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World Cup 2010: Anticipated Infections in Travelers to South Africa

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Synopsis: *Travelers who restrict themselves to World Cup venues in South Africa are not at an unusual risk of infectious diseases, but this may not be the case for those who add on travel to national parks or neighboring countries.*

Source: Mendelson M, et al. Health risks in travelers to South Africa: The GeoSentinel experience and implications for the 2010 FIFA World Cup. *Am J Trop Med Hyg*. 2010;82:991-995.

Before the 2010 FIFA World Cup competition began, it was anticipated that more than 350,000 visitors, including many from the United States, would descend upon South Africa.[1] It was further anticipated that almost one-third would extend their trip to visit other tourist sites within South Africa and other African countries, most often nearby countries such as Zambia. Unfortunately, some of these travelers will acquire an illness. Mendelson and colleagues have examined the GeoSentinel database to determine the pattern of illnesses in individuals returning from South Africa, and other countries on the continent, from 1997 through 2009, who were evaluated at one of 50 GeoSentinel sites in 23 countries.

The most frequently encountered clinical presentations of illness acquired in South Africa, as well as in countries of sub-Saharan Africa, were, in descending order, systemic febrile illness, dermatologic problems, and acute diarrhea. For South Africa-only travelers, 39% of presentations to GeoSentinel clinic sites were because of systemic febrile illness and, in contrast to visitors to other African countries, the predominant cause was spotted fever-group rickettsiosis, presumably due to *Rickettsia africae*. In contrast, only six of the 327 ill South Africa-only travelers (19 per 1,000 travelers) had confirmed malaria, and only one of these plasmodial in-

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fections was acquired during the winter months (June, July, August). Only one case each of hepatitis A and of typhoid fever was identified among South Africa-only travelers during the 13-year period that was examined, while there were 11 cases of influenza. The World Cup is, of course, occurring during the southern hemisphere's winter influenza season.

Respiratory illnesses were the fourth most common presentation in South Africa-only travelers, among whom 11 had influenza and one had measles.[2] Nine were given post-exposure prophylaxis for possible rabies exposure.

Sexually transmitted diseases were infrequently detected, but the extraordinarily high incidence of HIV infection (29.3% of pregnant women) must be kept in mind.

■ COMMENTARY

Additional infections not reported by Mendelson et al, which may be acquired by travelers to affected areas of South Africa and neighboring countries, may include dengue, filariasis, onchocerciasis, schistosomiasis, and trypanosomiasis. South Africa also has been experiencing an outbreak of Rift-Valley fever, with 186 human cases with 18 deaths identified as of May 10, 2010.[3] The risk to travelers is minimal, except for those coming in contact with farm animals or sleeping outdoors in affected areas. While these infections are not only of concern to visitors to sites of football competition, others may be acquired in the absence of additional travel. Thus, South Africa has had an ongoing outbreak of measles, a highly contagious disease, and has reported more than 9,000 confirmed cases during January 1, 2009 through March 12, 2010.[4] Also to be considered is the potential for exposure to tuberculosis, a disease with a high prevalence in South Africa, as well as HIV. ■

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Acinetobacter Spreads its Wings

ABSTRACT & COMMENTARY

By Ellen Jo Baron, PhD, D(ABMM)
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Dr. Baron reports no financial relationships relevant to this field of study.

Synopsis: *Serious infections caused by* Acinetobacter baumannii *are appearing in the community, spread by patients who acquired the organism in the hospital setting, and conversely, the organism is being introduced into the hospital from long-term nursing care patient settings. Resistance to antimicrobial agents has increased over the six-year study period, along with the severity of disease.*

Source: Sengstock DM, et al. Multidrug-resistant *Acinetobacter baumannii*: An emerging pathogen among older adults in community hospitals and nursing homes. *Clin Infect Dis*. 2010:50:1611-1616.

We have all watched as *Acinetobacter* morphed from an infrequently seen isolate of little clinical consequence to a frightening pathogen. Microbiologists used to recover *Acinetobacter lwoffii* from vaginal secretions in the days when we thought, incorrectly, that gram-

negative rods were pathogens in that site. Now we are faced with *Acinetobacter baumannii*, currently the most common *Acinetobacter* species seen in clinical samples, causing pneumonia, wound infections, urinary tract infections, and sepsis. The organism does not inherently have any toxins or cytolysins, and other conventional virulence factors have not been detected, as reviewed by Gordon and Wareham.[1] *Acinetobacter* does form biofilms, a trait that no doubt helps it survive in the environment, from which it infects humans.[2] And like *Salmonella, Yersinia pestis, Bacillus anthracis,* and other pathogenic siderophore-producing microbes, it accumulates iron from the environment and its host.[3] Probably the most important reason for its increasing importance is its multidrug resistance. In fact, almost every hospital laboratory in the United States has isolated at least one *A. baumannii* that is resistant to every antimicrobial that can be tested. Carbapenem resistance due to the $bla_{\text{OXA-23}}$ gene, common among injured Iraqi- and Afghanistan-conflict veterans, and spreading rapidly in the civilian population, was associated with prolonged stay in both the intensive care unit and the hospital, according to a recent report from a Veterans Administration system group studying patients at Walter Reed Army Medical Center.[4] However, a recent study from an excellent healthcare system in Porto Alegre, Brazil, showed that the risk of 30-day mortality in patients infected with a carbapenem-resistant outbreak strain of *A. baumannii* was related more to the patient's underlying condition and severity of infection at presentation than to the use of inappropriate therapy.[5] On the other hand, only one-third of the 66 patients received the correct therapy, due to many physicians underestimating the importance of the isolate. Early appropriate therapy has been shown in other studies to reduce mortality.[6] And the major study summarized here also found increasing morbidity related to increasing antibiotic resistance.

Its role as a hospital-acquired pathogen is well described, but Sengstock and colleagues extended their study to include all patients older than 60 years from whom *Acinetobacter* was isolated by a central reference microbiology laboratory over the years 2003-2008.[7] The laboratory serves four community hospitals in suburban Detroit. Only the first isolate from each patient was included in the database. The patient groups were divided into "community dwellings" and "nursing home dwellings"; patients admitted from long-term acute-care facilities were excluded, although the authors concluded that patients discharged to such facilities from hospitals were one source of multidrug-resistant *Acinetobacter* in the community. The 840 patients whose cultures were analyzed in the study included 560 community-dwelling (admitted from home) and 280 nursing home-dwelling (admitted from the nursing home) patients. Nosocomial infections were those acquired > 2 days after admission. Thus, the study allowed the authors to evaluate *Acinetobacter* prevalence in patients who acquired their infection in the hospital, in the community, or in a nursing home. More than half of cultures were from respiratory secretions (56%), but others came from wounds (22%), urine (12%), blood or catheter tip (10%), and stool (0.3%). These sources immediately bring up a potential problem, since *Acinetobacter* is certainly not a pathogen in stool. This is particularly bothersome with regard to sputum, where the organism is more often a colonizer than a pathogen. The publication reveals no information on laboratory protocols for determining significance of organisms and determining the extent of further workup, such as screening Gram stains of respiratory samples, a long-time proven method used to direct the culture processing of such samples.[8] The authors acknowledge that colonization was not differentiated from infection.

Given that caveat, the findings about the organisms themselves are certainly valid. From a relatively low number during 2003-2006, but dramatically exploding in 2007, the percentage of strains resistant to imipenem and/or ampicillin/sulbactam rose from < 5% to > 30%, and the percentage of strains considered pan-resistant (resistant to all eight antibiotic classes tested: ampicillin/sulbactam, aztreonam, cephalosporins, aminoglycosides, quinolones, carbapenems, tetracycline, and trimethoprim/sulfamethoxazole) rose from < 3% to a high of > 20%. The relative percentages of pan-resistant *Acinetobacter* isolates recovered from patients whose infection was acquired nosocomially (defined as infections acquired by any patient after day-two post-admission) and from patients admitted from nursing homes whose infection manifested within the first two days of admission (nursing home-dwelling) also rose steadily after 2005. In contrast, non-nosocomial isolates from community-dwelling patients showed relatively stable levels of pan resistance over the last three years of the study.

Even the overall numbers of *Acinetobacter* isolates increased from 189 in 2003 to 329 in 2007, and to 214 in 2008, a 25% increase among this older adult patient cohort ($p < 0.001$). And regardless of their previous habitat, patients with *Acinetobacter* infections had high rates of adverse outcomes. Only 25% of previously community-dwelling patients were released to home, with 31% being released to hospice care or were dying. Another 27% were released to acute-care, long-term care facilities. Fifty percent of previously nursing home-dwelling patients were released back to the home; 20% were transferred to other acute-care facilities, and 30% were referred to hospice or died. The authors found a direct correlation between increasing antibiotic resistance and adverse out-

come, although they noted that they could not establish causation. Of note, half of community-dwelling patients whose infection was caused by a pan-resistant strain expired; another third went to long-term acute-care facilities, and only 6 of 45 patients were discharged to home. Patients discharged to nursing homes hosted strains of increasing resistance over the study period.

■ **COMMMENTARY**

One message to take away from this large study is that both hospitals and long-term care facilities (nursing homes) are likely feeding resistant *Acinetobacter* to each other, which calls for a regionwide or systemwide strategy for reducing the spread of these strains. As has been witnessed with many other pathogens, failure to take measures early allows widespread dissemination of resistance factors. It may already be too late to prevent this under-rated pathogen from becoming the next MRSA or *Clostridium difficile*. And it may be stating the obvious to remind ourselves that while at least a few new antimicrobials are being developed for MRSA and *C. difficile, Acinetobacter* has yet to reach the "status" of meriting its very own antibiotic. ■

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Genome Determinants of HIV-1 Set Point in African-Americans

ABSTRACT & COMMENTARY

By Joseph F. John, Jr., MD

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

Sources: Pelak K, et al. Host determinants of HIV-1 control in African Americans. *J Infect Dis*. 2010;201:1141-1149; Motsinger-Reif AA. Discussion of a genome-wide association approach to determine HIV-1 set point in African Americans. *J Infect Dis*. 2010;201:1118-1120.

Healthcare providers have been constantly amazed at the variation in response to infection with HIV-1. In our clinic, we now routinely see elderly patients who have been on various antiretroviral regimens over the years but still persist with high CD4 counts and low viral loads. They are truly long-term non-progressors. Work with whole human genome analysis to discover host determinants of HIV-1 control has gained steam in the middle of this current decade, and is continuing. The current study from the Center for Human Genome Variation at Duke and several government agencies is part of a DoD HIV NHS natural history study started in 1985 (http://www.idcrp.org/hiv-natural-history-study.htm). The patients in this study continue to be seen every six months. Other cohorts like the MACS cohort are also included in the study. Using the HumanHap 1MDuo or Illumina HumanHap Bead Chips, 1,212,217 SNPs were analyzed. Complex statistical methods termed EIGENSTRAT were used to analyze the genetics of the human populations.

Study patients were from the U.S. Department of Defense Human Immunodeficiency Virus Natural History Study (DoD HIV NHS) or the Multicenter AIDS Cohort Study (MACS). Of 487 soldiers meeting criteria, 471 were successfully genotyped; 145 participants from the MACS cohort were also studied. No single, genome-wide SNP had an association with the set point, he viral load of which patients more or less stabilize after the burst of viral replication during primary infection. The most associated SNP in the African-American cohort was rs2523608, which is located on chromosome 6, in *HLA-*

B gene, HLA-B*5703. Note the same association is true for set-point regulation in patients of European ancestry. This allele, therefore, is the most important variant for the entire group in this study as the genetic locus that would affect viral load set point and could account for about 10% of the variation in viral load set point. Likewise, 10% of the patients in these studies progressed during the course of the studies to $CD4^+$ cell counts of < 200/mL within two years of seroconversion.

Other SNPs reported to have an association with viral-load set points were analyzed. For example, rs9261174, located near the ZNRD1 gene in MHC region, and CCR5-Δ32, a deletion in the *CCR5* gene (rs33) that is rare in non-Europeans, showed no association in this African-American cohort with viral-load set point. So, mutations in alleles that are considered "rare variants," as shown from this study, may have significant effects on an increased burden of disease in some populations.

■ **COMMENTARY**

This magnificent work aimed to define genome-wide variables that explain HIV progression has been made possible over many years, involving many willing and highly cooperative patients, and spending millions of dollars. We see how the genie of the genome can now open many secrets about HIV progression. In this study, it was surprising how few genetic variables were uncovered related to progression; in fact, it seems a rather obscure locus within HLA-B*5703. Nevertheless, there will be other regions recognized in the future. Our challenge will remain to find ways to exploit, in the future, the locus under question (and newer loci), and mechanisms that would silence or alter these alleles to allow better immune modulation of HIV infection.

There will be surprises along the way, like the one in the present study. A surprise, indeed, that the only uncovered genetic locus that affects viral-load variation in 515 African-Americans was the same one that is known to affect HIV+ patients of European ancestry. Along with the findings of genetic overlap among so-called races come implications that small segments of shared DNA among HIV-infected patients, regardless of racial background, are new targets for antiretroviral therapy or genetic immunomodulation. In an accompanying editorial, Dr. Allison Motsinger-Reif beautifully discusses the study that she thinks offers a "unique resource to study an important, understudied population — patients of African descent." She also makes a good point that using gene chips that are very generic will not uncover rare alleles.

Finally, Dr. Motsinger-Reif comments, and I would agree, that the ultimate regulation of viral load involves complex phenotypes. Clinicians would do well (and I keep telling myself!) to bone up on the evolving field of human genomics. Studies like this one, by Pelak et al, remind us that the field is evolving at warp speed. ■

Bacterial Enteritis and Childhood Intussusception

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD, FAAP

Professor of Pediatrics, Tufts University School of Medicine, and Chief Academic Officer, Baystate Medical Center, Springfield, MA

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

Synopsis: *Bacterial enteritis in children significantly increased the risk for intussusception, with a relative risk of 40.6 (95% CI = 28.6-57.5; p < 0.0001).*

Source: Nyland CM, Denson LA, Noel JM. Bacterial enteritis as a risk factor for childhood intussusception: A retrospective cohort study. *J Pediatr.* 2010;156:761-765.

A RETROSPECTIVE COHORT STUDY WAS CONDUCTED OF ALL children age birth to five years enrolled at a Department of Defense treatment facility between January 1998 and December 2005, who were diagnosed with bacterial enteritis. Their medical records were reviewed for the ensuing six months for a diagnosis code (DRG code 560.0) or procedure code consistent with intussusception.

A total of 387,514 children were enrolled in a treatment facility, yielding a total of 293 cases of intussusception and an incidence of 15.1 cases/10,000 children/year. Of the 1,412 cases of bacterial enteritis, intussusception ensued in 37 cases (13 in females and 24 in males), representing 12.6% of all cases of intussusception. The overall relative risk for intussusception in the six months following bacterial enteritis was 40.6 (95% CI = 28.6-57.5; $p < 0.0001$). The relative risk was greater in children 1-5 years of age (56.2 [95% CI = 36.0-87.8]) compared to children < 1 year of age (16.0 [95% CI = 9.1-28.2]). The absolute risk for intussusception following enteritis was 2.3% for children < 1 year of age and 3.3% for children 1-5 years of age.

The relative risk of intussusception was increased for all four major causes of bacterial enteritis: *Salmonella* (16 cases; 28.7 [95% CI = 7.2-113.4]); *Escherichia coli,* including enteropathogenic, enterotoxigenic, enteroinvasive, and enterohemorrhagic (13 cases; 25.0 [95% CI = 5.62-111.6]); *Shigella,* including *S. dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei* (six cases; 23.6 [95% CI = 3.6-156.0]); and *Campylobacter* (two cases; 32.9 [95% CI = 3.48-310.7]). No cases of intussusception followed *Yersinia enterocolitica* enteritis, likely resulting from the

low rate (1%) of *Yersinia* enteritis among this cohort.

The median interval between the episode of enteritis and development of intussusception was 58 days, with a range from 1 to 175 days. Using negative binomial regression for 30-day time periods while controlling for age, the relative risk for intussusception after bacterial enteritis was significantly increased for the first 30-day period (9.5 [95% CI = 2.5-35.8]; $p < 0.0009$). After the first 30 days, the risk decreased and did not reach significance, with the exception of the interval of 120-150 days.

■ COMMENTARY

Many studies have suggested an association between enteritis and intussusception, which is the prolapse of one part of the intestine into the lumen of an adjoining part, most frequently ileocolic. Lymphoid hyperplasia, or hypertrophy of Peyer's patches, is a common finding in intussusception that is felt to predispose to intussusception by serving as a mechanical lead point.

This retrospective study, using a large population cohort, showed a statistically significant increased risk of intussusception among children with bacterial enteritis within the previous six months. These results show the highest risk of intussusception in the first 30 days after enteritis, followed by a lower but continued risk through the subsequent six months. Physicians and parents should appreciate the increased risk, and should facilitate earlier recognition and prompt treatment of intussusception following bacterial enteritis. This study did not address the potential impact of antibiotic treatment on the risk for intussusception, which might be favorable. ■

Diagnostic Accuracy of Clinical Signs and Symptoms for Serious Bacterial Infection in Young Febrile Children

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD, FAAP

Synopsis: *Serious bacterial infections occur in about 7% of febrile children younger than five years of age presenting to the emergency department, and pose substantial diagnostic difficulties. In this study, antibiotics were prescribed acutely in only 66%-81% of cases of serious bacterial infections.*

Source: Craig JC, et al. The accuracy of clinical symptoms and signs for the diagnosis of serious bacterial infection in young febrile children: Prospective cohort study of 15,781 febrile illnesses. *BMJ.* 2010;340:c1594.

A TWO-YEAR PROSPECTIVE COHORT STUDY OF CHILDREN LESS than five years of age presenting with a febrile illness (≥ 38.0º C) to a single emergency department in Australia, used a standardized clinical evaluation with a mandatory entry for 40 clinical features between July 1, 2004, and June 30, 2006. Greater than 94% of the children with serious bacterial infections (defined as urinary tract infection, pneumonia, or bacteremia) had the appropriate tests (urine culture, chest radiograph, and blood culture). Follow-up data were available for 93% of the 15,781 cases of febrile illnesses.

Most febrile illnesses occurred in children under three years of age, with the peak between 1 and 2 years of age. There were 543 cases (3.4%) of urinary tract infection, 533 cases (3.4%) of pneumonia, and 64 cases (0.4%) of bacteremia, with a combined prevalence of 7.2%. Antibiotics were prescribed acutely in 66% (359/543) of children with urinary tract infection, 69% (366/533) with pneumonia, and 81% (52/64) with bacteremia. However, 20% (2686/13,557) of children without a serious bacterial infection were also prescribed antibiotics. Comparing data from the clinical evaluations with the confirmed diagnosis, physicians' clinical diagnosis of urinary tract infection, pneumonia, or bacteremia had low sensitivity (10%-50%) and high specificity (90%-100%).

The variable that was most predictive for presence of any serious bacterial infection was "appearing generally unwell," followed by increased temperature, no fluid intake in the previous 24 hours, increased capillary refill time, and pre-existing chronic disease. The presence of localizing symptoms and signs was significant for pneumonia and urinary tract infection but not for bacteremia.

■ COMMENTARY

Healthy children less than five years of age typically have 5-8 acute upper respiratory tract infections, 0-1 cases of acute otitis media, and 0-2 cases of enteritis each year. In most cases, these febrile illnesses are self-limited, presumably viral infections. It is often very difficult to clinically distinguish the non-serious viral infections from serious bacterial infections that require early antibiotic therapy. This is underscored in this study by the acute treatment of serious bacterial infections with antibiotics in only 66%-81%. This is not because the diagnoses are not considered (94% of the children in this study had the appropriate diagnostics tests) but because of the absence of objective information that identifies serious bacterial infection early, often with fever being the only finding. Difficulty interpreting and suboptimal sensitivity and

specificity of the urinalysis for urinary tract infection and chest radiograph for pneumonia further complicate early recognition. Physicians may underestimate the risk of infection in an individual patient because it is relatively low (7.2% in this study). Management of serious bacterial infection in this age group is also confounded because many of these serious bacterial infections can resolve without antibiotic treatment, such as occult bacteremia that occurs in children less than three years of age, which may give some providers a false sense of security.

The clinical variable with the strongest diagnostic significance for all serious bacterial infections was "appearing generally unwell." This is consistent with many other studies, and underlies the "art" of pediatrics in managing these children. The clinical features demonstrated in this study to be sensitive and specific for diagnosis of serious bacterial infections include the overall appearance of the child, urinary symptoms for urinary tract infection, and cough for pneumonia. ■

Anthrax in Heroin Users

SPECIAL FEATURE

By Stan Deresinski, MD, FACP

A CRITICALLY ILL PATIENT, WHO WAS A HEROIN USER, WAS admitted to a hospital in Scotland in December 2009 and was found to be infected with *Bacillus anthracis*.[1] He was not the last such patient and, as of June 11, 2010, Scottish health authorities had identified 45 confirmed cases of anthrax in heroin users; 13 of these cases were fatal. Cases were also identified in England and Germany.

Most of the affected cases injected their heroin, either intravenously, subcutaneously, or into muscle, but some also smoked or snorted it. Of the patients described to date, none have presented with classical presentations of anthrax cutaneous infection with a painless black eschar, inhalational disease with hemorrhagic mediastinal lymphadenopathy, or typical gastrointestinal disease.[2] Rather than the expected cutaneous ulcer, skin and soft-tissue infections in this outbreak have, instead, been quite variable in appearance, with the exception of the apparently universal presence of marked edema that appears to be in excess of the degree of induration. The induration, as well as any associated erythema is, in fact, often minimal. Systemic symptoms are variable and depend upon the stage of disease, but many patients have a normal temperature at presentation. Also commonly normal are the white blood cell count, CRP, and serum lactate concentration. In some patients, the illness has been biphasic, with an initial response to therapy, especially fluid infusion, followed by rapid deterioration with hypotension, third-spacing, and coagulopathy.

While classical inhalational anthrax has not been observed, pleural effusions are common. At presentation, some patients have abdominal symptoms, including nausea, vomiting, and abdominal pain, but the gastrointestinal mucosal ulcerations and associated hemorrhagic lymphadenopathy have not been seen. Ascites may occur. Some patients, not all of whom had evident soft tissue infection, presented with meningoencephalitis, with evidence of intracranial bleeding with features of a subarachnoid hemorrhage — a syndrome which has been universally fatal.

Management involves infusion of large volumes of fluid, antibiotics, and surgical debridement. The Health Protection Agency of Scotland recommends administration of ciprofloxacin together with an antibiotic with "CNS penetration," such as penicillin, ampicillin, meropenem, rifampin, or vancomycin, together with clindamycin, with the hope of reducing toxin production. The Scottish authorities recommend excision of affected skin with a margin greater than 2 cm, excision of needle tracks within muscle, and decompression in the presence of compartment syndrome. Debridement, which may have to be repeated one or more times, is complicated by the fact that, in contrast to findings in necrotizing fasciitis, the margins between normal and affected tissue may be indistinguishable. They state that pleural and ascitic fluid should be drained because it contains toxin. In addition to these measures, the Scottish authorities also recommend consideration of the use of Anthrax Immune Globulin Intravenous, an investigational preparation derived from vaccinated human volunteers that was made available to them by agreement with the U.S. CDC and FDA.

B. anthracis is widely distributed in soil, with appropriate physicochemical characteristics in which it can survive in spore form for decades. It is overwhelmingly likely, albeit unproven, that heroin contaminated by anthrax was the source of infection of these unfortunate patients. Contaminated heroin also has been the source of infection or intoxications by other spore-forming organisms in injection-drug users. There was, for example, a marked increase in such illnesses in the United Kingdom from 2000 to May 2004, during which the following were etiologic: *Clostridium novyi* (68 cases), *Clostridium histolyticum* (9), *Clostridium sordelli* (1), *Bacillus cereus* (1), together with 20 cases of tetanus and 57 of wound botulism.[3] ■

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Early vs. Delayed Initiation of HAART in Patients with Cryptococcal Meningitis

ABSTRACT & COMMENTARY

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Synopsis: *Fifty-four antiretroviral-naïve HIV-infected patients with first-episode cryptococcal meningitis (CM) were randomized to early (within 72 hours) vs. delayed (10 weeks) antiretroviral therapy (ART) following diagnosis and initiation of treatment for cryptococcosis. Three-year mortality was 88% in the early ART vs. 54% in the delayed ART groups.*

Source: Makadzange AT, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-Saharan Africa. *Clin Infect Dis*. 2010; 50:1532-1538.

This prospective, open-label, randomized clinical trial was conducted at a large tertiary teaching hospital in Harare, Zimbabwe, in adult ART-naïve HIV-infected patients who received a first CM diagnosis. Patients were randomized to early ART (within 72 hours of CM diagnosis and initiation of antifungal therapy) vs. delayed ART (after 10 weeks of antifungal treatment). Antifungal therapy was fluconazole dosed at 800 mg daily, and the ART regimen was d4T, 3TC, and nevirapine (NVP). Patients were followed for three years. Twenty-eight patients were enrolled in the early ART arm and 26 in the delayed ART arm. The overall mortality at three years was 88% in the early vs. 54% in the delayed ART arms ($p < .006$). Median duration of survival was 28 days in the early vs. 637 days in the delayed treatment arms (adjusted hazard ratio 2.85). The study was terminated early by the data safety monitoring committee.

■ **COMMENTARY**

This is an interesting study. While it suggests that caution be exercised in early initiation of ART in the setting of CM, the conclusions of the study may not be directly applicable to the management of CM in the developed world. Some of the limitations of this study include: 1) small sample size; 2) extremely early initiation of ART (72 hours vs. the more usual 1-2 weeks considered "early" in the United States); 3) use of fluconazole monotherapy rather than combination amphotericin B + 5-FC (as used for the initial two weeks of treatment in the United States); and 4) likely poor control of increased intracranial pressure in most of the patients.

It is of note that patients in this study were generally discharged from the hospital within seven days, and median follow-up time was only 27 days. Mortality typically occurred early, with most deaths occurring in both the early and delayed ART groups less than two weeks after enrollment. Causes of deaths were generally not known with certainty; autopsies were seldom performed. However, the authors speculate that immune reconstitution inflammatory syndrome (IRIS) may have been the most common cause of death in the early ART group.

I believe that the jury is still out on whether early institution of ART in the setting of CM is a bad idea in the developed world where increased intracranial pressure can be adequately managed. A similar prospective, randomized trial of early vs. delayed ART in patients with CM should be conducted in the developed world. My own anecdotal experience in managing about a dozen patients over the last seven years with CM in the setting of AIDS, in all of whom I started ARVs within 2-3 weeks of initiating antifungal therapy, has been positive. However, I treated all of these patients with two weeks of initial amphotericin B + 5-FC. In the two patients who did develop increased intracranial pressure (likely related to IRIS), I was able to manage this complication fairly easily with frequent LPs and short courses of glucocorticoids. ■

Cytokine Signaling and Susceptibility to Infectious Diseases

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Synopsis: *In a case-control study, an association between several cytokine-inducible SRC homology 2 (CISH) polymorphisms and susceptibility to bacteremia, severe*

malaria, and tuberculosis was observed. The overall risk of one of these infectious diseases was increased by > 18% among persons carrying CISH alleles.

Source: Khor CC, et al. CISH and susceptibility to infectious diseases. *N Engl J Med*. 2010;362:2092-2101.

In this study, 8,402 patients from seven case-control series were examined in this trial. The series included Kenyan children with bacteremia, patients with tuberculosis (TB) in Malawi, Hong Kong, and Gambia, and patients with severe malaria in Gambia, Kenya, and Vietnam. Standard methods for genotyping selected genes in PBMCs were employed. Gene expression following IL-2 and IL-3 stimulation was also done with extracted RNA, then quantified using real-time PCR of complementary DNA. Five single nucleotide polymorphisms (SNPs) were identified within the CISH-associated locus, which, considered together in a multiple-SNP score, were highly associated (p = 3.8x10 e-11) with susceptibility to bacteremia, severe malaria, and TB. The SNP at -292 accounted for most of the association (p = 4.58x10e-7). PBMC stimulation of cells containing the -292 SNP, as compared to wild type cells, showed a muted response to IL-2, with 25%-40% less CISH expression.

■ COMMENTARY

The complex and overlapping components of the human immune system (encompassing humoral and cellular immunity, cytokines and chemokines, the complement system, and the innate immune system) generally functions as a beautiful machine, protecting our bodies from most pathogens. While individual pathogens are relatively easily shown to vary in degree of pathogenicity (and pathogenic factors identified), differences in individual response of the host to specific pathogens are much more difficult to tease out.

The IL-2-mediated immune response is critical for host defense against many infectious agents. CISH domain protein is a suppressor of cytokine signaling (SOCS), and specifically controls IL-2 signaling. CISH is encoded on chromosome 3. Khor et al have taken advantage of the huge dataset (8402 patients) available from seven case-control studies of three diseases of huge global health importance.

While far from the definitive word on host factors affecting clinical outcome in bacteremia, severe malaria, and TB, this large, strongly powered study sheds some light on at least one plausible mechanism responsible for adverse outcomes of these three diseases in at least some patients. One of the paradoxes of the human immune response to many pathogens is the fine line that the host must walk in promptly recognizing and controlling infectious diseases vs. an overly vigorous immune response, which can lead to more severe illness and death.

In the conclusion of the paper, the authors speculate that pharmacologic manipulation of the SOCS pathway may have an effect on the treatment of multiple diverse infectious diseases. While only a few pharmacologic interventions targeting the host in the setting of infection have actually panned out, (and I am generally skeptical of targeting the host rather than the pathogen), the study represents some good basic science and sheds light on one mechanism contributing to adverse outcomes in a broad spectrum of infectious diseases. ■

CME Questions

1. Which of the following is correct?

a. *Acinetobacter lwoffii* is the most frequently isolated member of its genus in the United States.

b. *Acinetobacter* is a common gastrointestinal pathogen.

c. *Acinetobacter* is invariably susceptible to carbapenem antibiotics.

d. The incidence of multidrug-resistant *Acinetobacte*r infections is increasing in the United States.

2. Which of the following is correct with regard to travelers returning from South Africa who presented to a Geosentinel site?

a. The predominant cause of systemic febrile illness is due to a spotted fever group rickettsia.

b. Malaria is most commonly acquired during the winter months of June-August.

c. Acute diarrhea was the most common reason for seeking care.

d. Dermatologic problems were the third most frequent reason for seeking care.

3. Which of the following causes of enteritis has NOT been shown to be associated with an increased risk of subsequent childhood intussesception?

a. Salmonella

b. Shigella

c. Campylobacter

d. Yersinia

Answers: 1. (d); 2. (a); 3. (d)

CME Objectives

Upon completion of this educational activity, participants should be able to:

• discuss the diagnosis and treatment of infectious diseases;

• explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;

• discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and

• discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies. ■

In Future Issues:

Colistin Dosing in Renally Impaired Patients

UPDATES

By Carol Kemper, MD, FACP

Pat the Bunny (Don't Kiss It)

Source: Kawashima S, et al. *J neurol*. 2010;257:654-664.

THE AUTHORS DESCRIBE A PREVIOUSLY healthy 44-year-old woman who presented with bacterial meningitis. On presentation, she was alert but complained of high fever and meningismus. She had no other neurologic symptoms. Lumbar puncture showed 2,880 white blood cells per microliter, an elevated protein of 156 mg/dL, and a reduced glucose of 51 mg/dL. A Gram stain revealed gram-negative rods; she was treated with empiric vancomycin and meropenem. Blood and cerebrospinal fluid cultures grew *Pasteurella multocida*.

Further questioning revealed she not only kissed her dog's face — she fed it mouth-to-mouth. She described no scratches or bites and no other animal contact.

P. multocida is a gram-negative coccobacillus that is commonly present in the nasopharynx and gastrointestinal tract in animals, and a normal part of the oral mouth flora of dogs and cats (up to 75%). It is generally susceptible to penicillins, although cases of penicillin resistance have been described. Cellulitis and bacteremia may occur from infection with *P. multocida*, generally as the result of bites or scratches, but meningitis is rare. The presentation is similar to other common bacterial meningitides, and about 17%-22% have neurologic symptoms. The authors found three other cases in the literature of *P. multocida* meningitis as a result of mouth kissing of a pet cat, dog, or bunny. The authors cautioned that *P. multocida* should be considered in animal lovers, and people should refrain from close oral contact with their pets. I wonder, I mean really, how many women don't kiss their cats?

Airborne *C. difficile*?

Sources: Best EL, et al. The potential for airborne dispersal of *Clostridium difficile* from symptomatic patients. *Clin Infect Dis*. 2010; 50:1450-1457; Donskey CJ. Preventing transmission of *Clostridium difficile*: Is the answer blowing in the wind? *Clin Infect Dis*. 2010; 50:1458-1461.

NOT ONLY IS *C. DIFFICILE* IN THE HOSpital tough to eradicate despite enhanced infection-control measures and extensive cleaning and bleaching of rooms, but it often seems to come from nowhere. To test the theory that airborne transmission of *C. difficile* spores may occur, the authors sampled the air space around patients with symptomatic CDI. The first phase of the project sampled the air space of 50 patients being treated for confirmed CDI for one hour intermittently over several days (total 50 hours). Six (12%) of the samples were positive. A trend was observed toward more positive samples in patients with more active diarrheal symptoms than those without.

The period of air sampling was subsequently extended to 10 hours over two days (total 130 hours) in 10 patients with suspected CDI, pending laboratory confirmation, and those with symptomatic confirmed CDI. Environmental samples were also collected for comparison of isolates by DNA fingerprinting. Of those with suspected infection, three were confirmed by the laboratory based on cytotoxic studies; the other seven patients were considered "controls." Of the three CDI-positive patients, one had positive air samples on three different days (associated with various activities such as changing the bed, closing the curtain, and room cleaning). Two control subjects (diarrheal) with negative air samples for *C. difficile* had positive environmental samples (from the commode, sink, floor, bed, and bedside table), suggesting they may have been colonized with the organism.

When the duration of the air space sampling of 10 symptomatic patients with confirmed CDI was extended to 10 hours over several days, seven (70%) had positive air samples, four of whom had multiple positive samples intermittently over several days. Positive samples generally occurred during periods of activity around the patient, such as serving drinks or lunch, visiting hours, ward rounds, or bed changes.

Ten percent of environmental isolates from these patients were also positive, similar to the results of another recent study for symptomatic patients receiving treatment. In all, six of the 10 patients with confirmed CDI had positive air space and environmental samples. DNA fingerprinting confirmed the organisms from the airspace and those from the environmental were similar for an individual patient in three cases, suggesting an epidemiological link.

Current hospital infection-control measures (e.g., contact precautions) for *C. difficile* would not protect against airborne transmission of the organism. This study demonstrated that airborne transmission not only occurs, but occurs with surprising frequency (in up to 70% of symptomatic patients with C difficile infection [CDI]). This likely contributes to environmental colonization, especially during periods of activity in the room, such as bed changes. Dispersal of spores via the air may explain the fre-

quent colonization/exposure of healthcare workers, despite good handwashing and contact precautions, or the frequent gastrointestinal colonization of long-term care facility residents. Furthermore, *C. difficile* was found in the airspace of 30% of patients with diarrhea without laboratory-confirmed CDI, suggesting that even those patients with gastrointestinal colonization with diarrhea for other reasons (e.g., antibiotic-associated diarrhea) may contribute to environmental contamination.

Hospitals must consider these findings as they strive to beef up infection-control and environmental measures to combat the increasing presence of CDI in hospitals. Whether a HEPA filter or air exchanger would be beneficial in reducing environmental contamination was not addressed by this study. The accompanying editorial suggests that restricting patients with recognized CDI to a private room, daily room cleaning, and continuing contact precautions throughout the hospital stay may all be necessary but not sufficient to prevent environmental spread.

Travel Recommendations for the World Cup

Source: Blumberg LH, et al. The 2010 FIFA World Cup: Communicable disease risks and advice for visitors to South Africa. *J Travel Med*. 2010;17:150-152.

It is anticipated that more than 350,000 people will attend the World Cup games in South Africa, in June and July this year. Given the crowd conditions and mass gathering of people from all over the globe, there is a greater potential for outbreaks of communicable diseases, especially respiratory infections. The following is a list of precautionary measures recommended for 2010 World Cup travelers:

• Influenza vaccine is recommended for all travelers and team participants. During the 2009 South African influenza season, Influenza A H1N1 replaced the previous H3N2 strain. The risk of influenza transmission during the World Cup may be high.

• The Gauteng Province has been experiencing a measles outbreak since 2009, which has affected neighboring regions. In anticipation of an influx of large numbers of people, a mass measles campaign was planned for the country in April 2010. Pre-travel measles immunization is recommended for any non-immune persons.

• Consideration should be given to pre-exposure vaccination for meningococcal infection. Although the risk is considered low, a modest seasonal increase in meningococcal infections occurs in South African between May and October, and the crowd conditions may increase the risk for exposure. The dominant serotype in South Africa is W135.

• No case of wild-type polio has been reported in South Africa since 1989. However, polio boosters are recommended for persons traveling to South African from polio-endemic countries such as Nigeria, Pakistan, Afghanistan, and India, or for persons less than 15 years of age traveling from countries where polio has occurred.

• Since the stadia for the World Cup are outside malaria risk areas, the risk for malaria should be low and malaria chemoprophylaxis is not necessary for World Cup participants or observers; however, chemoprophylaxis is recommended for visitors who travel to Kruger National Park or other neighboring countries, such as Zambia, Mozambique, or Zimbabwe, along with the usual clothing and mosquito repellent precautions.

• While chemoprophylaxis is not necessary, South Africa is considered endemic for rabies, generally from contact with dogs. Persons with dog bites, or contact with other animals suspicious for rabies, should take appropriate steps.

• Finally, travelers to South Africa should be counseled regarding appropriate STD precautions. Travel sex is often a big part of travel for these kinds of events, and an increased demand for sexual services was seen at the 2000 Sydney Olympic Games. Approximately 29% of South African woman ages 15 to 49 years old are HIV+. Safe sex and use of condoms is essential.

HIV+ Patients Living Longer

Source: Van Sighem A, et al. Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. *AIDS*. 2010, May 12. (epub ahead of print).

Based on data derived from the ATHENA national observational HIV cohort in the Netherlands, these authors compared the life expectancy of 4,612 HIV+ individuals with age- and gender-matched uninfected controls. The patients presented for care between 1998 and 2007, and remained antiretroviral treatment-naïve for at least 24 weeks after diagnosis. Of these, 4,174 (90.5%) did not experience a CDC-B or –C event during those 24 weeks after diagnosis. For these individuals, a multivariate hazards model demonstrated that the median number of years lived from age 25 was 52.7 for HIV+ men and 57.8 years for HIV+ women. In other words, newly diagnosed HIV+ persons who did not experience a CDC-B or –C event within the first 24 weeks of presentation are expected to live nearly as long as their uninfected age-matched controls. For persons presenting at the age of 25, the number of life-years lost in the model was 0.4, and for persons diagnosed at age 55, about 1.4. The life-years lost for persons who experience a CDC-B event within 24 weeks of presentation were estimated to be 1.8 to 8 years. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

PPIs, *Clostridium difficile*, and Bone Fractures

In this issue: *New reports about proton pump inhibitors and the effects of gastric suppression, pioglitazone vs vitamin E for non-alcoholic steatohepatitis, metformin and vitamin B12 deficiency, and FDA Actions.*

PPIs, C. difficile, and bone fractures

Since H2 antagonists were introduced 30 years ago followed by proton pump inhibitors (PPIs) 20 years ago, there has been speculation whether long-term gastric acid suppression might have adverse effects. Billions of doses later, there is new evidence that chronic PPI use may lead to infections, especially *Clostridium difficile* infection (CDI), and may also contribute to bone fractures.

In the first of several studies published in the May 10 issue of *Archives of Internal Medicine*, researchers looked at more than 101,796 discharges from a tertiary care medical center during a five-year period, reviewing the level of acid suppression therapy and its relationship to CDI. As the level of acid suppression increased, the risk of CDI increased from 0.3% in patients not receiving acid suppressive therapy to 0.6% in those receiving H2 antagonists to 0.9% in those receiving daily PPIs and finally 1.4% in those receiving high-dose PPI therapy. After adjustment for a number of factors including comorbid conditions, age, and antibiotic use, the odds ratio for CDI infections were: 1 with no acid suppressing treatment, 1.53 (95% confidence interval [CI], 1.12-2.10) with H2 antagonist, 1.74 (95% CI, 1.39-2.13) with PPIs, and 2.36 (95% CI, 1.12-2.10) with high-dose PPI therapy. The authors conclude that increasing levels of pharmacologic acid suppression are associated with increased risk of nosocomial *C. difficile* infections, and the risk increases with more aggressive acid suppression (*Arch Intern Med* 2010;170: 784-790).

In a second study from the same journal, researchers from the VA system in Massachusetts performed a retrospective, cohort study of 1166 inpatients and outpatients with CDI to determine if PPI use affected recurrence rates. During treatment for CDI, 45% of patients received a PPI while 55% did not. Recurrent CDI was more common in those exposed to PPIs than in those not exposed (25.2% vs 18.2%). The hazard ratio for recurrent CDI in those exposed to PPIs was 1.42 (95% CI, 1.11-1.82). The risk was higher in patients older than 80 years and in patients exposed to antibiotics not targeted to CDI infections The authors conclude that PPI use during treatment for CDI was associated with a 42% increased risk of recurrence (*Arch Intern Med* 2010;170:772-778).

It has also been postulated that suppressing gastric acid may affect digestion and absorption of certain nutrients, specifically calcium. Although this has never been definitively proven, multiple studies have shown that chronic PPI use is associated with bone fractures. The most recent study, also published in the May 10 issue of *Archives of Internal Medicine*, was a prospective analysis of more than 160,000 women enrolled in the

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Women's Health Initiative study. In more than 1 million person-years of follow-up, there were 1500 hip fractures, 4881 forearm or wrist fractures, 2315 clinical spine fractures, and more than 21,000 total fractures. The multivariate-adjusted hazard ratios for current PPI use was 1 for hip fracture, 1.47 (95% CI, 1.18-1.82) for clinical spine fracture, 1.26 (95% CI, 1.05-1.51) for forearm or wrist fractures, and 1.25 (95% CI, 1.15-1.36) for total fractures. Bone mineral density did not vary between PPI users and non-users. The authors conclude that use of PPIs in women was not associated with hip fractures but was modestly associated with clinical spine, forearm or wrist, and total fractures (*Arch Intern Med* 2010;170:765-771). This study confirms the findings of several large epidemiological studies that suggest that PPI use is associated with increased osteoporotic fracture risk. On May 25, the FDA issued a warning regarding the possible fracture risk associated with high-dose long-term use of PPIs. The Agency will require labeling changes to describe the possible risk.

As noted in these studies, PPI use is associated with risk of osteoporotic fractures and *Clostridium difficile* infections. Other studies have linked the PPIs to a higher risk of hospital- and community-acquired pneumonia, as well as enteric infection such as *Salmonella* and *Campylobacter* gastroenteritis. In an editorial in the May 10 issue of *Archives of Internal Medicine*, Mitchell Katz, MD, notes that of the more than 110 million prescriptions for proton pump inhibitors filled each year, many are for inappropriate indications, making PPIs one of the most overprescribed medication classes in the world. He suggests that "for most patients the adverse effects of PPIs outweigh the benefits" and urges physicians to offer other treatments for dyspepsia, prescribe shorter courses, and consider a trial of discontinuing PPIs in patients who are asymptomatic (*Arch Intern Med* 2010;170:747-748). ■

Pioglitazone vs vitamin E for NASH

Non-alcoholic steatohepatitis (NASH) is a common liver disease that is difficult to treat and often progresses to cirrhosis. A new study compares the thiazolidinedione pioglitazone (30 mg daily) to vitamin E (800 IU daily) in a placebo-controlled trial for 96 weeks in 247 nondiabetic NASH patients. The primary outcomes were standardized scores for steatosis, lobar inflammation, hepatocellular ballooning, and fibrosis as determined by liver biopsy. Vitamin E therapy was associated with a significant improvement in non-alcoholic steatohepatitis (43% vs 19%; $P = 0.001$), but pioglitazone did not show statistical improvement (34% vs 19%; $P = 0.04$). Serum transaminases improved with both treatments, and both reduced hepatic steatosis and lobular inflammation, but neither improved fibrosis. Pioglitazone caused significant weight gain compared to vitamin E or placebo. The authors conclude that vitamin E was superior to placebo for the treatment of NASH in adults without diabetes (*N Engl J Med* 2010;362:1675-1685). ■

Metformin and vitamin B12 deficiency

Monitor your patients on metformin for vitamin B12 deficiency. This is the message of a recent study from the Netherlands. The study enrolled 390 patients with type 2 diabetes on insulin and initiated metformin 850 mg three times a day or placebo for an average of 4.3 years. Metformin treatment was associated with a mean decrease in vitamin B12 concentrations of 19% ($P < 0.001$) and an increase in homocysteine concentrations of 5% ($P = 0.091$). Longer-term treatment with metformin was associated with larger declines in vitamin B12 levels. The authors conclude that metformin likely causes malabsorption of vitamin B12 and recommends routine monitoring of vitamin B12 levels in patients who are treated with metformin (*BMJ* 2010;340:c2181). ■

FDA actions

The FDA has approved a new formulation of oxycodone (OxyContin®) that is designed to discourage chewing, crushing, or dissolving the drug. The FDA admits, however, that although the new formulation reduces the risk of snorting or injecting the drug, it can still be abused by simply ingesting larger doses than recommended. Vocal critics have called for oxycodone's withdrawal from the market due to an explosion in abuse of the drug nationwide and calls this new formulation "too little too late."

The FDA has recommended resuming use of Rotarix® rotavirus vaccine and to continue using RotaTeq® rotavirus vaccine. Rotarix was found to have elements of the porcine circovirus 1 (PCV1) in March, which resulted in an advisory to clinicians to stop using the vaccine. Subsequently, DNA from PCV1 and PCV2 was discovered in the RotaTeq vaccine. The FDA now says that there is no evidence that PCV causes illness or infection in humans while the benefits of the vaccine are substantial. ■