to a month or longer.

New Hepatitis C Drugs

The US Food and Drug Administration (FDA) approved two new drugs on July 24th for hepatitis C, one for genotype 3 and the other for genotype 4. The first is a combination of ombitasvir, paritaprevir, and

ritonavir (*Technivie,* AbbVie) in a tablet for use with ribavirin in adult patients with hepatitis C virus (HCV) genotype 4 infection without scarring and cirrhosis. This combination with ribavirin is the first that has demonstrated safety and efficacy to treat genotype 4 HCV infections without the need for co-administration of interferon. Genotype 4 is one of the least common. The safety and efficacy of Technivie were evaluated in 135 adults with chronic HCV genotype 4 infections without cirrhosis. All patients who received Technivie with ribavirin achieved sustained virologic response at 12 weeks (SVR12) compared with 91% of those who received Technivie without ribavirin. The most common side effects seen with Technivie plus ribavirin were fatigue, asthenia, nausea, insomnia, pruritus, and other skin reactions. Elevations of liver enzymes to greater than five times the upper limit of normal occurred in approximately 1% of study patients. The NS5A replication complex inhibitor daclatasvir (*Daklinza*, Bristol-Myers Squibb) also cleared the FDA today for use with sofosbuvir (*Sovaldi*, Gilead Sciences) to treat HCV genotype 3 infection. The safety and efficacy of daclatasvir plus sofosbuvir for 12 weeks were evaluated in 152 treatment-naive and treatment-experienced adults with chronic HCV genotype 3 infection. They were monitored for 24 weeks post treatment. SVR12 was achieved in 98% of the treatment-naive patients with no cirrhosis of the liver and 58% of the treatment-naive patients with cirrhosis. In the treatment-experienced group, 92% with no cirrhosis and 69% with cirrhosis achieved SVR12. Fatigue, headache, nausea, and diarrhea were the most common side effects seen with daclatasvir plus sofosbuvir. Daclatasvir carries a warning that symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is given with sofosbuvir in combination with daclatasvir.

INTERNATIONAL NEWS

Ebola Vaccine Shows Great Promise

Results from an interim analysis of the Guinea Phase III efficacy vaccine trial show that VSV-EBOV (Merck, Sharp & Dohme) is highly effective against Ebola. The independent body of international experts that conducted the review advised that the trial should continue. Preliminary results from analyses of these interim data are published in the British journal The Lancet. The Guinea vaccination trial began in affected communities on 23 March 2015 to evaluate the efficacy, effectiveness and safety of a single dose of the vaccine VSV-EBOV by using a ring vaccination strategy. To date, over 4 000 close contacts of almost 100 Ebola patients, including family members, neighbours, and co-workers, have voluntarily participated in the trial. The vaccine is showing 100% efficacy in individuals although more conclusive evidence is needed on its capacity to protect populations through so called “herd immunity”. The 'ring' vaccination method adopted for the vaccine trial is based on the smallpox eradication strategy. The premise is that by vaccinating all people who have come into contact with an infected person you create a protective 'ring' and stop the virus from spreading further. The trial stopped randomization on 26 July to allow for all people at risk to receive the vaccine immediately, and to minimize the time necessary to gather more conclusive evidence needed for eventual licensure of the product. The Guinea Ebola vaccine trial is the coordinated effort of many international agencies. WHO is the regulatory sponsor of the study, which is implemented by the Ministry of Health of Guinea, WHO, Médecins sans Frontières (MSF), EPICENTRE and the Norwegian Institute of Public Health. The trial team includes experts from The University of Bern, the University of Florida, the London School of Hygiene and Tropical Medicine, Public Health England, and the European Mobile Laboratories.

New Tool in the Effort to Eradicate Polio

Over the last few years, efforts to eradicate worldwide polio have been without full success. The biggest challenge standing in the way of eradicating polio has involved the operational logistics of getting the

vaccine to people who need it, especially in difficult areas plagued by violence or poverty. The microneedle patch, which resembles a small, round adhesive bandage, could bring polio vaccines to the people that need it. By applying it to the skin and pushing down, the vaccine is delivered in a matter of minutes. Rather than requiring highly trained medics, minimally trained personnel could go from door to door, quickly administering the vaccine. Polio was declared eradicated in the United States in 1979. But there are still districts where only 75% to 80% of children are covered, which allows the virus to continue circulating in Afghanistan, Pakistan and Nigeria.

Case Conference

Contributed by Shruti Patel, MD

A 3 year old female with a history of Acute Lymphoblastic Leukemia had persistent cough for one month. Pertussis was diagnosed one month ago and treated with azithromycin. Her household contacts received prophylaxis with azithromycin as well. Three days prior to admission, her productive cough, dyspnea, fever and fatigue worsened. Her chest radiograph showed prominent peribronchial markings with right upper lobe and lower lobe consolidation. She was admitted to intensive care unit with acute respiratory failure and pneumonia. She was started on empiric antibiotics regimen of vancomycin, ceftriaxone and fluconazole. Respiratory failure progressed with worsening hypoxia and she required BiPaP. She developed cardiopulmonary arrest and despite extensive efforts to resuscitate her, she expired within 24 hours of admission. Lung biopsies from her autopsy showed numerous coccobacilli at the luminal surface of the bronchial epithelium and respiratory spaces with alveolar hemorrhage and fibrinous edema which was consistent with fulminant pertussis pneumonia. One out of two blood cultures obtained on admission grew gram negative bacilli after six days of incubation, which was identified as *Bordetella pertussis* by outside labs and confirmed by Centers for Disease control.

Discussion

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1. Centers for Disesase Control and Prevention. Fatal case of unsuspected pertussis diagnosed from a blood culture - Minnesota. MMWR 2004; 53:131-2.
2. Janda WM, Santos E, Stevens J, Celig D, Terrile L, Schreckenberger PC.Unexpected isolation of *Bordetella pertussis* from a blood culture. J ClinMicrobiol. 1994 Nov; 32(11):2851-3. PubMed PMID: 7852585; PubMed Central PMCID: PMC264173.
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New Antimicrobials

Contributed by: Katelyn Booher, D.O.

Isavuconazonium sulfate (Cresemba) is a triazole antifungal approved for use March 2015. It is a pro-drug of isavuconazole and is indicated for use in the treatment of invasive aspergillosis and invasive mucormycosis. A randomized double-blind, controlled trial for treatment of invasive aspergillosis found that the efficacy of isavuconazole was noninferior to that of voriconazole[1]. An open-label trial that studied primary as well as salvage therapy of invasive mucormycosis showed efficacy with isavuconazole that was similar to that reported for amphotericin B and posaconazole[1].

Isavuconazonium sulfate can be given intravenously or orally in capsule form. The loading dose is 372mg every 8 hours for 6 doses (48 hours) by oral or IV routes. The maintenance dose is 372mg once daily via oral or IV routes starting 12 to 24 hours after the last loading dose. Each capsule contains 186mg of isavuconazonium sulfate and each single-dose vial for IV use contains 372 mg of isavuconazonium sulfate[1].

Contraindications include coadministration with strong CYP3A4 or inducers. Isavuconazonium sulfate is associated with dose-related shortening of the QTc interval, and is therefore contraindicated in patients with familial short QT syndrome[2].

Major warnings and precautions include reports of serious hepatic reactions and infusion-related reactions. The medication is pregnancy class C. The most frequent adverse reactions include nausea, vomiting, diarrhea, headache, elevated liver chemistry tests, hypokalemia, constipation, dyspnea, cough, peripheral edema, and back pain. Immunosuppressants such as tacrolimus, sirolimus, and cyclosporine may require therapeutic drug monitoring and dose adjustments if administered with isavuconazonium sulfate[2].

The bioavailability after oral administration is 98%. No dose adjustment is necessary in patients with renal impairment. The standard loading and maintenance doses should be used in patients with mild to moderate hepatic disease. However, no studies have evaluated isavuconazonium sulfate in the setting of severe hepatic impairment[2].

Similar to other azole antifungals, the mechanism of action of isavuconazonium sulfate is inhibition of ergosterol synthesis, a key component of fungal cell membranes. Specifically, lanosterol 14-alpha-demethylase, which normally converts lanosterol to ergosterol, is inhibited, leading to fungal cell membrane weakening[2].

References

1. Miceli MH, Kauffman CA. Isavuconazole: A New Broad-Spectrum Triazole Antifungal Agent. Clin Infect Dis. July 2015.
2. McCormack PL. Isavuconazonium: first global approval. Drugs. May 2015; 75(7):817-22.

Introductory Guide to Clinical Research Approval

Contributed by: Brittney Dietz, Summer Research Student

According to the U.S. Department of Health and Human Services, research can be defined as a "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge (Title 45 Code, 4). Before any research involving human subjects can be conducted, an institutional review board (IRB) must approve the research proposal. Requirements vary slightly from one IRB to another, but in general they require written protocol, informed consent document, and a request for approval. The IRB has the authority to approve, disprove, or require modification of the research plan. Depending on the degree of risk, the IRB will conduct continuing review of research activities intermittently throughout the research process.

A protocol typically includes four parts: background, methods, data to be collected, and references. The background should inform the reader of two things: what is already known about the subject in question and what the study seeks to know about the subject. Further, the background explains why the research is significant. The methods explain how the research will be conducted, and what tools and techniques are required to perform the research. The researcher must also divulge exactly what data was will be collected and examined, and how this data will be used. Finally, a list of trustworthy references and sources should be provided.

For those studies requiring an informed consent document, researchers must demonstrate to the IRB how each human subject will provide voluntary consent before participating in research. This document informs the subjects of the risks involved by participating, what data will be collected, and the benefits by participating in the study. It must be written at a level of understanding appropriate for the expected subjects - typically no higher than 8th grade reading level.

Many Dayton institutions including Wright State University, The University of Dayton, Dayton Children's Hospital, Miami Valley Hospital, and Wright Patterson Air Force Base Medical Center have registered IRBs. In addition to IRB approval, many hospitals and public health organizations require institutional review before research can be conducted. Some institutions, such as Wright State University and Kettering Health Network, require additional training in the protection of personal health information. Links to these institutions can be found at the bottom of the article.

The Wright State University IRB follows the regulations put forth in The Belmont Report, which was created by the U.S. Department of Health, Education, and Welfare in 1979 as a result of many unfortunate unethical research activities conducted on human subjects including the Nuremberg War Crimes and Tuskegee syphilis study (Belmont Report). The Belmont Report puts forth three main principles by which all IRBs should use to evaluate research proposals. The first principle is respect for persons, and requires that each participant must voluntarily consent and participate and in research after he or she has been thoroughly informed of the research activities and the risks involved. Further, the personal health information, privacy, and confidentiality of each participant must be protected. The second principle, beneficence, ensures the risks involved by participating are minimized, and that these risks are justified by the potential benefits to the participant or to society as a whole. Justice, the third principle, mandates that risks and benefits alike should be equally distributed amongst society, such that one subset of a population should not take all the risk and reap all of the benefits.

Research topics may qualify for an expedited review by the IRB to expedite the approval process if the research activities present no more than minimal risk and involve procedures in one or more of the following categories:

1. Studies on drugs and medical devices if one of the following is met:

   a. An investigational new drug application is not needed
   b. Research on medical devices where an investigational device exemption application is not mandatory or the medial device is approved and is being used in agreement with its approved labeling
2. Compilation of blood samples by heel stick, ear stick, finger stick, or venipuncture in the following ways:
   a. From non-pregnant, healthy adults weighing a minimum of 110 pounds - Blood may not be drawn more than twice a week and the amount drawn may not surpass 550 mL in an 8 week period
   b. From other adults and children, taking the health, age, and weight of the subjects into consideration - Blood may not be drawn more than twice a week and the amount drawn must be the lesser of 50 mL or 3 mL per 1 kg in an 8 week period
3. Collection of biological samples by noninvasive procedures. Examples include: hair, nail clippings, teeth if care requires an extraction, secretions, salvia, placenta removed at delivery, amniotic fluid prior to or during labor, dental plaque, skin cells collected by swabs or mouth washings or sputum after nebulization
4. Collection of data through noninvasive measures routinely performed in clinical practice (excluding x-rays and microwaves). Examples include: magnetic resonance imaging, electrocardiography, moderate exercise, musculoskeletal strength testing, body composition evaluation, flexibility testing,
5. Data that has been collected for non-research purposes, including medical treatment
6. Data from voice recordings, video recordings, or digital recordings
7. Research on individual or group behavior
8. The continuation of research that has been previously reviewed and approved by the IRB as follows:
   a. Research is indefinitely closed to new subjects, all subjects have completed research-related tasks, and research remains active only for long-term follow-up for subjects; or
   b. No subjects have registered and no other risks have been identified; or
   c. The remaining research related activities are restricted to data analysis
9. Continuation of research, not conducted under new drug application or device exemption where categories two through eight do not apply, but the IRB has approved research activities and agrees that no greater than minimal risks exist

Some studies may qualify for exempt status, but are subject to the same approval process. These categories include research conducted using commonly accepted educational practices; research involving the effectiveness of instructional techniques; research using educational tests or surveys; research utilizing existing and publically available data, documents, or records; food and taste quality/evaluation; and the use of information such that data cannot be linked to the individuals. Quality improvement projects, even if the goal is to publish the results, are also typically exempt.

Local Institutional Review Boards & Research Panels

Wright State University: Robin Wilks – Administrative Coordinator. Tel: 937-775-4462
Email: robyn.wilks@wright.edu http://www.wright.edu/research/compliance/human-subjects

University of Dayton: Mary Connolly – IRB Chair. Tel: 937-229-3493
Email: IRB@udayton.edu. https://www.udayton.edu/research/compliance/irb/

Dayton Children's Hospital: Beverly Comer – IRB Coordinator. Tel: 937-641-4218
E-mail: comerb@childrensdayton.org. http://www.childrensdayton.org/cms/sitelet/bc9dfdf115b94b14/index.html

Kettering Health Network: Gail Young – IRB Coordinator. Tel: 937-395-8409
Email: gail.young@khnetwork.org. https://www.irbnet.org/release/index.html

Wright Patterson Air Force Base Medical Center: IRB Main Office Tel: 937-904-8100
Email: 711HPW.IR.dl.all@wpafb.af.mil. http://www.wpafb.af.mil/library/factsheets/factsheet.asp?id=7496

Miami Valley Hospital Clnical Research Center: http://deptwebs.mvh.org/mvh/clinicalresearch/

Public Health – Dayton & Montgomery County: http://www.phdmc.org/research-review

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2. Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review. < http://www.hhs.gov/ohrp/policy/expedited98.html>. November 9, 1998.
3. How to write a good abstract for a scientific paper or conference presentation. U.S. National Library of Medicine National Institutes of Health. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136027/>.
4. Human Subjects: What Is an IRB? The Office of the Vice President for Research. Wright State University. < http://www.wright.edu/research/compliance/human-subjects>.
5. Institutional Review Board (IRB) Documentation. University of Dayton. <https://www.udayton.edu/research/compliance/irb/forms/index.php>.
6. Protection of Human Subjects. Title 45 Code of Federal Regulations Part 46. U.S. Department of Health and Human Services. January 15, 2009.
7. Collaborative Institutional Training Initiative: https://www.citiprogram.org

Upcoming Events

August 2015		
12	Journal Club	MVH 6NW
26	Case Conference	MVH Maxon Parlor
September 2015		
9	Journal Club	MVH 6NW
	Global Health Presentations, Dr. Timothy Brewer	Various
17-21	ICAAC http://www.icaac.org/	San Diego, CA
30	Case Conference	MVH Maxon Parlor
October 2015		
7-11	IDSA/ID Week https://www.idweekinternational.com/Home.aspx	San Diego, CA
14	Journal Club	MVH 6NW
25-29	American Society of Tropical Medicine & Hygiene https://www.astmh.org/Home.htm	Philadelphia,PA
28	Case Conference	MVH Maxon Parlor
November 2015		
11	Journal Club Case Conference cancelled	MVH 6NW
December 2015		
9	Journal Club Case Conference cancelled	MVH 6NW
January 2016		
13	Journal Club	MVH 6NW
27	Case Conference	MVH Maxon Parlor
February 2016		
22-25	Conference on Retroviruses and Opportunistic Infections http://www.croiconference.org/	Boston, MA
March 2016		
2-5	International Congress of Infectious Disease http://www.isid.org/icid/	Hyberabad, India
April 2016		
9-12	European Congress of Clin Micro & Inf Dis	Istanbul, Turkey
May 2016		
18-21	Society for Healthcare Epidemiology http://www.shea-online.org/Education/SHEASpring2016Conference.aspx	Atlanta, GA
June 2016		
12-14	Refugee Health Conference http://www.northamericanrefugeehealth.com/	Niagra Falls, NY