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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

SPECIAL REPORT

Ebola! Outbreak in West Africa raises Difficult Questions about Deadly Virus

Without effective vaccine, treatment Ebola mortality rate can hit 90%

By Philip R Fischer, MD

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

SOURCE: Centers for Disease Control and Prevention. Outbreak of Ebola in Guinea and Liberia. http://www.cdc.gov/vhf/ebola/outbreaks/guinea, accessed April 11, 2014.

In March 2014, Ebola virus infection emerged in Guinea, West Africa, and spread through communities in Guinea and Liberia. Additional reports of suspect cases in Sierra Leone and Mali are under investigation. As of April 14, 2014, the World Health Organization (WHO) and the Ministry of Health (MoH) of Guinea reported 168 probable and suspect cases, including 108 deaths. Of these suspect cases, 71 have been laboratory confirmed positive cases of Ebola hemorrhagic fever (EHF). One additional health care worker with clinical symptoms has been reported since April 7, increasing the total to 15 health care workers. All cases reported in Conakry, Guinea (20) have been laboratory confirmed. Other districts with confirmed and suspected cases include Guekedou, Macenta, Kissidougou, Dabola, and Djingaraye.

Initial reports came from forested areas in southeastern Guinea near the Liberia border. Subsequently, there were the aforementioned 20 cases reported in Conakry, the capital of Guinea on the western coast. The initial Liberia-based patients had recently traveled from Guinea. The CDC regularly updates a map showing the location of cases (http://www.cdc.gov/vhf/ebola/resources/distribution-map-guinea-outbreak.html).

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Testing facilitated by the Pasteur Institute (laboratories in France and Senegal, collaborating in Guinea) confirmed that the causative agent in this outbreak is indeed Ebola virus, the Zaire ebolavirus strain that was last reported in 2009 in the Democratic Republic of Congo. Ministries of Health in the involved countries have been assisted by the WHO as well as by multi-national non-governmental groups including Doctors without Borders, International Red Cross, and Samaritan's Purse.

■ COMMENTARY

Connected with concerned people around the world, many of us involved with *Infectious Disease Alert* were asked questions about Ebola as news media covered the current outbreak. Here, we review established knowledge and recent studies to provide a basis for responding to common questions.

Q: Should meeting organizers allow a physician and nurse from Guinea to attend a medical conference in Europe?
A: Responding to this question required an understanding of the transmission of Ebola virus, the pre-symptomatic incubation time, and measures to decrease the risk of becoming infected in healthcare settings.

It is not certain just how Ebola virus is transmitted, but it seems contagious to people who come into physical contact with a sick person or an infected animal, particularly fruit bats. The initial case in outbreaks sometimes seems to have picked up the virus through contact with an infected animal (such as a bat). Then, it seems that contact with infected blood and bodily secretions (or contaminated needles) can lead to transmission of the virus from one person to another, but the details of transmission are not fully known.[1] The incubation period is usually eight to ten days, but it can range from two to 21 days.

Prevention of Ebola virus infection apart from outbreaks can be facilitated by avoiding contact with living or dead animals such as bats. During an outbreak, the infection can spread quickly in healthcare facilities. It is important to implement strategies whereby patients and staff avoid direct physical contact with sick individuals. Use of masks, gowns, and gloves is advised (even for visitors). Secretions and contaminated needles should be disposed without requiring direct human contact. (Full sterilization of needles can be effective if there is not an adequate supply of needles available.)

During an outbreak, any individual with Ebola-compatible symptoms should be isolated so as to decrease direct physical contact with uninfected people. People who have had contact with an infected person or his/her secretions should avoid contact with others during the period of two to 21 days following their last contact with the sick person.

The physician and nurse that served as the basis of this question were advised to avoid contact with bats and to follow careful mask-gown-glove procedures while having patient care contacts with potentially infected individuals. They were told to come along to the European meeting if they remained asymptomatic at least 21 days after any known contact with a potentially infected patient. So far, they have not had contact with seemingly infected patients, and they have not touched bats. If things continue to go well, they expect to attend the meeting.

Interestingly, an international traveler did import Lassa fever to Minnesota.[2] While Lassa fever is sometimes asymptomatic and has a lower case-fatality rate than does Ebola, all health care providers must be careful to obtain travel histories, to isolate patients with suspected viral hemorrhagic fevers, and to avail themselves of etiologic testing for accurate diagnoses in patients. We must remain vigilant with the risks of imported diseases.

Q: A middle aged man arrived at a small mission hospital in Guinea with signs suggestive of Ebola virus disease. The hospital has no isolation rooms. Should they care for the patient or refer him elsewhere?
A: Faced with a patient who is sick with a possible viral hemorrhagic fever, a care team has several goals: 1) compassionately care for the patient while seeking a favorable medical outcome (cure), 2) protect health care workers and other patients at the

facility from becoming infected, and, 3) collaborate with governmental and non-governmental groups to identify, track, and abort outbreaks.

Currently, there is no curative treatment for human Ebola virus disease. Care is supportive with institution of comfort measures, fluid management, provision of blood products as needed, and management of whatever super-infections and complications arise.

Isolation measures center on keeping the patient and his or her secretions and blood away from direct contact with other people. All persons involved in the care of the patient suspected of harboring Ebola virus should use protective masks, gowns, and gloves. Linens, and medical equipment contaminated with blood and secretions should be sterilized or discarded. Similarly, bodies of patients who succumb to Ebola should be handled without direct contact.

During the current outbreak, government health ministries and non-governmental groups are collaborating effectively to ensure that sampling and testing are available and that isolation supplies are distributed to health centers and hospitals in endangered areas. Hospitals should ensure that space and equipment are available should the need arise.

The non-hypothetical situation that prompted this question took place early in the outbreak when the hospital in question was not yet confident that they had the staff, space, and supplies to manage the patient. The patient was referred to a government hospital a few miles farther down the road but then reportedly left against medical advice during the first night at that facility — before testing could confirm the diagnosis.

Q: Ten percent of Ebola patients survive. Is there a way to predict clinical outcomes?
A: Ebola presents with fever and headache. Patients often have other aches and pains as well as fatigue and gastrointestinal symptoms before they develop hemorrhagic complications. In sub-Saharan Africa, these same symptoms can be due to malaria and typhoid fever, and several other less grave conditions. So, it is important during outbreaks to remember that not every sick person has Ebola. While isolating patients for the possibility of Ebola, they should receive appropriate evaluation and care for whatever else might be ailing them.

Anita McElroy and colleagues retrospectively studied biomarkers in stored serum taken from patients in the 2000-2001 Ugandan Ebola outbreak.[3] Fifty-five different biomarkers were assessed.

Death was associated with higher levels of several pro-inflammatory cytokines; this suggests that an aggressive inflammatory response to the infection is part of the pathophysiology of severe disease. Elevated levels of ferritin, an acute phase reactant, were also associated with death. Interestingly, higher levels of sCD40L (a platelet-derived product that might reflect ongoing endothelial repair by activated platelets) were found in patients who survived.

These data give clues as to the pathophysiology of severe Ebola disease, but they do not yet help us clinically identify which patients are more likely to survive. Still, Ebola is a devastating infection, and aggressive supportive care is required for all potentially infected patients.

Q: We treat other serious viral infections. Why can't we treat Ebola?
A: There is currently no medication available to favorably impact the outcome of Ebola virus infection. But, there are some potential treatments on the horizon.

BCX4430 is a novel synthetic adenosine analogue that inhibits RNA polymerase function and acts as a non-obligate RNA chain terminator.[4] In rodent models of Ebola, post-exposure injection of this product prevents clinical disease. And, perhaps more relevant to humans, monkeys are protected from Marburg virus disease when they get this product up to 48 hours after exposure. If this broad-spectrum product turns out to be effective in primates with Ebola virus, too, then there might be potential that it would help humans.

Favipiravir is a pyrazinecarboxamide derivative known as T-705. In cell cultures, it suppresses replication of the Zaire strain of Ebola virus. Further, this product has promoted viral clearance, reduced biochemical evidence of severe disease, and completely prevented death in mice infected with Ebola virus up to six days prior to treatment.[5,6] This product might soon reach the market as an influenza treatment, and human studies of its efficacy against Ebola virus infection are warranted.

Another approach to pharmacologic treatment of Ebola virus is to give passive immunization with specific monoclonal antibodies. In non-human primates, monoclonal antibody treatment was shown to fully cure experimentally infected animals even when administered days after the onset of clinical symptoms.[7]

So, there is currently no effective treatment for Ebola-infected humans. But, further studies with the adenosine analog and/or favipiravir and/or specific monoclonal antibodies might prove successful in identifying effective human therapies.

Q: Is there hope for a vaccine?
A. Similarly, there is currently no effective vaccine for

Ebola virus infection. A variety of approaches toward development of Ebola vaccine have been tried — DNA vaccines, subunit vaccines, and both replicating and non-replicating viral vectors.[8] In mice and guinea pigs, vaccines have been 60-100% effective in blocking the establishment of infection following exposure. Some of the strategies involving recombinant viral vector vaccines have also been evaluated in non-human primates with up to 100% efficacy in early studies.[8] Experiments so far have been limited to phase I trials.

Tragically, Ebola virus is killing scores of people in West Africa. Isolation strategies can help stop the spread of this infection, and supportive care is sometimes helpful. Work continues on medical treatments and vaccinations, but no effective product has yet become available for clinical human use.

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SPECIAL REPORT

Stanford Division of Infectious Diseases Guidelines for the Treatment of *Clostridium Difficile Infection* (CDI)

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

There have been several advances in medical understanding of the prevention, diagnosis and treatment of CDI since the last national guidelines were published in 2010. A lack of more contemporary guidelines incorporating these new innovations led to heterogeneity of practice at our institution, which could increase cost and decrease efficacy of care. For that reason, the Infectious Disease Division developed these guidelines for use at Stanford University Hospital and Clinics and believe they may be of use to other institutions while awaiting new U.S. national guidelines.

DIAGNOSIS:

Diagnostic Criteria (Distinct from Testing Criteria Below):[1,2]

1. Diarrhea (≥3 loose or watery stools per day for at least 2 consecutive days or ≥8 loose stools in 48 hours) OR significant worsening in patients with chronic diarrhea (e.g. inflammatory bowel disease) OR increased output from any ostomy site in the setting of recent antibiotic use. These criteria are most useful for diagnosis in the absence of obvious alternative explanations such as laxative use or recent initiation of enteral feedings.
AND
2. A positive stool PCR for *C. difficile* toxin B or visualization of pseudomembranes on endoscopy.

OR

Abdominal distension and severe pain after a period of diarrhea without current stooling may be a rare finding if ileus or toxic megacolon present. In this setting, effort should be made to send toxin PCR from a rectal swab trace amount of stool (notify microbiology lab prior to

Table 1. Stanford Division of Infectious Diseases Suggested Guidelines for the Treatment of *Clostridium Difficile* Infection (CDI).

Clinical Severity/Stage	First Line Regimen	Alternative Therapy
Mild/Moderate	Metronidazole 500mg PO TIDx10-14d	Vancomycin 125 mg PO q6h x 10-14d.
Severe (WBC >= 15K and Cr >= 1.5x Baseline)	Vancomycin 125 mg PO q6h x 10-14d.	Fidaxomicin 200mg PO BIDx10d.
Severe Complicated (septic shock, ileus or toxic megacolon due to CDI)	SURGICAL AND INFECTIOUS DISEASES CONSULT Vancomycin 500mg PO q6h + Metronidazole IV 500mg TID. Consider PR Vancomycin 500mg in 100ml NS enema q6h	Replace Metronidazole IV with Tigecycline IV 50mg BID.
First Recurrence	Same as above based on severity	
Multiple Recurrence	For Severe Complicated – Treat as above until stable. For all others – if not previously used: Fidaxomicin 200mg PO BID x 10d	**OR** Vancomycin 125mg PO q6h for 14d followed by Rifaximin 400mg PO BID for 21d **OR** Vancomycin PO 125mg q6h x10d, then BID x7d, then qd x7d, then qod x21d **OR** Fecal Microbiota Transplant. Consult ID and GI

sending, swab specimens will be rejected unless prior approval from lab is given).

Testing Criteria (Must be met for lab to accept sample):
1. ≥3 loose or watery stools per 24 hr.
2. Unformed stool specimen (conforms to the shape of the container). Exceptions include patients with ileus or toxic megacolon. Please contact the lab if you are requesting an exception to this policy.
3. No repeat testing within the last 7 days.

Important:

Stool PCR for *C. difficile* toxin B is thought to be 98% sensitive for disease or colonization, there is no indication for repeat testing within 7 days of a negative result. Repeat testing after that only if initial symptoms resolve and new diarrhea starts.[3] Asymptomatic colonization with toxigenic *C. difficile* is relatively common and treatment is not indicated for this. It is therefore important that patients meet testing criteria for CDI, before sending stool for *C. difficile* toxin PCR. Currently there is not an indication for a test of cure for CDI. Patients with CDI should be followed clinically for improvement.

Staging Disease:
After the diagnosis is made, it is important to stage the disease to guide treatment by both severity (mild -> severe complicated) and symptom recurrence (first occurrence-> multiple recurrence):[1,2]

• Mild disease- Diarrhea only, no systemic inflammatory response as assessed by other symptoms (fatigue, fever), leukocytosis, or elevated serum creatinine.

• Moderate disease- Systemic symptoms present and or moderate elevations in white blood cell count (WBC) <15,000 cells/μL AND serum creatinine elevation <1.5 times the premorbid level.

• Severe disease WBC >=15,000 cells/μL OR serum creatinine elevation >=1.5 times the premorbid level due to CDI.

• Severe Complicated meets criteria for septic shock due to CDI OR radiographic and clinical

Table 2. Cost Table of Recommended Antimicrobial CDI Therapies•				
Drug	**Unit**	***AWP Cost per Unit**	**AWP Cost per Day**	**AWP 14 day course**
Metronidazole tablet	500mg tablet	$0.82	$2.46	$34.44
Metronidazole injection	500mg bag	$2.16	$6.48	$90.72
Vanc oral solution	125mg solution	$4.03/vial	$4.03	$56.42
Vanc capsule (generic)	125mg capsule	$31.30	$125.20	$1,752.80
	250mg capsule	$57.77	$231.08	$3,235.12
Vanc capsule (brand name)	125mg capsule	$34.80	$139.20	$1,948.80
	250mg capsule	$64.20	$256.80	$3,595.20
Fidaxomicin**	200mg tab	$177.47	$354.94	$4,969.16
Tigecycline injection	50mg bag	$114.71	$229.42	$3,211.88
Rifaximin	200mg TID	$16.03	$48.09	$1,009.89 (21 days)
	400mg BID	$32.08	$64.16	$1,347.36 (21 days)

**Average wholesale price (data provided by Emily Mui PharmD).*

***Various programs are available for cost reduction in specific circumstances.*

evidence of ileus (lack of stooling/flatus, abdominal distension with air fluid levels on radiography) OR toxic megacolon (severe disease with colonic distension on radiography 6cm< in any segment) OR has peritonitis on exam, free air in abdomen by radiography AND/OR colonic perforation.

• Recurrent-renewed disease meeting the above diagnostic criteria after initial resolution of symptoms has occurred AND occurring within 8 weeks of previous episode or after new systemic antibiotic use. Note: After clinical response, it may take weeks for stool consistency and frequency to become entirely normal.

• Multiply Recurrent disease - >1 recurrence of disease, with each distinct episode meeting the diagnostic criteria above.

TREATMENT:

In addition to recommendations below, discontinue administration of unnecessary antibacterial agents and proton pump inhibitors (PPIs).

Mild/Moderate disease[1,2] – Metronidazole 500mg PO TID for 10-14 days (note median time to symptom resolution is 5-6 days). If symptoms resolve within 7 days, 10 days of therapy is sufficient; if >7 days, 14 days may be preferred (do not use for more than 14 days due to potential neurotoxicity). ALTERNATIVE THERAPY: Vancomycin 125 mg PO q6h (generic liquid formulation) for 10-14d.

Severe disease[1,2,5]- Likely requires hospitalization, also consider serial abdominable X-rays if patient has abdominal distension, tenderness. Consultation with Infectious Diseases is recommended. Antimicrobials: Vancomycin 125 mg PO q6h (generic liquid formulation) for 14d. ALTERNATIVE THERAPY: Fidaxomicin 200mg PO BID for 10d may be considered in failures of prior therapy, particularly if concurrent antibiotics are required, but there are no data available regarding the efficacy of this drug in severe life-threatening disease. Fidaxomicin use is restricted at Stanford. An ID consult not required only if patient meets following criteria:
a. Proven *C. difficile* disease AND
b. Recurrent disease AND
c. ≥3 of the following:
i. Age >65 years
ii. Significantly immunocompromised
iii. ≥2 SIRS criteria
iv. meets criteria for severe CDI disease
v. Continued broad-spectrum antibacterial therapy.
Severe-Complicated[1,2,6,7]- SURGICAL AND INFECTIOUS DISEASE CONSULTATION STRONGLY INDICATED. Serial AXRs necessary if

surgery deferred. Antimicrobials: Vancomycin 500mg PO q6h and IV metronidazole 500mg TID. Consider PR vancomycin 500mg in a 100ml normal saline retention enema q6h unless toxic megacolon (high perforation risk), total course at least 10d but longer courses can be determined from time of symptom resolution. ALTERNATIVE THERAPY: Replace IV metronidazole with IV tigecycline 50mg BID.

Surgical intervention is indicated in case of:
• Perforation of the colon
• Systemic inflammation and deteriorating clinical condition despite maximal antibiotic therapy; this includes the clinical diagnoses of toxic megacolon, acute abdomen and severe ileus. Colectomy should preferably be performed before colitis becomes very severe. Serum lactate may serve as a marker for severity (operate before lactate exceeds 5.0 mM/dL).

A potential alternative to colectomy may be diverting loop ileostomy and colonic lavage, combined with antibiotic treatment — a method that remains under investigation.

First Recurrence – Same therapy as for initial episode, adjusted for severity as above.

Multiply Recurrent Disease[1,2,8-10]– Infectious Diseases consultation strongly indicated. If severe-complicated, treat as above until stabilized, then continue as discussed below.
Can choose from the following options:
1. Fidaxomicin 200mg PO BID for 10d. See Stanford restriction criteria above.
2. Vancomycin 125mg PO q6h for 14d followed by Rifaximin 400mg PO BID for 21d.
3. Vancomycin PO 125mg q6h for 10d, then BID for 7d, then daily for 7d, then every other day for 21d or until symptoms tolerate.
4. Fecal Microbiota Transplant. Requires BOTH Infectious Diseases and Gastroenterology consults.

Recurrence prevention:
Limit repeat antibiotic use and proton pump inhibitor (PPI) use- these are the epidemiologic risk factors most associated with recurrence. Call ID consult or make urgent ID outpatient referral if possible prior to starting systemic antibiotics in patient with known CDI history, as it may be possible to minimize antibiotic use and duration. Would consider prior CDI, particularly severe or multiply recurrent disease as a relative contraindication to antibiotics and PPIs, e.g use only if absolutely necessary. If antibiotic use necessary in a patient with a history of CDI, if possible AVOID clindamycin, cephalosporins, monobactams, carbapenems, flouroquinolones and β-lactamase inhibitor combinations. Macrolides, sulfonamides, penicillin or aminopenicillins and aminoglycosides are possibly associated with a relatively lower risk of CDI than the other antibiotic classes listed above. Metronidazole and tetracyclines, particularly doxycycline, are the antibiotic classes associated with the least risk of CDI and may even be protective. Lower risk antibiotics should be used preferentially where appropriate. Using multiple antibiotics simultaneously should be avoided if possible as each additional agent used increases the risk of CDI, therefore regimens should be kept as simple as possible.[11-13]

Probiotics[14,15]: Available evidence for use of probiotic preparations (capsules, powder, yogurts) to prevent CDI occurrence is equivocal, but risk is low in immunocompetent patients. IF USED: Preparations should include greater than 1 x 109 colony forming units (CFU) of either *Saccharomyces cerevisiae* subtype boulardii (a strain within the species), bifidobacterium spp or lactobacillus spp. Use should be restricted to prevention in patients currently requiring systemic antibiotics, NOT in patients with active CDI. Use should be carefully considered in immunocompromised patients as risk may outweigh benefit in this population.

INFECTION CONTROL:

Current recommendation is for inpatients with positive *C difficile* toxin PCRs to be placed in contact isolation. Hand washing with soap and water (not alcohol based cleansers) is necessary with soiling of hands or bodily fluids after contact with CDI patients OR in outbreak situations, otherwise standard hand hygiene recommendations apply as per CDC/SHEA guidelines[1].

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ABSTRACT & COMMENTARY

Combination Therapy for Carbapenemase-Producing *Klebsiella pneumoniae* Bacteremia Reduces Mortality

By Richard R. Watkins, MD, MS, FACP

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

SYNOPSIS: In an observational study of 205 patients with bloodstream infections caused by strains of carbapenemase-producing Klebsiella pneumoniae, mortality was higher in patients who received monotherapy vs. those treated with combination therapy (44.4% vs 27.2%, P = 0.018). The greatest mortality reduction was observed with combinations that included a carbapenem.

SOURCE: Daikos GL, et al. Carbapenemase-Producing Klebsiella pneumoniae Bloodstream Infections: Lowering Mortality by Antibiotic Combination Schemes and the Role of Carbapenems. *Antimicrob Agents Chemother* 2014;58:2322-28.

The ongoing spread of carbapenemase-producing Klebsiella pneumoniae (CPKP) poses a serious threat to global public health. Infections from these strains are associated with high morbidity and mortality. Moreover, current therapy is limited by toxicities (e.g. colistin) and concerns about efficacy (e.g. tigecycline and fosfomycin). Daikos and colleagues sought to determine whether combination antibiotic therapy improves mortality from infections caused by CPKP compared to monotherapy alone.

The study was conducted at two hospitals in Athens, Greece between August 2009 and December 2010. It had a retrospective observational design that included patients with *K. pneumoniae* bloodstream infections (BSIs), defined as at least one positive blood culture, and symptoms of the systemic inflammatory response syndrome (SIRS). The main outcome measured was all-cause mortality within 28 days after the onset of bacteremia. Of the 338 patients with Klebsiella pneumoniae BSIs, 205 were infected with CPKP strains. The mean age of the patients was 63 years and all episodes of CPKP BSIs were either hospital acquired (93%) or health care associated (7%). The probable source of bacteremia was the lung in 43 patients, the abdomen in 29, an intravascular

catheter in 22, the genitourinary tract in 19, the skin in 6, and the central nervous system in 3. No portal of entry could be ascertained in 83 patients. Of the 205 CPKP strains, 163 (79.5%) produced KPC-2 and the remaining 42 isolates produced VIM-1. The most active antimicrobials were tigecycline and colistin although 15% and 25% of isolates were resistant to these two drugs, respectively. Antibiotic therapy was at the direction of the attending physician and appropriate source control (e.g. line removal and debridement/drainage) was performed in all cases. Eighteen patients died before antibiotic susceptibility results became available. Of the 175 patients who were treated with at least one active drug, 103 were given combination therapy (31 received a carbapenem-containing regimen and 72 a carbapenem-sparing regimen). Monotherapy was used for the remaining 72 patients. Older patients were more likely to have received monotherapy than their younger counterparts.

The all-cause mortality at 28 days was high with 82 of 205 patients (40%) dying during that timeframe. Univariate analysis revealed a higher risk for an adverse outcome among females, those with advanced age, a higher Charlson index, neutropenia, polymicrobial bacteremia, and severe sepsis or septic shock. Characteristics of the infecting CPKP strain and the timing of effective antibiotic therapy did not affect outcome. Overall mortality was lower in those patients treated with combination therapy compared to monotherapy (27.2% vs 44.4%, P = 0.018). Among the combinations used, those that contained a carbapenem had the lowest mortality rate (19.3%). Notably, all 11 patients treated with a carbapenem plus tigecycline plus an aminoglycoside or colistin survived. However, when the carbapenem MIC increased from ≤8 µg/ml to ≥8 µg/ml, mortality increased from 19.3% to 35.5%. Among those who received a carbapenem with an elevated MIC and an inactive drug, mortality was 58.3%. Combination therapy also provided a significant therapeutic benefit over monotherapy in patients with septic shock (odds ratio [OR] of survival: 0.22; 95% confidence interval [CI], 0.05 to 1.0; P = 0.045) and for those with rapidly fatal underlying disease (OR of survival: 0.08; 95% CI, 0.01 to 0.52; P = 0.001). Finally, combination therapy was an independent predictor of survival (hazards ratio of death for monotherapy vs. combination therapy, 2.08; 95% CI, 1.23 to 3.51; P = 0.006).

■ COMMENTARY

The two most significant findings from this study were the impressive mortality benefit observed with combination therapy and that the mortality benefit was greatest when the regimen contained a carbapenem. This latter observation seems paradoxical and possible explanations include additive or synergistic effects from the carbapenem, although differences in MIC reporting i.e. Etest vs. automated systems may have played a role. It was interesting that the investigators did not find an association between the timing of effective therapy and outcomes. Indeed, one of the central principles of sepsis management is administration of effective antibiotic therapy in a timely manner.[1] Although Daikos and colleagues did not find a statistically significant difference between those who received timely active therapy and those who did not (P = 0.086), patients who received effective therapy ≤48 h into their BSI had better survival (65.8%) compared to those treated at ≥48 h (53.2%). It isn't clear if additional evaluation of these data would have produced different results and further investigation is warranted.

As with all observational studies, unmeasured variables may have led to selection bias that influenced the results. Moreover, differences in colistin dosing that occurred over the course of the study could have led to delays in pharmacokinetic and pharmocodynamic targets. The safety and efficacy of combination therapy has been controversial, with some authors arguing the addition of a second antimicrobial agent to treat a Gram-negative organism that is susceptible to a single agent may actually lead to increased antimicrobial resistance, adverse effects, and costs.[2] Thus, concerns about drug-induced toxicities might have been the reason that most older patients received monotherapy. Another interesting finding was the high prevalence of CPKP strains to non-CPKP ones (205 vs. 133, respectively), a rate fortunately not seen at present in North American hospitals.

Despite the limitations of the study, the robust mortality benefit from combination therapy provides clinicians a potential approach for dealing with the difficult challenge of CPKP BSIs. Hopefully prospective, randomized clinical trials that compare monotherapy to combination therapy and evaluate the efficacy of different combination regimens for CPKP infections will be conducted in the near future.

References

1. Dellinger RP, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013;39:165-228.
2. Tamma PD, et al. Combination therapy for treatment of infections with gram-negative bacteria. *Clin Microbiol Rev* 2012;25:450-470. ■

Updates

By Carol A. Kemper, MD, FACP

Newer lab tests for GC/ Chlamydia

Centers for Disease Conrol and Prevention. Recommendations for the laboratory-based detection of Chlamydia trachomatis and Neisseria gonorrhoeae - 2014. *MMWR* 2014;63(RR02);1-19.

Our county-based HIV/AIDS Clinic in San Jose, California provides STD screening of the rectum, oropharynx, and urethra for all new and returning HIV+ patients – with increasingly alarming results. In calendar year 2013, a total of 500 men who have sex with men (MSM) were screened for GC/Chlamydia using nucleic acid amplification testing (NAAT; APTIMA GenProbe Unisex swab testing kit) (informal data, Wilson Ly, Pharm. D.). The patients did self-swabbing of all 3 sites, under the supervision of the HIV Pharmacy Specialist, who assists with the initial intake visit. Overall, 14% of cultures from all sites were positive for at least one organism. The highest prevalence of GC was 11% in the oropharynx; and the highest prevalence for Chlamydia was 23% from the rectum. Most of these infections were asymptomatic. Follow-up proof of cure NAAT testing is provided for anyone testing positive for GC.

Revised CDC guidelines now recommend routine laboratory screening for GC and chlamydia of all genital and extra-genital sites for all sexually active MSM – and they are specifically recommending the routine use (for all 3 sites) of the newer NAAT laboratory screening tests, which are superior to earlier screening laboratory STD tests. While earlier non-culture tests based on DNA or RNA sequences frequently failed to detect a good number of infections (especially chlamydia), the newer tests are much more sensitive and specific.

The CDC cautioned that laboratories should maintain capability for culturing these organisms for several reasons: for suspect cases of treatment failure for GC; for sexual assault cases (where the reliability of the NAAT screening tests is not known); and to monitor for evolving antibacterial resistance. ■

Hospitals should remain alert for MERS-CoV

Arabi YM, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Ann Intern Med* 2014; 160:389-97; and accompanying editorial: Perl TM, et al. Medusa's ugly head again: From SARS to MERS-CoV. *Ann Intern Med* 2014; 160: 432-433.

Since the world was alerted September 15, 2012 to (another) new virus – more than 200 cases of MERS-CoV have been reported, and new cases continue to occur. Similar to SARS, MERS-CoV results in a severe respiratory illness for which there is no effective therapy. It tends to affect middle-aged persons and spare children. All cases have been directly or indirectly linked to travel to or from key countries within the Arabian Peninsula. In this article, Arabi and colleagues report on 12 consecutive cases with severe respiratory failure and sepsis requiring critical care, with a mortality of 68%. All of the patients had comorbidities including diabetes, kidney disease or heart disease. One-third of these cases were hospital-acquired.

It is still not clear whether infections are occurring from episodic contact with infected animal sources (both bats and camels have been implicated), or from low-level sustained transmission between humans. But what is clear is that many of the cases have occurred in health care personnel. Of the first 160 reported cases, 30 (18.6%) were in HCWs. The rapid recognition of a suspect case on first presentation is therefore critical.

• Patients who should be immediately screened and placed in airborne and contact isolation include: (1) A person with fever (≥38 C, 100.4 F) and pneumonia or acute respiratory distress syndrome (based on clinical or radiological evidence); and either

(2a) history of travel from countries in or near the Arabian Peninsula within 14 days before symptom onset; or (2b) close contact with a symptomatic traveler who developed fever and acute respiratory illness (not necessarily pneumonia) within 14 days after traveling from countries in or near the Arabian Peninsula; or (2c) is a member of a cluster of patients with severe acute respiratory illness (e.g., fever and pneumonia requiring hospitalization) of unknown etiology in which MERS-CoV is being evaluated.

The Arabian Peninsula or

neighboring countries include: Bahrain, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Palestinian territories, Oman, Qatar, Saudi Arabia, Syria, the United Arab Emirates, and Yemen.

All hospitals should have Infection Control Guidelines developed for known or suspected MERS-CoV infection, and work with their Emergency Room and critical care personnel to be alert to potential travelers at risk who meet the above criteria. The World Health Organization and the CDC split on the need for airborne precautions (the CDC favors airborne precautions), since the exact mode of transmission of the virus is not known. Earlier outbreaks were apparently thwarted in the Al-Hasa province of Saudi Arabia using intensive surveillance and contact and droplet precautions alone.

Fortunately, preliminary modeling of the Basic Reproductive Number (Ro) for MERS-CoV is estimated to be 0.6 to 0.69. This provides a mathematical estimate of the number of secondary infected individuals produced by an individual in its lifetime. In comparison, the Ro for SARS is variously estimated at 0.19 to 1.08, depending on the location of the outbreak examined, and Ebola has an Ro of 1.34-1.83. It is a grim reminder that >90% of cases in the SARS outbreak in Toronto were hospital-acquired. ■

Heart disease in HIV

Post WS, et al. Associations between HIV infection and subclinical coronary atherosclerosis. *Ann Intern Med* 2014; 160:458-467.

Primary care of my aging HIV patient population has become much like primary care for any patient group – it's all about diabetes, HTN, heart disease, and the usual colds and flus - with the added twist of monitoring and managing generally well-controlled HIV infection. But as many HIV+ patients stare down 60 years of age – the question remains whether HIV and /or HIV medications are significantly associated with an increased risk of heart disease. Studies have been inconsistent on this point, although they suggest an increased relative risk of about 50% compared with the rest of the population. Increased levels of systemic inflammation and immune system activation associated with HIV infection may be responsible, although mechanisms of plaque development and stenosis are not well understood.

The Multicenter AIDS Cohort Study (MACS) is a well-established cohort study with a well-matched control group, created to examine the natural history of HIV. Now in its third decade, it continues to track more than 7,000 gay men, including both HIV+ and HIV- men, at four different sights in the United States, including UCLA, Northwestern University in Chicago, the University of Pittsburgh, and Johns Hopkins. The cumulative dropout rate over two and half decades is astoundingly low at 15%. The project even rates its own Wikipedia page.

These authors examined the degree of coronary artery plaque characteristics and severity in a group of HIV+ and HIV- men ages 40-70, weighing < 200 lbs, and having no history of cardiac surgery or intervention. In all, a total of 1001 men were studied, including 618 HIV+ men. More HIV+ men were smokers, had longer cumulative smoking years, lower body mass index, and higher serum creatinine. They also had lower LDL and HDL levels, but higher triglyceride levels; and one-third were using lipid lowering agents.

All of the participants underwent non-contrast cardiac CT scan, which were reviewed by blinded readers. Coronary arteries were defined as normal, or containing non-calcified, mixed, or calcified plaque — and the extent of the plaque was graded as mild, moderate or severe. Stenosis was also graded, and a composite score was created for each scan. In addition, 759 men underwent coronary arteriography. In all, 53% of HIV+ men had evidence of any coronary calcium compared with 52% of non-infected men. After adjusting for age, race, and cohort, HIV+ men had a higher rate of coronary artery calcium and plaque, including both non-calcified ($p < .001$) and mixed plaque ($p< .004$) than un-infected men. Scores measuring both the extent of plaque and the segment involvement were greater for HIV+ men compared with their HIV- cohort. In addition, HIV+ men had a higher prevalence of coronary artery stenosis (>50%) compared with the HIV- cohort (16.9% vs 14.6%), although this difference did not appear statistically significant, even after adjusting for age, race and cohort. However, a longer duration of antiretroviral therapy and a lower nadir CD4 count were both associated with an increased risk of coronary stenosis (> 50%) ($p = .005$).

Both the extent and severity of non-calcified coronary artery plaque is significantly greater in HIV+ men compared with their uninfected counterparts. An interesting clue to the mechanism of plaque development may be the greater degree of coronary artery involvement in persons who have ever had more advanced HIV/AIDS disease, presumably reflecting a period of sustained immune system impairment. ■

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CME QUESTIONS

1. Which of the following responses is true?

A. Ebola virus infections are fatal in 90% of human cases.
B. Ebola outbreaks are currently active in Mali and Ethiopia.
C. Ebola virus is exquisitely susceptive to a variety of anti-viral agents.
D. Ebola infection in primates cannot be prevented by vaccination.

2. Which of the following is correct with regard to the study of bloodstream infections due to carbapenemase-producing *Klebsiella pneumoniae* by Daikos et al?

A. The all-cause 28-day mortality was 5%.
B. All isolates were susceptible to colistin.
C. All isolates were susceptible to tigecycline.
D. Combination therapies that contained a carbapenem had the lowest mortality and all patients who received a carbapenem together with tigecycline and either colistin or an aminoglycoside survived.

3. Which of the following is correct with regard to *Clostridium difficile* infection.

A. Testing by PCR detection of toxin genes has a sensitivity <60%.
B. Toxic megacolon is an indication for surgical intervention.
C. All patients should undergo tests of cure.
D. A negative PCR should routinely be repeated twice in patients with continuing diarrhea.

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

"And it was in the midst of shouts rolling against the terrace wall in massive waves that waxed in volume and duration, while cataracts of colored fire fell thicker through the darkness, that Dr. Rieux resolved to compile this chronicle, so that he should not be one of those who hold their peace but should bear witness in favor of those plague-stricken people; so that some memorial of the injustice and outrage done them might endure; and to state quite simply what we learn in time of pestilence: that there are more things to admire in men than to despise."

Albert Camus, *The Plague*

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Infectious Disease Alert

Reader Survey 2014

In an effort to ensure *Infectious Disease Alert* is addressing the issues most important to you, we ask that you take a few minutes to complete and return this survey. The result will be used to ensure you are getting the information most important to you.

Instructions: Mark your answers by filling in the appropriate bubbles. Please write in your answers to the open-ended questions in the space provided. Either fax the completed questionnaire to 404-492-5933, or return it in the enclosed postage-paid envelope. The deadline is **July 1, 2014**.

In future issues of *Infectious Disease Alert*, would you like to see more or less coverage of the following topics?

	A. more coverage	B. less coverage	C. about the same amount
1. antibiotic resistance	O A	O B	O C
2. emerging infectious diseases	O A	O B	O C
3. therapeutic advances	O A	O B	O C
4. bacterial infections	O A	O B	O C
5. antimicrobials	O A	O B	O C
6. HIV/AIDS	O A	O B	O C
7. vaccines	O A	O B	O C
8. hospital epidemiology	O A	O B	O C
9. mycobacterial infections	O A	O B	O C
10. pathogenesis	O A	O B	O C

11. What other topics would you like to see discussed in *Infectious Disease Alert*? _____

_____

12. Are the articles in *Infectious Disease Alert* written about issues of importance and concern to you?

O A. always O B. most of the time O C. some of the time O D. rarely O E. never

13. What type of information not currently provided in *Infectious Disease Alert* would you like to see added?

_____

_____

Please rate your level of satisfaction with the items listed.

	A. excellent	B. good	C. fair	D. poor
14. quality	O A	O B	O C	O D
15. article selections	O A	O B	O C	O D
16. timeliness	O A	O B	O C	O D
17. quality of commentary	O A	O B	O C	O D
18. clearness of abstracts	O A	O B	O C	O D
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21. Are the articles in I*nfectious Disease Alert*:

O A. too short O B. too long O C. about right

22. Please describe your work place.

O A. private practice O B. hospital O C. government institution O D. research

O E. Other (please specify) _____

23. To which other publications or information sources about infectious diseases do you subscribe?

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24. Which publication or information source do you find most useful, and why? _____

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25. Please list the top three challenges you face in your job today.

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26. What do you like most about *Infectious Disease Alert*?

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28. What issues would you like to see addressed in *Infectious Disease Alert*?

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29. Has reading *Infectious Disease Alert* changed your clinical practice? If yes, how? _____

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