Infections and Anesthesiologists

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This abstract will review two deadly infections that are rare, avian influenza A and extremely resistant tuberculosis. However, given that these infections proliferate in the airways of patients who often require endotracheal intubation, these infections are of grave risk to anesthesiologists and other health care personnel exposed to airway secretions. The other two infections discussed, MRSA and *C. difficile* are much more common and most health care workers will be exposed to these bacteria. These bacteria are found on patients as well as on the belongings of patients and on furniture and in the environment near infected patients. All these infections can cause harm to health care providers; awareness of the details of these infections suggest that protective eyewear, N95 masks that are fitted, protective clothing, and gloves are important adjuncts to be utilized in daily routines for the safety of health care providers.

(Anesth Analg 2008;106:●●●–●●●)

RARE BUT DEADLY INFECTIONS IN THE AIRWAYS OF PATIENTS

Avian Influenza A [H5N1] Virus

The avian influenza A viruses are found in poultry in Asia, Africa, and perhaps in the Middle East.[1] The avian influenza virus that infects humans comes from birds, both from poultry and from wild birds. Migratory birds may spread H5N1 viruses to new geographic locations, but their importance as a reservoir of these viruses is not clear.[1] Despite widespread exposures to infected poultry, human disease due to H5N1 influenza A virus is rare.[1] As of December 14, 2007, there have been 340 reported cases.[1] The data regarding these cases shows that the patient's median age is 18 years and that 90% of these patients are under 40 years of age.[2] The fatality rate is 61% with the most frequent deaths in patients 10–19 years of age.[2]

The cases seem to occur in cooler months, associated with outbreaks in poultry.[3] Limited data has shown that asymptomatic or mild human influenza A infections are rare but do occur.[4]

Infection occurs after transmission of the virus from avian-to-humans; handling of sick or dead poultry during the week before the onset of the illness is the most commonly recognized risk factor.[5] Other risk factors include: slaughtering, defeathering, preparing sick poultry for cooking, playing with or holding diseased or dead poultry, handling fighting cocks or ducks, and consuming raw or undercooked poultry or poultry products.[5–8] It is believed that most of the patients were exposed to the poultry. In some limited, nonsustained cases there may have been human-to-human transmission where there was close and unprotected contact with a severely ill patient.[9,10] Respiratory secretions and all body fluids, including feces, are potentially infectious.[1] It is thought that some of the cases were due to inhalation of aerosolized infectious excreta.[1] After exposure to infected poultry, the incubation period is approximately 7 days.[1]

The pathologic process that appears to cause death is fulminant viral pneumonia.[1] The virus replicates in type 2 alveolar cells and in macrophages.[11,12] Ultimately, however, high titers of virus are detectable in the throat and in tracheal aspirates from humans infected with the H5N1 virus.[13] Ability of the virus to replicate may influence outcome; larger loads of virus were found in the throats of patients who died when compared to the loads in patients who lived.[13] Disseminated infection can clearly occur; virus has been detected in blood, cerebrospinal fluid, and in various viscera of patients who have died.[13]

Symptoms and signs include fever, cough, respiratory distress, and at times vomiting, diarrhea, leucopenia, lymphopenia, thrombocytopenia, and increased aminotransferase levels.[1] The infection can be detected by real-time reverse-transcriptase polymerase chain reaction.[14] Multiple samples should be obtained from the nose or throat; tracheal aspirates have higher viral titers and yields than specimens from the upper respiratory tract.[13]

Treatment

Early treatment with oseltamivir is recommended.[15] A higher dose of oseltamivir (i.e., 150 mg b.i.d. in adults) for 10 days has been recommended when disease progresses despite early treatment.[1]

Extensively Drug Resistant-Tuberculosis: XDR-TB

There are approximately 9 million new cases of TB in the world annually with 1.6 million deaths; over 80% of the cases occur in Asia or Africa.[16] Nine countries in sub-Saharan Africa have annual incidences in excess of 600 cases per 100,000, a burden of disease not seen since therapy has been available.[17] This increase is largely due to the AIDS epidemic in this region and the weak health care delivery systems.

Resistance to at least two major anti-tuberculosis drugs, isoniazid and rifampicin, has been called multidrug-resistant tuberculosis, MDR-TB. Approximately 425,000 MDR-TB cases occur annually worldwide, representing nearly 5% of the world's annual TB burden.[18] Treatment of MDR-TB requires a more prolonged therapy, a course of 24 months, and more expensive chemotherapy (of up to 300-fold higher costs) than non-MDR-TB and often leads to increased toxicity. When tuberculosis becomes resistant to the second-line therapy it is known as extensively drug resistant-tuberculosis or XDR-TB. Countries in Eastern Europe, the former Soviet Union, regions of China as well as sub-Saharan Africa have an increased burden MDR-TB and now XDR-TB. MDR-TB and XDR-TB are associated with very high mortalities, due to the vulnerable patient population and the problems in finding therapies that do not interact with antiretroviral agents.[19–21]

For persons infected with *M. tuberculosis*, HIV infection is the strongest risk factor for the development of active TB.[18] TB is the leading cause of death among HIV-infected persons and may accelerate the course of HIV infection, increasing the viral load in some patients.[18,22–24] In a 1996 study from New York City, 72% of HIV-infected patients with MDR-TB died during treatment, compared with 20% of MDR-TB patients without HIV; median survival was 14 months.[25] Surgery improves treatment outcomes in selected patients with MDR-TB and warrants further evaluation for XDR-TB.[18,26]

China has the greatest estimated burden of MDR-TB worldwide (~140,000 cases annually) and India has the world's highest burden of TB overall, with about 90,000 cases of MDR-TB annually.[18] Mexico has 2500 cases of MDR-TB annually. In contrast, the United States has about 121 cases of MDR-TB annually but had 15 cases of XDR-TB.[18]

TB transmission to health care providers has increasingly occurred. In Zambia, there were 8 nurses that developed TB in the 1980s and all were successfully treated. Between 1990–1996, 114 nurses died of TB at the same hospital.[18]

MORE COMMON AND LESS DEADLY INFECTIONS: MRSA AND *C. DIFFICILE*

MRSA

Hospital-acquired MRSA infections have been associated with poor patient outcomes; recently, community-acquired MRSA infections in the United Kingdom and United States are being reported to be associated with poor patient outcomes, including death.[27] Patients with community-acquired MRSA were more likely to be male and to have comorbidities than similar patients without MRSA. Furthermore, the patients with MRSA had an increased likelihood of dying within 1 year of the diagnosis.[27] The community acquired MRSA, CA-MRSA strains, have been associated with skin and soft tissue infections, bacteremia, endocarditis, pneumonia and empyema, osteomyelitis, and pyelonephritis.[28,29] Evaluating consecutive patients undergoing operative debridement for complicated skin and soft tissue infections from 2000–2006 in a Houston VA hospital, it was found that there were 288 patients with skin and soft tissue infections. About 70% of the infections were culture positive for *S. aureus* and 49% were MRSA in 2006; in contrast, in 2000 only 34% of the cultures were positive for MRSA.[30] This data suggests there has been a significant increase in CA-MRSA and suggests that precautions should be taken when touching patients' skin or fomites that have been on patients.

Not only is the incidence of MRSA increasing in communities, but there is concern that the exposure of MRSA to chlorhexidine is increasing resistance of *S. aureus* to chlorhexidine. Chlorhexidine is now routinely used as a cleansing agent on the skin of patients as well as an oral antiseptic to prevent ventilator associated pneumonia and other hospital-acquired infections.[31–34]

One hundred and twenty clinical MRSA strains were collected from the clinical microbiology laboratories in Edinburgh and were evaluated for the presence of chlorhexidine resistance genes using PCR. The isolates were also exposed to chlorhexidine for 5 minutes, and survival of the exposed bacteria was determined. There are at least 12 "biocide resistance genes" including *qacA-qacJ*, *smr*, and *norA*. These genes appear to confer resistance not only to cationic antiseptics but also to biguanides.[35] The *smr* gene encodes a protein that functions as a drug pump; the gene is often on plasmids that are <3 kb. *qacA* and *B* genes are on large plasmids, >20 kb, and mediate an energy-dependent export system. The blaZ β lactamase gene resides on a common plasmid with the *qacA*/B genes.[35]

All of the 120 MRSA isolates were mecA-positive. *qacA/B* was detected in 10 isolates (8.3%), *nor* A was detected in 44 [37%], *smr* in 53 isolates [44%] and *blaZ* in 117 [97.5%]. Only 5 isolates had both *qacA/B* and *smr*. All the isolates that had the *qacA/B* gene also contained the β lactamase transposon, blaZ, but not all the isolates with the blaZ gene contained *qacA/B*. This suggests that not all antibiotic resistant strains are resistant to biocides, but that strains resistant to biocides tend also to be resistant to antibiotics genes.[35]

C. difficile

Clostridium difficile lives as an anerobic spore, and the spores can survive on inanimate surfaces for months. Recently a study documented that *C. difficile* spores are in the air of hospital wards; indeed it appears that air vents and other surfaces are probably contaminated with *C. difficile* spores.[36] Reports have shown that the bathrooms and toilets are among the most contaminated areas in the hospital but notably this recent study documented that the *C. difficile* spores were found in the air in a ward where there had not been a patient with *C. difficile* associated

diarrhea (CDAD) for 7 weeks.[36] *C. difficile* spores do survive for less time on copper alloy surfaces suggesting that specific surfaces can discourage the survival of this pathogen possibly by forming hydroperoxides.[37] Also, it appears that many asymptomatic patients have *C. difficile* in their stool. A recent investigation documented that 51% of patients were asymptomatic carriers of *C. difficile*, and that these patients also had these organisms on their skin. Samples taken from the environment near these patients also documented environmental contamination. Previous antibiotic usage was strongly associated with asymptomatic *C. difficile* carriage.[38] All this data suggests that health care workers should assume all patients potentially carry *C. difficile* and that even touching objects inpatient's rooms can lead to contamination by *C. difficile*. Hand washing is required to get rid of *C. difficile*; alcohol washes do not eliminate the spores.

REFERENCES

1. Writing committee of the second world health organization consultation on clinical aspects of human infection with avian influenza A [H5N1] virus: update on Avian Influenza A [H5N1] virus infection in humans. N Engl J Med 2008;358:261–73
2. World Health Organization Update November 25, 2003–4; November 2006. Wkly Epidemiol Rec 2007;82:41–8
3. Park AQ, Glass K. Dynamic patterns of avian and human influenza in east and southeast Asia. Lancet Infect Dis 2007;7:543–8
4. Vong S, Coghlan B, Mardy S. Low frequency of poultry-to-human H5N1 virus transmission, Southern Cambodia. 2005 Emerg Infect Dis 2006;12:1542–7
5. Dinh PN, Long HT, Tien NTK. Risk factors for human infection with avian influenza A H5N1, Vietnam 2004. Emerg Infect Dis 2006;12:1841–7
6. Oner AF, Bay A, Arslan S. Avian influenza A [H5N1] infection in eastern Turkey in 2006. N Engl J Med 2006;355:2179–85
7. Areechokchai D, Jiraphongsa C, Laosiritaworn Y, Hanshaoworakul W, O'Reilly M. Investigation of avian influenza A [H5N1] outbreak in humans-Thailand, 2004. MMWR Morb Mortal Wkly Rep 2006;55(Suppl 1):3–6
8. Sedyaningsih ER, Isfandari S. Setiawaty V. Epidemiology of cases of H5N1 virus infection in Indonesia, July 2005-June 2006. J Infect Dis 2007;196:522–7
9. Ungchusak K, Auewarakul P, Dowell SF. Probably person-to-person transmission of avian influenza A [H5N1] N Engl J Med 2005;352:333–40
10. Osen SJ, Ungchusak K, Sovann L. Family clustering of avian influenza A [H5N1]. Emerg Infect Dis 2005;11:1799–801
11. Gu J, Xie Z, Gao Z. H5N1 infection of the respiratory tract and beyond: a molecular pathology study. Lancet 2007;370:1137–45
12. Yamada S, Suzuki Y, Suzuki T. Haemagglutinin mutations responsible for the binding of H5N1 influenza A viruses to human-type receptors. Nature 2006;444:378–82
13. de Jong M, Simmons CP, Thanh TT. Fatal outcome of human influenza A [H5N1] is associated with high viral load and hypercytokinemia. Nat Med 2006;12:1203–7
14. World Health Organization. Collecting, preserving and shipping specimens for the diagnosis of avian influenza A [H5N1] virus infection: guide for field operations; http://www.who.int/csr/resources/publications/surveillance/whocdscsredc2004.pdf
15. World Health Organization. WHO rapid advice guidelines on pharmacological management of humans infected with avian influenza A [H5N1] virus 2006. http://www.who.int/medicines/publications/WHO_PSM_PAR_2006.6.pdf
16. Zager EM, McNerney R. Multidrug-resistant tuberculosis. BMC Infectious Diseases 2008;8:10
17. Corbett EL, Marston B, Churchyard GJ. Tuberculosis in sub-Saharan Africa: opportunities, challenges, and change in the era of antiretroviral treatment. Lancet 2006;367:926–37
18. Wells CD, Cegielski P, Nelson LJ. HIV infection and multidrug-resistant tuberculosis: the perfect storm. J Infect Dis 2007;196: S86–107
19. Leimane V, Riekstina V, Holtz T. Clinical outcome of individualized treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. Lancet 2005;365:318–26
20. Shin SS, Pasechnikov AD, Gelmanova IY. Treatment outcomes in an integrated civilian and prison MDR-TB treatment program in Russia. Int J Tuberc Lung Dis 2006;10:402–8
21. CDC. Extensively drug-resistant tuberculosis-USA, 1993–2006. MMWR Morb Mortal Wkly Rep 2007;56:250–3
22. Podlekareva D, Mocroft A, Dragsted UB. for the EuroSIDA Study Group. Factors associated with the development of opportunistic infections in HIV-1 infected adults with high CD4+ cell counts: a EuroSIDA study. J Infect Dis 2006;194:633–41
23. Day JH, Grant AD, Fielding KL. Does tuberculosis increase HIV load? J Infect Dis 2004;190:1677–84
24. Whalen C, Horsburgh CR, Hun D. Accelerated course of HIV infection after tuberculosis. Am J Respir Crit Care Med 1995;151:129–35
25. Park MM, Davis AL, Schluger NEW. Outcome of MDR-TB patients, 1983–1993; prolonged survival with appropriate therapy. Am J Respir Crit Care Med 1996;153:317–24
26. Chan ED, Laurel V, Strand MJ. Treatment and outcome analysis of 205 patients with multidrug resistant tuberculosis. Am J Respir Crit Care Med 2004;169:1103–9
27. Delaney JAC, Schneider-Lindner V, Brassard P. Mortality after infection with methicillin resistant *Staphylococcus aureus* diagnosed in the community. BMC Med 2008;6:2
28. Crum NF, Lee RU, Thornton SA. Fifteen year study of the changing epidemiology of methicillin-resistant *Staphylococcus aureus.* Am J Med 2006;119:943–51
29. Naimi TS, LeDell KH, Como-Sabetti K. Comparison of community and health care associated methicillin-resistant *Staphylococcus aureus* infection. JAMA 2003;290:2976–84
30. Awad SS, Elhabash SI, Lee L. Increasing incidence of methicillin-resistant *Staphylococcus aureus* skin and soft-tissue infections: reconsideration of empiric antimicrobial therapy. Am J Surg 2007;194:606–10
31. Edmiston CE, Seabrook GR, Johnston CP. Comparative of a new and innovative 2% chlorhexidine gluconate-impregnated cloth with 4% chlorhexidine gluconate as a topical antiseptic for preparation of the skin prior to surgery. Am J Infect Control 2007;35:89–96
32. Chlebicki MP, Safdar N. Topical chlorhexidine for prevention of ventilator-associated pneumonia: a meta-analysis. Crit Care Med 2007;35:595–602
33. Koeman M, van der Ven AJAM, Hak E. Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia. Am J Respir Crit Care Med 2006;173:1348–55
34. Segers P, Speekenbrink RGH, Ubbink DT. Prevention of nosocomial infection in cardiac surgery by decontamination of the nasopharynx and oropharynx with chlorhexidine gluconate-a randomized controlled trial. JAMA 2006;296:2460–66
35. Vali L, Davies SE, Lai LLG. Frequency of biocide resistance genes, antibiotic resistance and the effect of chlorhexidine exposure on clinical methicillin-resistant *Staphylococcus aureus* isolates. J Antimicrob Chemother (Epub ahead of print)
36. Roberts K, Smith CF, Snelling AM. Aerial dissemination of clostridium difficile spores. BMC Infectious Diseases 2008;8:7
37. Weaver L, Michels HT, Keevil CW. Survival of *Clostridium difficile* on copper and steel: futuristic options for hospital hygiene. J of Hospital Infection 2008;1:1–7
38. Riggs MM, Sethi AK, Zabarsky TF. Asymptomatic carriers are a potential source for transmission of epidemic and nonepidemic *Clostridium difficile* strains among long-term care facility residents. Clin Infect Dis 2007;45:992–8

AUTHOR QUERIES

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