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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ID Grand Rounds - Stanford University

Woman, 58, with Fever and Abdominal Pain

By Dana Clutter MD,

Postdoctoral Fellow in Infectious Diseases , Stanford University

Dr. Clutter reports no financial relationships in this field of study.

A 58-year-old woman from Southern Australia with a history of medically-managed liver abscess eight months prior to admission and recurrent urinary tract infections presented to our hospital with two weeks of fever and right upper quadrant pain. She initially presented to an outside hospital with fever, and was treated with norfloxacin for a presumed urinary tract infection. Despite this treatment, her fevers persisted and were associated with fatigue, arthralgias and night sweats. One day prior to admission she developed severe, constant right upper quadrant pain that was worse -with any movement. She denied any nausea, vomiting, diarrhea, dysuria, flank pain, or jaundice.

Her past medical history was notable for a liver abscess eight months prior to presentation that was not aspirated, but that was treated in Australia with one month of an unknown course of antibiotics. She also had a history of nephrolithiasis associated with recurrent urinary tract infections, *Plasmodium vivax malaria*, and irritable bowel syndrome. On arrival she was not taking any medications, but had just completed a 2-week course of norfloxacin. Regarding potential exposure history, she was visiting her daughter in California. She had an extensive travel history, including sub-Saharan Africa and Indonesia. Her hobbies include fly-fishing, and she eats wild game and raw fish regularly.

Physical Examination

On physical examination, her temperature was 37.3 °C, blood pressure was 98/43 mmHg, heart rate was 78 beats per minute, and respiratory rate was 16 breaths per minute.

Thin and in no acute distress, she had significant right upper quadrant tenderness with voluntary guarding and hypoactive bowel sounds.

The remainder of her examination was normal.

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Lab Tests, Clinical Management

Laboratory investigations revealed a leukocytosis with 17.3 white blood cells/µL (74% neutrophils), AST 64 U/L, ALT 31 U/L, alkaline phosphatase 222 U/L, normal bilirubin, albumin 2.2 g/dL, and protein 7.1 g/dL. Her urinalysis showed no pyuria. A CT scan of her abdomen with intravenous contrast showed a hypodense lesion with a surrounding halo measuring 4.5 x 5.5 cm in the right hepatic lobe, as well as two smaller satellite lesions.

On the day of admission, the patient underwent ultrasound-guided aspiration of the dominant liver abscess. Trichrome stain of the abscess fluid revealed neutrophils, red blood cells, and trophozooites containing ingested red blood cells, morphologically consistent with Entamoeba species Her serum was positive for *Entamoeba histolytica* IgG and she was diagnosed with amebic liver abscess.

She received treatment for amebiasis with oral metronidazole for 10 days, followed by one week of paromomycin. By the time of discharge, her abdominal pain had improved and her fevers had resolved.

Discussion

Entamoeba histolytica is a protozoan parasite for which humans are the only known host. It is transmitted via the fecal-oral route, and exists in two forms: cysts and trophozooites. Worldwide, there are 34-50 million symptomatic cases of amebiasis per year and up to 100,000 deaths. In the US, major risk factors include travel to an endemic area, and institutionalization. Amebic liver abscess is much more common in men than in women (10:1), has a predilection for the right hepatic lobe, and often presents as a solitary abscess. Amebic liver abscesses are associated with other GI symptoms in 10-35% of cases .[1]The recommended diagnostic approach in suspected amebiasis includes both microscopy and serology because the sensitivity of either test alone is suboptimal. The mainstay of therapy for invasive amebiasis consists of oral metronidazole for 7-10 days or oral tinidazole for 5 days. Because 40%-60% of patients treated with a nitroimidazole will have persistent luminal disease, a 7-day course of paromomycin following nitroimidazole treatment is needed.[2] When there is uncertainty surrounding the cause of a liver abscess, diagnostic aspiration is recommended. The same is true for complicated amebic liver abscesses. These are defined as amebic liver abscesses greater than 5cm in diameter, those in the left hepatic lobe, those with bacterial superinfection, or multiple amebic liver abscesses. Although conventional teaching advises against drainage of uncomplicated amebic liver abscesses, a 2009 Cochrane review on the subject found that the studies available were small, had suboptimal methods, and had findings that were too heterogeneous for meaningful conclusions to be drawn.[3]

Diagnosis: Amebic liver abscess.

Acknowledgements: The following participated in the care of the patient: Trip Sweeney, Niaz Banaei, Sean Collins, Andrew Zolopa.

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A Strategy for Early Discontinuation of Antibiotics in Febrile Infants

By Philip R. Fischer, MD, DTM&H

Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic.

Dr. Fischer reports no financial relationships in this field of study.

SYNOPSIS: Approximately half of blood cultures taken from febrile infants with bacteremia turn positive within 15 hours of sampling. By 24 hours, 91% have become positive, and 96% have become positive by 36 hours. Understanding time to culture positivity can help judicious clinicians avoid unnecessarily prolonged antibiotic courses.

SOURCE: Biondi EA, et al. Blood culture time to positivity in febrile infants with bacteremia. *JAMA Pediatrics* published online July 21, 2014, doi:10.1001/jamapediatrics.2014.895.

Infants with life-threatening bacteremia often present with fever without localized signs. To avoid delays in life-saving treatment, most pediatricians obtain culture samples and treat febrile infants with parenteral antibiotics for two or more days pending culture results. Approximately 99% of these infants do not have serious infection for which antibiotics are needed, but "overtreatment" is accepted as necessary to prevent undertreatment of the few individuals who actually need antibiotics. Effective means to shorten the duration of antibiotic use could be an important aspect of antimicrobial stewardship programs.

Collaborators at 17 hospital systems in the United States reviewed data from 392 pathogenic blood cultures obtained from febrile infants admitted to general care units. The mean time to culture positivity was 15.4 hours. Ninety-one percent of cultures that ultimately yielded pathogens were identifiably positive by 24 hours, 96% by 36 hours, and 99% by 48 hours.

The authors suggest new standardized protocols for antibiotic treatment of otherwise healthy-seeming febrile infants while awaiting culture results. They note that 91% of pathogens are identified within 24 hours. Shortening the coverage with antibiotics from 48 to 24 hours would decrease the environmental load of resistance-promoting antibiotic exposures.

Currently, admissions for these febrile infants cost an average of $6613; a shortened stay would decrease costs. Shorter durations of administration of intravenous antibiotics would also decrease the risks of infiltration and adverse medication effects. It is estimated that the incidence of hospital-acquired infection is one per 1000 patient days on general pediatric hospital units. Comparing statistics, the authors suggest that for each febrile infant who is identified to be bacteremic with a pathogen after 24 hours, there would be one infant affected by a hospital acquired infection.

COMMENTARY

What should pediatricians do? The authors advocate shortening the "usual" admission for "rule out sepsis" from 48 to 24 hours.

A dictionary defines "stewardship" as "the careful and responsible management of something entrusted to one's care." While antimicrobial stewardship often focuses on avoiding the development of resistance (and is sometimes perceived as a punitive program designed to regulate physician behaviors), true stewardship should also involve the responsible use of antimicrobial agents in view of benefits, costs, and complications as experienced by patients. As discussed by Biondi and colleagues, shortening the duration of antibiotic use for a common pediatric condition (the febrile newborn) would decrease costs, prevent adverse effects, and avoid complications – all without increasing risk to the child. And, this could also slow the development of antimicrobial resistance. Focusing on what is actually best for patients could lead to shorter courses of therapy. As noted by Pavia and colleagues, physicians respond well to concerns about risks and benefits, and such arguments can serve helpfully in discussions of antimicrobial stewardship.[1]

Appropriate antibiotic use depends on accurate diagnostic strategies. With automated systems electronically identifying growth in liquid culture media before it would be visible by a human eye, blood cultures become positive more rapidly than they did in previous generations. Biondi and colleagues in the Pediatric Research in Inpatient Settings Network collaborated to show that current laboratory techniques used in the United States lead to positive blood cultures within 24 hours in the vast majority of truly infected individuals. Similarly, studies in hospitalized newborns more than a decade ago showed that 77% and 89% of blood cultures were positive by 24 and 36 hours.[2] Likewise, in a study of outpatient children, 87% and 92% of cultures were positive by 24 and 36 hours.[3] Treatment decisions should be modified to keep pace with diagnostic sensitivity.

At the same time, however, there are still diagnostic problems. In Biondi's study, 1447 of 2103 (69%) positive cultures were not considered to be pathogens. In the outpatient study, 52% of positive cultures only revealed germs considered to be contaminants.[3] In a separate study of febrile infants in the United States, 74% of positive cultures were not treated as pathogenic.[4] Decreasing the proportion of positive cultures that are due to non-pathogenic contamination of samples should be a priority in our efforts for antibiotic stewardship.

How long should children who actually do have serious bacterial infections continue to receive antibiotics? A careful review recently challenged current practice and suggested that data do not necessarily support the current fixed durations of parenteral therapy for meningitis, bacteremia, urinary tract infection, and osteomyelitis.[5] Part of antimicrobial stewardship should involve considering patient factors, and such consideration might lead to more judicious (ie, less) antimicrobial use.

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Dosing of Beta-Lactam Antibiotics in Critically Ill Patients Is Often Inadequate

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University, Editor of Infectious Disease Alert

SYNOPSIS: Dosing of beta-lactam antibiotics in critically ill patients is often inadequate and results in poor clinical outcomes.

SOURCE: Roberts JA, Paul SK, Akova M, et al; DALI Study. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis*. 2014; 58:1072-83.

The in vivo antibacterial effect of beta-lactam antibiotics is time-dependent. That is, it depends on the proportion of the inter-dosing interval that the serum concentration of free (non-protein bound) drug remains above the minimum inhibitory concentration (MIC) of the infecting pathogen. A number of studies have suggested that usual antibiotic dosing practices often produce inadequate drug exposure in critically ill patients. This is frequently the consequence of the fact that these patients often exhibit pharmacokinetics (PK) that differ from those seen in the healthy volunteers who participate in Phase 1 studies that evaluate dosages.

In addressing this issue, Roberts and colleagues evaluated the adequacy of clinician-chosen dosing of beta-lactam antibiotics in critically ill patients by performing a point-prevalence study of pharmacodyamics (PD) target achievement. They studied 361 evaluable adult patients in 68 ICUs in 10 countries. All had a creatinine clearance >30 mL/min; their mean Apache score was 18. The antibiotics were administered for prophylaxis in approximately one-third and for therapy of infection in the remainder.

Among those with infection, a bacterial pathogen was isolated in 72.9% and an MIC was available in 34.2% of these. Of the pathogens identified, 18% were *Pseudomonas aeruginosa* and 16% were *Escherichia coli*. A positive clinical outcome was achieved in 144 of the 248 (58.1%) who received the antibiotic because of existing infection. One or more antibiotics in addition to a beta-lactam was administered to 77 (62%) of patients and a favorable outcome was achieved in 63% compared to 50% in the beta-lactam monotherapy cohort.

The beta-lactam was administered by prolonged infusion (>2 hours) to one-third of patients and by "bolus" in the remainder. While prolonged infusion failed to achieve the minimal target of 50% fT>MIC (free drug concentration greater than the MIC for greater than 50% of the dosing interval – the least aggressive target) in only 7%, bolus administration missed this pharmacodynamics target in 20%. Of the total treated for infection,16% failed to achieve this pharmacodynamic target and, when compared to those who reached it, these were 32% less likely to have a favorable clinical outcome (OR, 0.68; 95% CI 0.52 to 0.91; P=0.009). Multivariate regression analysis identified the following as independent factors associated with clinical outcome: APACHE II score, SOFA score, and PK/PD targets – both 50% fT>MIC and 100% fT>MIC. Of note is that achieve-

ment of the 100% fT>MIC was associated with a somewhat higher likelihood of a positive clinical response than was 50% fT>MIC. Among the 24 patients with bacteremia, reaching 50% fT>MIC was associated with a significantly improved likelihood of a favorable clinical outcome when compared to those who did not achieve this threshold, but this was not demonstrated with either pulmonary or intra-abdominal infection.

COMMENTARY

This study, while ambitious and yielding useful results, has a number of shortcomings that have been acknowledged by the authors.

These include lack of identification of a pathogen in many patients as well as a lack of accurate (or, in some cases, any) MIC data for many isolates – a problem that was dealt with by using the high end of published data.

The fact that only 38% of patients received monotherapy with a beta-lactam is another obvious confounder. Actual antibiotic doses administered are also not reported.

Nonetheless, the results are consistent with an expanding literature regarding the inadequacy of antibiotic dosing in many critically ill patients together with retrospective studies reporting improved outcomes in patients with Gram-negative bacteremia receiving prolonged, as opposed to brief, beta-lactam infusions.[1]

This is, in part, likely a consequence of the fact that pharmacokinetics are frequently altered in critically ill patients who may have increased volume of distribution and, in some, increased drug clearance.

Overall, the data are as clear as they are likely to get that many critically ill patients receiving beta-lactam therapy are significantly under-dosed, either in terms of actual dose or of the duration of infusion, and that such under-dosing is associated with poor clinical outcomes.

All patients in this study had creatinine clearances >30 mL/min. One also wonders what proportion of patients receiving renal replacement therapy are receiving beta-lactam antibiotics in doses according to published guidelines are achieving even minimal pharmacodynamic targets.

An immediate solution to the problem of inadequate beta-lactam exposure in critically ill patients is intervention by knowledgeable Infectious Diseases consultants and Antimicrobial Stewardship Programs. The ultimate answer is therapeutic drug monitoring, something that is not currently generally available.

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Tapered antibiotics with kefir may be effective in recurrent C. difficile infection.

By Richard R. Watkins, MD, MS, FACP

Division of Infectious Diseases, Akron General Medical Center, Akron, OH; Associate Professor of Internal Medicine, Northeast Ohio Medcal University,m Rootstown, OH.

SYNOPSIS: A prospective case series that included patients with recurrent Clostridium difficile infection found that treatment with tapered antibiotic therapy and the probiotic drink kefir resulted in a clinical cure of 84% (21 out of 25 patients).

SOURCE: Bakken JS. Staggered and tapered antibiotic withdrawal with administration of kefir for recurrent Clostridium difficile infection. *Clin Infect Dis* 2014; advance access published 6/27/14; DOI:10.1093/cid/ciu429

Management of recurrent *Clostridium difficile* infection (CDI) is challenging. Fecal transplantation is becoming increasingly accepted for recurrent CDI after a recent report showed significantly improved outcomes compared with standard care. In this study, 81% of participants had resolution of *C. difficile*-associated diarrhea after the first stool infusion.[1] However, many patients remain reluctant to undergo the procedure and it is not widely available. Thus, effective alternative therapies for recurrent CDI are needed. Kefir is a fermented dairy product with a diverse collection of probiotics that is commonly available in food stores. Bakken sought to determine if the addition of kefir to

a tapered course of antibiotics would be effective in treating patients with recurrent CDI.

The study was a prospective case series from a single institution in Minnesota conducted between 2005 and 2013. The author treated 25 patients with a mean number of CDI relapses of 4 (range, 1-9). Between 2005 and 2006, an oral metronidazole taper was used along with a 5 oz glass of kefir with each meal or ad libitum as tolerated, and then from 2006 to 2013 an oral vancomycin taper along with kefir was prescribed. Also, the patients were instructed to continue to drink kefir for at least two months after finishing the antibiotics. The most common infections that preceded recurrent CDI were respiratory tract infection, diverticulitis and urinary tract infection. Ceftriaxone was the most common inciting antibiotic, followed by fluoroquinolones, azithromycin and clindamycin. Close to one-third of the patients were taking an H2 blocker and 4 patients were on immunosuppressive therapy.

All 25 patients had normal bowel function (i.e. no diarrhea) at the end of the antibiotic tapering therapy. However, 4 patients relapsed with CDI which was confirmed by a positive *C. difficile* assay between 24 and 45 days after completing the taper. These patients were then given a 2-week course of oral vancomycin 125 mg qid followed by a 2-week course of rifaximin 200 mg bid. Upon completing the vancomycin and rifaximin course, all 4 patients remained symptom-free after 12 months of follow-up. There was no association found between CDI relapse and H2-blocker usage, immunosuppressive therapy, comorbid illnesses, or predisposing infectious illnesses.

COMMENTARY

Data on the benefit of probiotics for CDI have been mixed. A Cochrane review that included 23 randomized controlled trials found moderate quality evidence that probiotics are both safe and effective for preventing *Clostridium difficile*-associated diarrhea.[2] There are many kinds of probiotics sold over the counter and prescribed by physicians in health care settings. The choice of kefir in this study was interesting because, unlike conventional yogurt, it contains 7 to 10 billion colony forming units of 10 different bacterial strains (www.kefir.com). The investigator hypothesized that tapered antibiotic therapy would allow *C. difficile* spores to germinate during the drug-free periods and the kefir would replete and diversify the colon microbiome. Over time the pool of spores would be reduced and eventually subdued by the restored colonic flora. The primary treatment success rate of 84% seems to support the biologic plausibility that restoring the colon microbiome is the key to resolving recurrent CDI.

The study had some limitations. First, it had a small number of subjects and was conducted at a single institution. Thus, the results may not be generalizable to other settings or patient populations. Second, no control group was included, although the author stated that each patient served as his or her own control because they had all received oral antibiotics but not kefir for previous episodes of CDI. Finally, patient compliance with kefir was not directly reported.

For many patients, recurrent CDI is a devastating illness that profoundly impacts their quality of life. While fecal transplantation has been shown to be more effective than conventional antibiotic therapy for recurrent CDI, many insurance companies have been unwilling to cover the cost.
Based on this small study, kefir appears to be an effective adjunct to antibiotic tapering therapy without any observed risk. Larger, prospective studies on treatment of recurrent CDI that include kefir would be beneficial.

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Treatment of Dengue – Failure of a Novel Agent

By Joseph F. John, Jr., MD, FACP, FIDSA, FSHEA

Associate Chief of Staff for Education, Ralph H. Johnson Veterans Administration Medical Center; Professor of Medicine, Medical University of South Carolina, Charleston

Dr. John reports no financial relationships in this field of study.

SYNOPSIS: There was no evidence of significant benefit from the administration of the antiviral agent, celgosivir, in the treatment of patients with dengue fever.

SOURCE: Low JG, et al. Efficacy and safety of celgosivir in patients with dengue fever (CELADEN): a phase 1b, randomised, double –blind, placebo-controlled, proof-of-concept trial. *Lancet Inf Dis* 2014;14:706-715.

Dengue is a miserable disease that occurs worldwide and has at times resulted in massive epidemics. Almost 400 million cases occur globally each year. There are no vaccines to prevent the disease and there is no proven therapy. Some antiviral chemotherapies have focused on inhibition of two genes, NS3 and NS5, that regulate polyprotein processing and RNA replication respectively. Celgosvir (sometimes called Bu-Cast and manufactured by Dalton Pharma Services, Toronto, Canada) is a 6-O butanoly prodrug of castanospermine, a compound that occurs naturally in the seeds of Castanospermum australe. It blocks the endoplasmic reticulum of all four serotypes of the virus.

This trial involved 50 subjects from among 69 who were screened. 18 (34%) had secondary dengue infection as evidenced by the presence of preexisting antibody to the virus.. Subjects were all from Singapore and received a loading dose of 400 mg and thereafter a dose of 200 mg every 12 hours. Subjects were admitted to a hospital for 5 days to participate in the study.
There was actually an international team running the study which had genomic and immunologic input. Statistical analysis was strong. A process called a finite mixture model was used to analyze the viral loads at day 2 and day 4. Clearance of the protein NS1 was also measured up through day 15. Use of drugs between day 1 and 5 was also measured.

The outcomes were disappointing for efficacy but the data generated by the study were most interestng. Viral loads and fever quantity were higher for the celgosivir than for placebo but the differences were not significant. Both for the treatment and placebo group, body temperature began above 38.0 degrees C for all subjects. By 90-96 hurs, almost all subjects had temperatures of 37 C. There were only about 5 severe events in both treatment and placebo groups. There was more diarrhea in the celgosvir group than in the placebo group. All patients recovered from their illness.

COMMENTARY

The results from this treatment study of dengue fever in Singapore showed that an antiviral medication, celgosivir, was well tolerated but resulted in no reduction in symptoms, hematological abnormalities nor in reduction of viral load. Patients were enrolled by point of care testing which did not detect all the secondary cases. The fact that 34% of cases were secondary was a potential confounding factor since recurrences of dengue are often more severe. Nevertheless, the fever curves and viral load reductions were so very similar that this particular confounding likely did not affect the outcomes.

As the authors point out the study was not powered to detect small changes in viral load so celgosivir may be worthy of further investigation, perhaps as combinational therapy or in increased dosage. This study was very useful to show that the serotype did not seem to influence the clinical course, hospitalization of patients may have resulted in a lack of fatality, and that this type of antiviral medication, an alpha-glucosidase inhibitor, could be well tolerated. The data were very useful also to show that fever reduction correlated with clearance of virus. There is a continued rationale, therefore, that antivirals aimed at reducing Dengue virus load may result in reduction of the disabling symptoms with this rampant mosquito-borne illness.

Out of Africa: Ebola Cases come to U.S.

CDC issues isolation precautions, clinical care guidance

By Gary Evans, Executive Editor

As the first cases of Ebola ever treated in the U.S. were recently admitted to a special containment unit at Emory University Hospital in Atlanta, clinicians and public health officials continued to reassure a jittery public that infection control measures would prevent transmission and contain the virus.

"We are talking about a virus that is spread in a way that we are quite used to — HIV, hepatitis B, hepatitis C. It's the same algorithm and we use the same kind of precautions on those patients on a daily basis," **Bruce Ribner,** MD, an infectious disease physician at Emory, said at an Aug. 1 press conference. "All of these viruses are spread by close contact with blood and body fluids. I will be one of the individuals coming into direct contact with the patients. I have no concerns about either my personal health or the health of the other health care workers who will be working in that unit."

This reassurance, while accurate from a medical standpoint, could nevertheless be seen as something of a disconnect when you are admitting patients into a specially designed unit with elaborate and redundant systems to contain any pathogen within. There are a few such units in the country, so the Ebola patients – a volunteer American physician and a medical missionary worker infected in the ongoing West African outbreak – were hospitalized under extreme infection control precautions that belie Ribner's business-as-usual tone. The Centers for Disease Control and Prevention often finds itself delivering a similar mixed message with an exotic pathogen, reassuring that there is little threat to public safety while taking extensive measures with the first cases out of an abundance of caution.

CDC surge in Africa, isolation guidelines in U.S.

As of Aug 12, 2014 the CDC reported the Ebola outbreak in West Africa included 1,848 suspected and confirmed cases with 1013 dead, a mortality rate of some 55%. As cases continued to be reported, the CDC dramatically ramped up its presence in the region and activated its Emergency Operations Center in the U.S. As this issue went to press, the CDC had 55 people deployed to West Africa, including 14 in Guinea, 18 in Liberia, 16 in Sierra Leone, and seven in Nigeria. In a painstaking attempt to stop the outbreak, CDC epidemiologists are identifying new Ebola cases and then tracking their contacts for signs and symptoms within a 21-day incubaton period.

Meanwhile, in the U.S., the CDC posted Ebola information for clinicians and recommendations for infection control precautions in hospitals admitting suspected or confirmed casess. (http://1.usa.gov/1kz43R9) The CDC recommends a combination of standard, contact, and droplet precautions for management of hospitalized patients with known or suspected Ebola hemorrhagic fever. The recommendations were based upon the best available information as of July 30, 2014 and took into account the following considerations:[1]

- High rate of morbidity and mortality among infected patients
- Risk of human-to-human transmission
- Lack of FDA-approved vaccine and therapeutics

The CDC recommends an Ebola patient should be placed in a single patient room containing a private bathroom with the door kept closed. Facilities should maintain a log of all persons entering the patient's room. Consider posting personnel at the patient's door to ensure appropriate and consistent use of PPE by all persons entering the patient room. All persons entering the patient room should wear at least, gloves, gown (fluid resistant or impermeable), eye protection (goggles or face shield), and a facemask. Additional PPE might be required in certain situations (e.g., copious amounts of blood, other body fluids, vomit, or feces present in the environment). These would include but are not limited to: double gloving, disposable shoe covers, leg coverings.

Ebola does not spread through the air, but workers should wear respiratory protection at least to the level of an N95 respirator if they are doing procedures on an Ebola patient or fluids that could generate aerosols. The CDC recommends avoiding aerosol generating procedures (AGPs) on Ebola patients if possible. If performing AGPs, use a combination of measures to reduce exposures from aerosol-generating procedures when performed on Ebola HF patients. Conduct the procedures in a private room, ideally in an Airborne Infection Isolation Room (AIIR) when feasible. Room doors should be kept closed during the procedure except when entering or leaving the room, and entry and exit should be minimized during and shortly after the procedure. In addition to a respirator, health care workers performing an AGP on an Ebola patient should wear gloves, a gown, disposable shoe covers, and either a face shield that fully covers the front and sides of the face or goggles. Dedicated medical equipment (preferably disposable) is recommended, with the use of sharps and needles limited as much as possible. All needles and sharps should be handled with extreme care and disposed in puncture-proof, sealed containers, the CDC recommends.

No asymptomatic transmission

Ebola does not spread in the absence of symptoms while the patient is in the incubation phase. "Ebola is spread as people get sicker and sicker, they have fever and they may develop severe symptoms," CDC director **Tom Frieden**, MD, said at a press conference. "Those symptoms and the body fluids that may be shed during that time, those are the infectious risk entities."

U.S. hospitals should have no problem isolating Ebola patients, but personnel must be meticulous in following the measures, he added.
"American health care workers are much more familiar with how to isolate patients and how to protect themselves against infection," he said. "In fact, any advanced hospital in the U.S. — any hospital with an intensive care unit — has the capacity to isolate [Ebola] patients," Frieden said. "There is nothing particularly special about the isolation of an Ebola patient other than it's really important to do it right. So ensuring that there is meticulous care of patients with suspected or confirmed Ebola is what's critically important."

Seeking a second opinion, we asked an Ebola expert if U.S. hospitals adopting such measures could contain Ebola and protect their health care workers.

"Yes, I think they can," says **Thomas Geisbert**, PhD, Ebola researcher and professor of microbiology and immunology at the University of Texas Medical Branch at Galveston. "Because there is an understanding and a recognition in the U.S., especially after the anthrax letters and 9/11. There is [heightened] awareness in U.S. hospitals. Most of them have isolation rooms, good barrier precautions and things like that. Quick identification is the key. Identifying that you have a problem quickly — a definitive diagnosis to rule [Ebola] in or out. I think any of the really good hospitals in this country that have good isolation procedures and rooms would have no problem."

The CDC recommends that U.S. health care settings be alert for possible incoming cases of Ebola, emphasizing these basic points:
•Take good travel histories of patients to identify any who have traveled to West Africa within the last three weeks.
•Know the symptoms of Ebola — fever, headache, joint and muscle aches, weakness, diarrhea, vomiting, stomach pain and lack of appetite and, in some cases, bleeding.
•Know what to do if you have a patient who has Ebola symptoms. First, properly isolate the patient. Then, follow infection control precautions to prevent transmission. Most importantly, avoid contact with blood and body fluids of infected people.

Reference

1. CDC. Infection Prevention and Control Recommendations for Hospitalized Patients with Known or Suspected Ebola Hemorrhagic Fever in U.S. Hospitals. July 30, 2014. http://1.usa.gov/1pvUSQz

Lab incidents divide scientists on research

Some warn of unleashing a pandemic

A series of biosafety breaches in federal labs working with highly pathogenic agents has created a rift in the research community, with some calling for a moratorium until safety can be assured and other scientists arguing that this important work should continue with appropriate precautions to prepare for pandemics and bioterror attacks.

"There is no doubt that the episodes of laboratory safety that have been in the news recently have reignited the scientific discussion about whether this type of research should take place, whether specific projects ought to be reviewed, and -- if the research takes place — should it be restricted to only certain investigators in certain institutions. I think it is a valid debate," says **William Schaffner**, MD, chairman of the Department of Preventive Medicine at Vanderbilt University Hospital in Nashville. Distinguished scientists and researchers are divided on the issue, as evidenced by the signatures on position states by the opposing groups, one calling itself the Cambridge Group and the other Scientists for Science.

'Difficult or impossible to control'

The Cambridge Group said the recent series of laboratory breaches with potential pandemic agents indicates an urgent need for a thorough reassessment of biosafety. "Laboratory creation of highly transmissible, novel strains of dangerous viruses, especially but not limited to influenza, poses substantially increased risks," the group said in a position statement.
"An accidental infection in such a setting could trigger outbreaks that would be difficult or impossible to control. Historically, new strains of influenza, once they establish transmission in the human population, have infected a quarter or more of the world's population within two years."
For any experiment, the expected net benefits should outweigh the risks, the group argued.
"Experiments involving the creation of potential pandemic pathogens should be curtailed until there has been a quantitative, objective and credible assessment of the risks, potential benefits, and opportunities for risk mitigation, as well as

comparison against safer experimental approaches," the Cambridge group recommended.
Scientists for Science issued a countering statement expressing confidence that biomedical research on potentially dangerous pathogens can be performed safely and is essential for a full understanding of microbial disease pathogenesis, prevention and treatment.

"The results of such research are often unanticipated and accrue over time; therefore, risk-benefit analyses are difficult to assess accurately," the pro-research group said. "If we expect to continue to improve our understanding of how microorganisms cause disease we cannot avoid working with potentially dangerous pathogens."

BSL-3, BSL-4 labs mitigate risks

In recognition of this need, significant resources have been invested globally to build and operate BSL-3 and BSL-4 facilities, and to mitigate risk in a variety of ways, involving regulatory requirements, facility engineering and training.

"Ensuring that these facilities operate safely and are staffed effectively so that risk is minimized is our most important line of defense, as opposed to limiting the types of experiments that are done," Scientists for Science stated.

The most controversial aspect of this issue is so-called "dual use" research, which is defined by the National Institutes of Healh as "as life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security. "
The federal government's oversight of dual use research is aimed at preserving the benefits of life sciences research while minimizing the risk of misuse of the knowledge, information, products, or technologies provided by such research, the NIH states.
There have been suggestions that the two research groups hold a meeting called by an impartial and respected scientific body.

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

TB in domestic cats

Cases of TB in domestic cats and cat-to-human transmission: risk to public very low. https://www.gov.uk/government/news

A rare thing - TB in cats. We've heard of cattle, deer, elk, and elephants at the zoo – and in a famous "Doc Marten" episode – badgers in the U.K. as a source for human infection. But feline TB is fairly uncommon.

Public Health England (PHE) and Animal Health and Veterinary Laboratories Agency (AHVLA) investigated a cluster of TB infection in domestic cats in 2013. Initially, a single veterinarian identified the illness in 9 very ill cats from households within a few miles of each other near Newbury. The infection proved to be due to *Mycobacterium bovis* — and indeed, investigation of a nearby herd of cattle revealed a small number of animals with active infection with the same strain of M. bovis. Thirty-nine people with cat contact were offered testing; only 24 of whom accepted — 2 had active TB. Molecular analysis confirmed the strains were identical to the cat strains. Two additional people were found to have latent TB infection (unclear whether cat-related).

The PHE commented that *M. bovis* is responsible for fewer than 40 human cases of TB per year in the U.K., most of which are related to livestock exposure or occur in elderly people with a remote history of raw milk exposure. It is illegal to sell unpasteurized milk products in the U.K. But could someone have fed it to the cats?

A snap shot of HIV in the U.S.

Centers for Disease Control and Prevention. Behavioral and clinical characteristics of persons receiving medical care for HIV infection – Medical Monitoring Project, United States, 2009. *MMWR* 2014;63(ss05):1-22.

By the end of 2009, 864,748 persons were living with HIV in the United States. While the U.S. HIV surveillance programs track basic demographic information about these cases, the Medical Monitoring Project, which is a national, cross-sectional surveillance project, collects much more intensive clinical and behavioral information on a subset of randomly selected participants. Study participants complete a detailed questionnaire and physicians provide abstracted chart data.

From January to April 2009, 421,186 HIV-positive adults > 18 years of age presented for outpatient care in the U.S. Of these, 9,338 subjects were selected from 461 participating sites (we were one of them); 4,217 patients completed the questionnaire and formed the basis for this report. While the detailed data is provided in the lengthy report, several points standout:

- 71% were male
- 50% identified as heterosexual and 50% as GBLT
- Three-fourths were > 40 yrs of age; and 54% had been HIV+ for 10 or more years;
- 44% were living below the poverty line and 9% were homeless;
- 81% had some kind of health coverage, including Medicaid (40%), Medicare (26%), or private insurance (30.6%)
- 68% had been diagnosed with AIDS; 87% had CD4 counts > 200 cell/mL within the previous 6 months;
- 88% were currently prescribed antiviral therapy; 6% had never been prescribed antivirals and the remainder had been treated but stopped therapy for various reasons.
- 72% had an undetectable HIV viral load < 200 copies/mL within the previous 6 months;
- 42% were current smokers;
- Alcohol use was common; half drank alcohol within the previous 3 months with an average of 3.1 drinks per day;
- 27% used non-injectable drugs, including marijuana (22%), crack (5%), cocaine (5%); and a much smaller number (2.1%) used injectable drugs;
- 25% of the female patients had been pregnant at least once since testing HIV+.

Indigenous Hepatitis E in the U.K.

Ijaz, s, et al. Indigenous Hepatitis E in England and Wales from 2003 to 2012: Evidence of an emerging novel phylotype of viruses. *JID* 2014; 209:1212-1218.

Given a rise in cases of Hepatitis E virus (HEV) infection in England and Wales the past 10 years, many of which appeared unrelated to international travel, Public Health England (PHE) has amped up efforts to improve surveillance testing and molecular characterization of HEV. In 2010, two PHE reference laboratories changed the assays used for antibody detection. And they began doing viral load testing, with PCR amplification and genotyping of isolates. In order to examined the relatedness of cases and identify clusters, a phylogenetic tree was created.

Between 2003 and 2012, 2713 cases of HEV were identified within England and Wales; of these, 51% were believed to be indigenous and unrelated to travel activity. Peaks of HEV infection occurred in 2005 (n = 329) and again, beginning in 2010- 2012, with up to 579 cases reported in 2012, 71% of which were believed to be indigenous. Analysis indicated this was not the result of heightened awareness and an increase in the number of samples being submitted to the laboratories.

Genotypic analysis confirmed that most of the travel-related cases were due to genotype 1 (G1) infections, mainly from the Indian subcontinent, whereas all of the indigenous isolates were Genotype 3 viruses. Of these G3 viruses, 215 of 229 isolates (94%) from 2003-2009 were group 1 and 6% were group 2. But from 2010-2012, there was a decided shift, with emergence of group 2 viruses in 58% of cases. Clearly the spike in indigenous cases observed from 2010-2012 coincided with the appearance of these newer viruses. Sequencing and phylogenetic analysis revealed the emergence of newer group 2 subtype viruses - seen only after 2010.

In conclusion, molecular analysis demonstrated that two distinct and somewhat overlapping low-level indigenous outbreaks were occurring in England and Wales during this 10 year period, with the emergence of novel group 2 subtypes during the past 3 years.
Demographic data failed to point to a clustering of cases, as would be observed with a food-borne outbreak. The question remains, where did these novel HEV genotype 3 subtype viruses come from? Two theories are actively being investigated, including the possibility that one or more individuals with chronic immunosuppression, which can result in chronic HEV infection, could excrete low levels of the organism in the environment. In addition, there is some evidence that HEV viruses can infect pigs, although no direct link has been established. HEV infection can become established in countries not previously thought endemic for this infection.

CME INSTRUCTIONS

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

1. Read and study the activity, using the provided references for further research.
2. Scan the QR code to the right or log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME QUESTIONS

1. Which of the following is correct?

A. Probiotics have unequivocally been shown to be an effective therapy of C. difficile infection.

B. Probiotics have unequivocally been shown to prevent recurrences of C. difficile infection.

C. Kefir contains large quantities of bacteria.

D. None of the above.

2. Which of the following is correct with regard to the study of blood cultures in febrile infants?

A. 91% of pathogens were detected within 24 hours

B. 96% of pathogens were detected within 36 hours

C. 99% of pathogens were detected within 48 hours

D. All of the above are correct.

3. Which of the following is correct?

A. Critically ill patients often have an increased volume of antibiotic distribution.

B. Beta-lactam antibiotic activity is concentration, rather than time-dependent.

C. Empiric studies have found that critically ill patients often receive excessive doses of beta-lactam antibiotics.

D. Prolongation of beta-lactam infusions (as opposed to bolus infusion) diminishes their antibacterial effect.

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 latent 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

TIPPING POINT

"[The 1918] Influenza killed more people in a year than the Black Death of the Middle Ages killed in a century; it killed more people in twenty-four weeks than AIDS has killed in twenty-four years. The influenza pandemic resembled both of those scourges in other ways also. Like AIDS, it killed those with the most to live for."

John Barry, *The Great Influenza*