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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

New Recommendations for HIV Testing

Detecting HIV early creates opportunity for treatment, reduces transmission risk

By Stan Deresinski, MD, FACP, FIDSA

Dr. Deresinski is Clinical Professor of Medicine, Stanford University, Editor of Infectious Disease Alert.

SOURCE: Centers for Disease Control and Prevention and Association of Public Health Laboratories. Laboratory testing for the diagnosis of HIV infection: updated recommendations. Available at http://www.cdc.gov/hiv/pdf/HIVtestingAlgorithmRecommendation-Final.pdf

Recommendations for testing for HIV infection have continually evolved as the result of improving technology and clinical knowledge. The latest generation assays allow earlier detection of infection and avoid the frequent false-negative and indeterminate results seen with use of Western blot or immunofluorescence assays (IFA) for confirmation in patients with early infection. This is of importance because of the recognition that the risk of transmission is highest during the acute early phase of infection and because treatment is beneficial in all phases of infection, including the early phase. Furthermore, while HIV-2 infection remains rare in the U.S., use of the HIV-1 Western blot misclassifies the majority as HIV-1 infection. Western blot and IFA tests are no longer included in the testing algorithm.

As a consequence of this evolution, CDC and the Association of Public Health Laboratories have provided new recommendations for HIV testing of serum or plasma that supersede previous ones (*See algorithm page 122*). The changes take into full account the sequence of appearance of laboratory markers in the course of HIV-1 infection. Thus, HIV-RNA becomes detectable by nucleic acid amplification tests (NAT) approximately 10 days after infection and increases to very high concentrations. Four to 10 days after viral RNA is detectable, 4th generation immunoassays are able to detect P24 antigen, but this is transient as the result of the appearance of antibody — unless special methods to disrupt antigen-antibody complexes are used. IgM antibody may be detected by 3rd and 4th generation immunoassays 3-5 days

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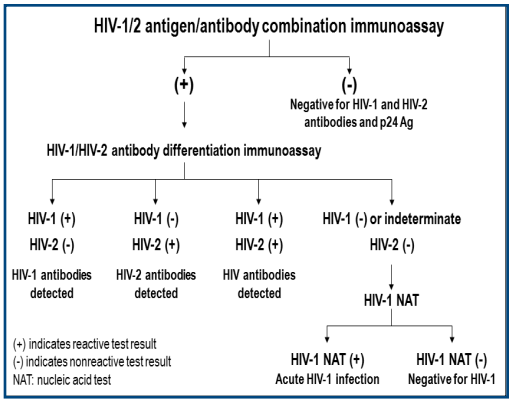

after P24 antigen is first detectable and 10-13 days after the appearance of viral RNA. The sequence can be more broadly considered to consist of an initial eclipse period when no markers are detectable, a seroconversion window between initial infection and first detection of antibodies, acute HIV infection describing the interval between HIV RNA and antibody detectabilities, and established HIV infection beginning with a fully developed IgG antibody response.

Initial testing should be with an FDA-approved antigen/antibody combination (4th generation) immunoassay that detects antibodies to both HIV-1 and HIV-2 as well as HIV-1 p24 antigen. If this test is negative, no further testing is indicated. If the test is reactive, additional testing with an FDA-approved antibody immunoassay that differentiates antibody to HIV-1 and HIV-2 should be performed. If the 4th generation immunoassay is reactive but the antibody differentiation test is negative or indeterminate, an FDA-approved HIV-1 NAT should be performed.

■ COMMENTARY

These recommendations emerge from the continuing advance in the technological and clinical aspects of testing for HIV-1 infection. The elimination of Western blot and IFA testing for confirmation of the presence of specific antibody is important given the subjectivity and both indeterminate falsely negative results seen with these assays. The ability to detect HIV-1 infection in its earliest phase provides the opportunity to initiate treatment which is clinically beneficial to the patient and reduces the risk of transmission during a time when viral loads reach their highest levels in plasma in the absence of therapeutic intervention. ■

ABSTRACT & COMMENTARY

Acute HIV Infection a Common Cause of Fever in Africa

By Dean L. Winslow, MD, FACP, FIDSA

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Dr. Winslow is a consultant for Siemens Diagnostic.

SYNOPSIS: Among 3602 young adults from coastal Kenya, the overall prevalence of HIV-1 infection was 3.9%. Of 241 patients presenting with fever, 4 patients (1.7%) had acute HIV infection (AHI). 1 of 265 (0.4%) of non-febrile patients had AHI. Malaria was confirmed by PCR in 4 (1.7%) of the febrile patients.

SOURCE: Sanders EJ, et al. Acute HIV-1 infection is as common as malaria in young febrile adults seeking care in coastal Kenya. *AIDS* 2014;28:357-63.

Between February and July 2013, 3602 young adults were screened for this study (out of 8013 young adults seeking care). Overall 24.9% of patients met criteria for AHI risk. 3.9% of these patients were found to have previously undiagnosed HIV infection using a combination antibody and p24 antigen assay. (Patients with "prevalent" HIV infection had HIV antibodies present on the initial test. Patients with AHI had initially negative or positive p24 antigen with negative antibodies and

were subsequently found to seroconvert 2-4 weeks following enrollment.) Patients with prevalent HIV infection were more likely to meet AHI risk criteria than seronegative patients (7.6% vs. 2.6%). Patients with fever were more likely to be HIV-infected than those without fever (9.1% vs. 3.3%). Of the 897 patients meeting AHI risk criteria, 375 did not enroll in the study but were more likely to be found to be HIV-infected than patients who enrolled (18.1% vs. 3.1%). Testing and counseling identified 139 patients who were found to have previously-undiagnosed prevalent HIV infection. Of the 506 HIV seronegative or serodiscordant patients enrolled (including 241 with documented fever), AHI was diagnosed in 5. AHI prevalence was 1.7% among patients with fever vs. 0.4% among patients without fever. All 5 patients (4 women and 1 man) had positive p24 antigen and negative rapid HIV-1 antibody tests at initial screening. 4/241 (1.7%) febrile HIV-1 seronegative patients had malaria confirmed by PCR and none were found to have AHI.

■ COMMENTARY

This study rather alarmingly shows that AHI has become as common as malaria as a cause of fever in young adults in Coastal Kenya. While great gains have been made in dissemination of antiretroviral therapy in Africa, transmission of HIV continues at a high rate. Both in the developed world and in the developing world, much HIV transmission is thought to be driven by patients with either early asymptomatic HIV infection or even acute HIV infection. Patients with AHI may be particularly efficient at transmitting HIV to others due to the very high viral loads they typically have (often running in millions of copies/mL in blood and body fluids). Awareness of the common occurrence of AHI in young adults presenting with fever, and incorporating p24 antigen testing (in addition to rapid diagnostic tests for HIV-1 antibodies) should significantly improve the early diagnosis of HIV infection. One other unique aspect of this study is that some of the screening sites were pharmacies, which could potentially initiate antiretroviral therapy at the same visit where the diagnosis of AHI was made. This would likely have the beneficial effects of reducing HIV transmission and potentially would have direct clinical benefit for the patient since some studies suggest that early treatment of AHI may favorably affect immunologic reconstitution and alter "viral set-point." ■

ABSTRACT & COMMENTARY

Mobilizing for Global Health

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: The Baylor College of Medicine International Pediatric AIDS Initiative at Texas Children's Hospital created a global health corps named the Pediatric AIDS Corps in June 2005. Over a period of five years, 128 physicians were employed overseas by the Pediatric AIDS Corps with generally high levels of satisfaction and favorable impact on health. A review of that experience offers insights to guide national and personal involvement in global health activities.

SOURCE: Schultze GE, et al. The Pediatric AIDS Corps: A 5-year evaluation. *Pediatrics* 2014;133:e1548.

From July 2006 through June 2011, the Pediatric AIDS Corps employed 128 physicians to provide care and education directed at improving the treatment of HIV-infected infants and children in under-resourced countries. Using surveys, program leaders then assessed impacts of the program.

Of the 128 physician participants, 111 (88% of the 126 still living at the time of the study) completed follow-up surveys. All respondents were happy with their decision to participate in the program, and all but one would recommend the program to others. The majority (87%) reported that the experience affected their future career choices, with most choosing to remain focused on global health and about half choosing to pursue further training.

Most (73%) survey respondents thought that patient care was the most rewarding aspect of the program. Nonetheless, there were difficulties, including dealing with patient deaths, accepting the limitations of the local health care system, and coping with local managerial decisions. In addition, 41% had problems returning home, with personal issues and job-related difficulty being the most common reasons. However, the feelings about the overseas work and the personal relationships that developed lingered as the "best parts" of participation in the program.

While overseas, 42% reported being victims of crimes. Eleven percent identified depression as a problem while serving abroad, and 2% required international evacuation for stabilization of psychiatric conditions. Latent tuberculosis developed in 7% of participants. Interestingly, only 27% of those for whom malaria prophylaxis was indicated were compliant with their treatment; seven individuals were treated for malaria at least once.

■ COMMENTARY

There are potential implications of this new review of Baylor's experience with the Pediatric AIDS Corps. First, as suggested by the authors, one can consider implementation of a national global health corps program. Second, individuals might choose to personally engage in global health activities.

Increasingly, Americans are following an established European habit of taking a "gap year" between the completion of high school and matriculation into university studies. Favorable benefits of inter-cultural and geographically distant experiences are anticipated as students become better prepared for further studies and career decision-making. Americans have also used the completion of university education as an opportunity to spend time overseas providing tangible service instead of simply soaking in the benefits of travel. Since 1961, Peace Corps has mobilized over 200,000 young Americans to spend two years working in 139 countries of the world. AmeriCorps, begun in 1994, similarly mobilizes college graduates for domestic service, and Teach for America places new teachers in schools in low-income areas.

Increasingly, Americans want to serve. The new generation of freshly trained health care professionals wants to provide valuable benefit to the global community. In 2012, Peace Corps launched the Global Health Service Project to provide adjunct faculty for training centers in other countries; in July 2013, the first cohort of 31 medical and nursing professionals went to serve in Tanzania, Malawi, and Uganda. (http://www.peacecorps.gov/volunteer/globalhealth/?from=hpsl)

Thus, the Baylor experience is instructive. Through one institution, 128 physicians were mobilized to serve HIV-infected patients in Africa and Asia. As with "gap years" for younger students, the experience was viewed favorably and impacted subsequent career decisions. As with Peace Corps, significant work was done to the benefit of local populations. Other academic institutions and non-governmental groups employ smaller numbers of physicians spending one to two years overseas, and faith-based groups place many professionals in short- and long-term service locations. What if a national group organized two-year post-training international experiences for physicians? It is anticipated that benefits to self and others would be accrued, and a larger national organization would be able to offer such opportunities to far more individuals than have been able to participate with the Baylor program. Whether the educationally-focused Global Health Service Project grows to fulfill this opportunity or whether other clinically-oriented organizations rise to the challenge, there is good opportunity to mobilize American health care workers for global service.

Of course, potentially starting a new national service group raises lots of logistic issues. Who should pay? How should government, non-government, and academic groups interact in organizing such a program? How would recipient/host sites be selected? Even while answering those questions, the Baylor group offers good data that can prompt us to continue conversations about a global health service corps.

Along the way, though, what about those of us who look back on our training from a greater distance? What can we do to more fully engage on the enthusiastic "bandwagon" of global health? What preparation would be useful?

CHALLENGE OF SERVICE: 'ATTITUDE MATTERS'

There is still some disconnection between the fields of "tropical medicine" and "global health." From infectious disease backgrounds, we are comfortable dealing clinically with contagious conditions and diseases of poverty. Across the "aisle," however, our global health colleagues prompt us to consider epidemiology and public good; they prompt us to view health pro-actively rather than as the mere treatment and subsequent absence of disease. In less-resourced regions of the world, limited economic means can favorably impact more lives for more years when they are dedicated to health promotion and disease prevention than when they are focused on curative treatment. Each of us getting involved in international service should be aware of the principles and practices involved in healthcare, and we should carefully see how our personal involvement best fits in.

There are resources to help us understand both the principles and practices of sound medicine in other countries. Unite for Sight (http://www.uniteforsight.org/global-health-university/) offers online training. Several institutions (listed under "Approved Diploma Courses" at http://www.astmh.org/Education.htm) offer approved short (about two-month) courses that prepare future overseas workers and can lead to specific certification. Academic centers and professional

organizations offer conferences that help prepare and network professionals for international work; examples are the Global Health and Innovation Conference each spring at Yale University and the Global Missions Health Conference each fall in Kentucky.
Where and with whom should we go? There are many groups that offer logistical support for people wanting to provide either clinical or educational service. Interested individuals can connect with whatever faith-based, institutional, or professional groups seem most suited to them. As the Baylor experience demonstrates, illnesses such as tuberculosis and depression can complicate terms of service, and it is wise to have adequate personal and institutional support to be able to deal with the rigors of overseas work.

And, attitude matters. Moving from a resource-rich area to serve in a resource-limited area leads some people to think that they are better or more right than the people they are serving. We should also be careful not to assume that the provision of resources solves health problems. (Books like Dead Aid by Dambisa Moyo and Toxic Charity by Robert Lupton can challenge us to see beyond finances as we look to help others.) We should all go as humble learners to participate with colleagues.
As we travel and serve, though, we might still struggle with big issues. Should the use of resources be prioritized from the top down, or should people at the "grass roots" peripheral places choose how to spend money? We can get guidance from people like Jeffrey Sachs (The End of Poverty) and William Easterly (The White Man's Burden), but we will still have to decide how we each fit in. Even well-meaning people with great training can end up causing more harm than good (as discussed in When Helping Hurts by Steve Corbett and Brian Fikkert and in When Healthcare Hurts by Gary Seager).

Thus, the now-published Baylor experience is informative for infectious disease professionals, but it goes farther in inciting us to consider a national response to global health needs and in inspiring us to get involved personally. ■

ABSTRACT & COMMENTARY

Delaying Initiation of Antiretroviral Therapy for Cryptococcal Meningitis Improves Survival

By Richard R. Watkins, MD, MS, FACP

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

SOURCE: Boulware DR, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med* 2014;370:2487-2498.

SYNOPSIS: HIV-infected patients diagnosed with cryptococcal meningitis who received antiretroviral therapy (ART) 5 weeks after starting antifungal therapy had improved survival at 26 weeks compared to similar patients who received ART at 1-2 weeks (45% vs 30%, respectively, P=0.03).

Cryptococcal meningitis causes significant mortality in patients with HIV, especially in sub-Saharan Africa. The timing of ART initiation in these patients has been controversial due to the risk of developing immune reconstitution inflammatory syndrome (IRIS), which may be fatal when it involves the central nervous system, vs. the survival benefit from ART. Therefore, Boulware and colleagues sought to determine if early initiation of ART, defined as 1-2 weeks from the diagnosis of cryptococcal meningitis, led to a difference in 26 week survival compared to delaying ART for 5 weeks after diagnosis.

The study was conducted at 2 hospitals in Uganda and 1 in South Africa from November 2010 until enrollment was stopped by the Data and Safety Monitoring Board (DSMB) in April 2012 due to excess mortality in the earlier ART group. Patients entered the trial after 7 to 11 days of amphotericin B and fluconazole combination therapy. They were randomized in a 1:1 ratio to receive ART within 48 hours of randomization or at 4 weeks after randomization. The primary end point of the study was survival at 26 weeks. Secondary endpoints were survival through 46 weeks, cryptococcal IRIS, relapse of cryptococcal meningitis, fungal clearance, HIV viral load suppression at 26 weeks, adverse events and discontinuation of ART for more than 3 days for any reason.

After 389 patients were screened, 177 were randomized to one of the two treatment groups. The baseline and demographic characteristics of the groups were very similar. The number of patients who died by 26 weeks was significantly greater in the earlier-ART group compared to the later-ART group (40 of 88 [45%] vs. 27 of 89 [30%]; hazard ratio for death, 1.73; 95% confidence interval [CI], 1.06 to 2.82; P=0.03). The difference in mortality occurred early in treatment, during study days 8 through 30, when the patients were receiving consolidation fluconazole therapy. During this time frame, 21 of 75 patients (28%) in the earlier-ART group and 8 of 80 (10%) in the later-ART group died (hazard ratio, 3.10; 95% CI, 1.37 to 7.00; P=0.007). Mortality was not significantly different between the two groups after 30 days (P=0.87). By 46 weeks, 1 additional patient in the earlier-ART group and 2 in the later-ART group died (hazard ratio 1.66; 95% CI, 1.03 to 2.68; P=0.04). Furthermore, subgroup analysis showed that a CSF white-cell count of <5 cells per cubic millimeter was associated with higher mortality in the earlier-ART group than with later-ART.

Survival was similar between treatment groups in the subgroup with CSF white-cell counts of ≥5 cells per cubic millimeter. Earlier-ART was not favorable in any subgroup including patients with CD4 counts <50 per cubic millimeter. Participants at lower risk of death, such as those with lower CSF fungal burden at day 7 of antifungal therapy, also did not benefit from earlier ART. Timing of ART did not affect any of the secondary endpoints. Interestingly, the incidence of cryptococcal IRIS did not differ significantly between the earlier-ART vs. later-ART groups (20% [17 of 87] and 13% [9 of 69], respectively; P=0.32). Adverse events were similar between the two groups and were mostly related to amphotericin. Causes of death were also similar except for an excess of cryptococcal meningitis-related deaths in the earlier-ART group vs. the later-ART group (19 vs 10 deaths, respectively).

The only benefit for earlier ART in the study was on the immune response in the CSF. At day 14 of amphotericin therapy, the proportion of patients who had CSF white blood cell counts of 5 per cubic millimeter or higher was greater in the earlier-ART group (58%) than in the later-ART group (40%; P=0.047). However, this finding did not seem to translate into any appreciable clinical benefit.

■ COMMENTARY

This was a critical study because it helps clarify an important clinical dilemma, when to start ART in cryptococcal meningitis. On the one hand, the benefits of early ART in patients with HIV and AIDS are clear and DHHS guidelines now recommend initiating ART regardless of a patient's CD4 count. On the other, the risk for IRIS should not be overlooked, especially in those with central nervous system infections where it is particularly hazardous. The investigators found that delaying ART for 5 weeks after initiating antifungal therapy improved survival in patients with cryptococcal meningitis. Moreover, besides a slightly improved immune CSF response, there were no significant benefits from earlier ART. Indeed, earlier ART was actually associated with more deaths from cryptococcal meningitis, leading the DSMB to stop the trial early. Since IRIS with CNS infections causes an intense local inflammatory response within a confined space, the authors hypothesized that earlier-ART was most harmful in high-risk patients with a predisposition to cryptococcal IRIS and it was this mechanism that drove the results of the study. Thus, certain patients who had not yet recovered from the detrimental effects of their cryptococcal meningitis were especially susceptible to a second insult from IRIS, which was insurmountable and led to their deaths.

One of the limitations of the study was the difficulty in determining whether progressive clinical deterioration was due to cryptococcal meningitis or cryptococcal IRIS, which probably resulted in ascertainment bias and an underdetection of early IRIS events. Another limitation was that the trial was stopped early which may have caused an overestimation of the magnitude of benefit or harm. Finally, the relatively small sample size limits the power of the subgroup analysis to provide guidance for individual patients. Despite these limitations, Boulware and colleague's carefully conducted study shows the benefit of delaying ART in cryptococcal meningitis while amphotericin is being given. Although the trial was conducted in a resource-limited setting, it seems logical that delaying ART will also benefit HIV-infected patients with cryptococcal meningitis in high-income countries like the United States. ■

Ebola in West Africa — It's Not Going Away

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: The current ongoing Ebola virus outbreak in West Africa is the largest ever recorded.

Sources: World Health Organization. Global Alert and Response. Ebola virus disease, West Africa – update. 24 June 2014. http://www.who.int/csr/don/2014_06_24_ebola/en/; Center for Disease Control and Prevention. *MMWR* Ebola viral disease outbreak – West Africa, 2014. http://1.usa.gov/1osPCv6

Outbreaks of Ebola virus infection usually are of relatively brief duration — this is not the case with the current outbreak in West Africa. As a consequence, 3 days after a similar warning was issued in Sierra Leone, the president of Liberia, Ellen Johnon Sirleaf, on June 28 announced on radio "Let this warning go out: Anyone found or reported to be holding suspected Ebola cases in homes or prayer houses can be prosecuted under the law of Liberia". The World Health Organization, calling it a sub-regional crisis stated that the outbreak in Guinea, Liberia and Sierra Leone is "the largest in terms of the number of cases and deaths, as well as the geographic spread of the disease."

The current Ebola outbreak is already the largest ever recorded. As of July 1, WHO reported 413 cases (293 confirmed, 88 probable, and 32 suspected) in Guinea and 239 (199 confirmed, 31 probable, 9 suspected) in Sierra Leone, as well as 107 cases (52 confirmed, 21 probable, 34 suspected) in Liberia. There have been 467 deaths among the total of 759 cases. The outbreak appeared to be waning in late April, but it then resurged.

WHO has concluded that 3 major factors account for the continuing outbreak:

- transmission within rural communities, together with traditional beliefs and cultural practices
- transmission in densely populated periurban areas of Conakry in Guinea and Monrovia in Liberia
- transmission across country borders.

CDC has indicated that the key elements in the control of Ebola outbreaks include:

- active case identification and isolation of patients from the community to prevent continued virus spread
- identifying contacts of ill or deceased persons and tracking the contacts daily for the entire incubation period of 21 days
- investigation of retrospective and current cases to document all historic and ongoing chains of virus transmission
- identifying deaths in the community and using safe burial practices
- daily reporting of cases.

Education of health-care workers regarding safe infection-control practices, including appropriate use of personal protective equipment, is essential to protect them and their patients because health-care–associated transmission has played a part in transmission during previous outbreaks. The geographically dispersed nature of the outbreak will also require regional cooperation, something that WHO is working to make happen by, among other things, convening a special meeting of Ministers of Health from the region. ■

ABSTRACT & COMMENTARY

Antimicrobial Prophylaxis for Children with Vesicoureteral Reflux

By Philip R. Fischer, MD, DTM&H, Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN.

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

SYNOPSIS: Antimicrobial prophylaxis reduces the rate of recurrent urinary tract infection in children with vesicoureteral reflux, but it does not alter the rate of renal scarring. Intestinal flora develop antimicrobial resistance in children receiving prophylaxis.

SOURCE: RIVUR Trial Investigators. Antimicrobial prophylaxis for children with vesicoureteral reflux. *New Engl J Med* 2014;370:2367-2376.

The value of antimicrobial prophylaxis for children with vesicoureteral reflux is controversial. A collaborative effort included investigators at 19 sites in the United States. Otherwise healthy children aged 2 to 72 months without structural urologic abnormalities were enrolled after either a first or a second urinary tract infection if they had vesicoureteral reflux (grade I to grade IV). Subjects were randomized to receive either placebo or trimethoprim-sulfamethoxazole and were followed

for evidence of recurrent urinary tract infections. Technetium-based renal scans were done at baseline and after one and two years of treatment. Rectal swabs at the end of the two-year study period were used to evaluate for *E. coli* resistance to trimethoprim-sulfamethoxazole.

A total of 607 children (92% female, median age 12 months) were enrolled in the study between June 2007 and May 2011. Most (91%) were enrolled after a first urinary tract infection, and 86% had been febrile with the initial urinary tract infection. Vesicoureteral reflux was graded II or III in 80% (and grade IV in just 8%) of subjects and was bilateral in 48%. Approximately one-fourth of parents discontinued use of the study medication.

There were 171 recurrent infections among 111 children; children treated with trimethoprim-sulfamethoxazole had only half the risk of recurrent infection as those treated with placebo. The risk of renal scarring was similar between groups (11.9% with prophylaxis, 10.2% with placebo, a statistically non-significant difference). Of children with a first recurrent urinary tract infection due to *E. coli*, rectal isolates showed trimethoprim-sulfamethoxazole resistance in 63% of those receiving prophylaxis and in 19% of those receiving placebo. Reflux had resolved in 51% of children by two years of study.

Thus, antimicrobial prophylaxis reduced the risk of recurrent urinary tract infection in children with reflux, but it did not alter the risk of developing renal scarring. The authors suggest that their findings might rightly prompt reevaluation of the "watchful waiting" approach to first urinary tract infections whereby imaging to identify reflux (and potentially give preventive antibiotics) is not recommended.

COMMENTARY

There is significant controversy regarding the evaluation and management of children following initial urinary tract infections. In 2011, the American Academy of Pediatrics (AAP) published a practice guideline suggesting that children aged 2 to 24 months with an initial febrile urinary tract infection not undergo testing for reflux (voiding cystourethrogram) since antimicrobial prophylaxis in children with reflux was not effective in reducing the risk of subsequent recurrent infection.[1] The AAP's Section on Urology challenged the data underlying the AAP recommendation and countered with support of imaging following initial urinary tract infections;[2] the original AAP group remained convinced of its recommendation.[3]

This new study provides data in support of the challenge to the AAP clinical practice guideline. This multi-centered study included only children with rigorously diagnosed urinary tract infection (allowing only catheterized or suprapubically aspirated urine for culture) and shows conclusive evidence that prophylaxis is associated with a decreased risk of subsequent infection. Logically, since the evidence underlying the AAP clinical practice guideline is now supplemented with good contradictory evidence, there is reason to reconsider the AAP recommendation.

However, "reason to reconsider" is not the same as "reason to replace" the AAP recommendation. There are several "costs" associated with imaging and prophylaxis, including:

- the physical discomfort, potential psychological sense of being violated, and financial expense associated with voiding cystourethrograms in infants and young children
- the hassle of daily preventive medication (perhaps a reason that one-fourth of study subjects failed to continue the daily treatment)
- the risk to individuals and contacts of spreading organisms with enhanced antimicrobial resistance.

And, while these new data are clear about a reduced risk of subsequent infection with urinary prophylaxis, the extent of "benefit" of prophylaxis is not clear. Yes, preventive treatment will reduce infection (and, thus, discomfort, medical visits, and antimicrobial costs), but these new data show no change in renal scarring. If the benefit of prophylaxis is only on infection rates and not associated with any change in later outcomes or changed renal function, then the "benefit" of prophylaxis is somewhat limited.

Thus, further studies and further cost-benefit analyses are needed. As mentioned in an editorial accompanying the RIVUR paper, a move to recommend prophylactic antibiotics "awaits more evidence before universal adoption."[4] Despite remaining questions,[5] it is anticipated that ongoing study will provide answers to guide future practice.

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The Effect of Birth Month on RSV Hospitilization

By Hal B. Jenson, MD, FAAP

Dean, Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo, MI

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

SYNOPSIS: Compared to manual surveillance methods, an electronic surveillance tool for catheter-associated urinary tract infections had a high negative predictive value but a low positive predictive value.

SOURCE: Wald HL, et al. Accuracy of electronic surveillance of catheter-associated urinary tract infection at an Academic Medical Center. Infect Control Hosp Epidemiol 2014;35:685-91.

The effect of birth month on the risk of respiratory syncytial virus hospitalization in the first year of life in the United States. Pediatr Infect Dis J 2014;33:e135-e140.

A total of 82,296 respiratory syncytial virus (RSV)-related infant (<12 months of age) hospital admissions were identified from statewide inpatient data in five states (Arizona, Iowa, New York, Oregon, and Wisconsin) from July 1996 through June 2006. The relative risk of RSV during the first year of life was determined using an age cohort approach. The overall RSV-related hospital admission rate was 13.9 per 1000 person-years among infants. Among all hospitalized infants, 42% of the infants were female, 73% were <6 months of age, and 3.9% had an underlying condition such as bronchopulmonary dysplasia, cystic fibrosis, or congenital anomaly of the respiratory tract.

In all states, infants born in December and January had approximately 2-3 times greater risk for RSV-related hospitalization during their entire first year of life than infants born in July (RR: 9.8, 95% CI 7.8-12.4). One-month-old infants born between November and February had a significantly increased risk of RSV-confirmed hospitalization compared to one-month old infants born in October; the peak month of risk for one-month-olds was December (RR: 3.30, 95% CI 2.88-3.78). Two-month-olds born in November and December had significantly increased risk of RSV-confirmed hospitalization compared to two-month-olds born in October; the peak month of risk for two-month olds was November (RR: 1.21, 95% CI 1.09-1.35). In all states, the highest risk for RSV-confirmed hospitalization in the first year of life was among children born between October and February, with the highest risk among one-month-olds who were born between November and March.

■ COMMENTARY

Almost all children have at least one symptomatic episode of RSV infection during the first two years of life. Upon first exposure, approximately 25-40% of infants develop clinical signs of bronchiolitis or pneumonia, and 0.5-2.0% require hospitalization, generally infants less than 6 months of age. In the United States, RSV bronchiolitis accounts for 1.5 million outpatient visits among children younger than 5 years of age, and 100,000 to 126,000 hospitalizations among children younger than 1 year of age.

In temperate climates such as the United States, RSV infections peak during winter and early spring, typically with onset in December-January and ending by April-May. The finding that birth-month influences an infant's risk of serious RSV infection requiring hospitalization indicates that certain cohorts of infants are more vulnerable than others. This provides an opportunity for anticipatory guidance — avoiding ill contacts, early symptoms and signs of bronchiolitis, when to present for care — to parents of those children who are more vulnerable, those who are born between October and February.

There are significant hurdles to RSV vaccine development, including clarity of which immune cell populations or effector molecules are responsible for the clinical manifestations. Testing vaccine candidates will receive intense scrutiny because of the experience in the 1960s when children vaccinated with a formalin-inactivated RSV vaccine developed serious RSV disease upon natural exposure to RSV, including two vaccine-related deaths. In the past 20 years, an attenuated

vaccine developed by cold adaptation caused upper respiratory tract congestion and was deemed unacceptable for further development. Recent vaccine candidates based on a combination of mutations and gene deletions, using reverse genetics to manipulate the viral genome, have led to RSV reversions and compensatory mutations. Attenuated RSV vaccines are being tested in adults and children.

The findings of this new study suggest that a strategy that includes maternal vaccination may be necessary to achieve the greatest impact to prevent RSV disease. ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Outcomes in patients with XDR TB

Pietersen E, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: A cohort study. *Lancet* 2014: dx.doi.org/10.1016/S0140-6736 (13)62675-6.

The escalating presence of XDR TB in South Africa has created a public health crisis, squeezing already scarce public health dollars. While drug resistant TB represents a small percent of the total TB case load in South Africa, the cost of care for those patients soaked up nearly half of the government's entire TB budget for 2010 (about $126 million USD). In 2011, more than 8000 cases of MDR TB were identified in South Africa, at least 500 of which were confirmed XDR by culture (defined as multi-drug resistance plus resistance to a fluoroquinolone and either capreomycin, amikacin or kanamycin). Current South African health policy dictates that persons with XDR TB should be admitted to one of 3 designated treatment facilities until culture conversion, death, or treatment failure.

To evaluate outcomes of patients with XDR TB, a cohort of 107 patients receiving medical treatment based on the results of extended susceptibility and genotypic testing, HIV treatment as needed, and hospital care were followed from 2008 to 2012. The median age was 33 years, 54% were male and 41% were HIV positive (median CD4 count 365 cells/ml). They received a median of 8 anti-tuberculous drugs, ranging from 6 to 10 agents. Agents most frequently used included Terizodone (a cycloserine derivative) (in 93%), capreomycin (in 92%), para-aminosalicylic acid (in 90%), pyrazinamide (in 78%), clarithromycin (in 75%), ethionamide (in 64%), and amoxicillin/clavulanate (in 61%). Clofazimine, for which we no longer have access in the United States, was used in 21%.

Isolates were obtained every month to determine smear and culture status, and phenotypic susceptibility testing to rifampicin, isoniazid, ofloxacin, amikacin and ethionamide was performed at the discretion of the treating physician. A subset of 56 isolates was genotyped, with spoligotyping and targeted DNA sequencing to identify mutations conferring resistance. Of these, 36 (64%) were resistant to 8 or more agents. Resistance to a greater number of agents was more commonly associated with the Beijing genotype.

At 24 months, nearly half (46%) of the patients had died, 23% were failing therapy, and 7% had interrupted therapy for 2 or more consecutive months. Only 17 (16%) were considered treatment cures and/or had completed therapy.

At 60 months, 73% had died, 10% were failing therapy, and only 12 (11%) were considered treatment cures and/or had completed therapy. Patients discharged from hospital died within an average of 19 months (range, 4 to 26 months).

Sputum culture conversion (defined as 2 negative sputums at least 30 days apart) was observed in 22 patients (21%), with a median time of 8.7 months (range, 5.6 to 26 months). Time to culture conversion was not associated with a better outcome. Mortality in patients with culture conversion was 27% (all 6 of whom had HIV). Predictors of response to therapy included no prior history of MDR TB, the use of clofazimine, and antiretroviral therapy in those with HIV.

Clusters of XDR cases were identified within families and communities. Many of these patients were younger, in the prime of their life, and had families they were supporting. The economic cost of drug resistant TB is enormous, and despite maximal care, the mortality is high. Countries with constrained resources may end up making tough choices, if they wish to continue to support their existing TB control programs.

Anti-NDM-1 compound found

King Am, et al. Aspergillomarasmine A overcomes metallo-beta-lactamase antibiotic resistance. *Nature* 2014;510:503-6. ProMED-mail post. June 25, 2014; Antibiotic resistance – new meatallo-beta-lactamase (NDM-1) inhibitor. www.promedmail.org

Researchers have discovered an inhibitor of NDM-1 enzyme,

which may be useful in treating human infection due to these impossibly resistant organisms. The compound derives from a fungus found in soil samples from Nova Scotia. Original efforts to identify a compound that could effectively inhibit the actual bacteria itself from more than 10,000 soil compounds taken from across Canada and maintained in a library proved fruitless. But the investigators tried a different tack. They examined compounds that might inhibit the actual NDM-1 enzyme — and found one — called Aspergillomarasmine A (AMA for short), derived from Aspergillus versicolor.

In murine models infected with NDM-1-containing *Klebsiella pneumoniae*, 95% of the mice survived when treated with a carbapenem antibiotic plus AMA. The exact mechanism of action on the NDM-1 enzyme is not yet understood. It may be analogous to clavulanic acid, which has only weak antibacterial activity against most organisms, but is a potent inhibitor of many bacterial beta-lactamase enzymes. Beta-lactamases generally work in two different ways: metallo-beta-lactamases use zinc ions at the active site of the enzyme to hydrolyze beta-lactams – and serine beta-lactamases, such as the "KPC" and "OXA" carbapenemases, which attack serine at the active site of the enzyme. For example, clavulanate is considered a "suicide inhibitor" of many of the beta-lactamase enzymes by covalently bonding to this serine residue – this compound is then attacked by another amino acid molecule, which permanently deactivates the enzyme.

There is a long slog ahead to demonstrate the safety and efficacy of AMA in humans. But the mice fared well.

Yelp — a resource to public health departments

CDC Using online reviews by restaurant patrons to identify unreported cases of food borne illness – New York City, 2012-2013. *MMWR* 2014;63: 441-5.

New York being a mecca for restaurants, the New York City Department of Health and Mental Hygiene (DOHMH) maintains a telephone hot line and website for reporting possible food borne illness. They receive more than 3000 calls per year, approximately 1% of which prove to be related to an outbreak of food borne illness. It turns out that people more often report food borne illness on social media websites like Yelp than to their local public health departments. In fact, many people may not be aware that their local public health departments are interested in this information.

Recognizing this problem, the New York City DOHMH began a pilot project in conjunction with Yelp, the business review website, in 2012. The DOHMD reviewed data feed from Yelp restaurant reviews on a weekly basis containing the keywords sick, vomit, diarrhea and food poisoning. To select for reviews pointing to possible outbreaks and not just illness in one person, a narrower set of criteria were applied including reviews describing scombroid-like illness in one person or >2 people with similar complaints, incubation times > 10 hours, and reviews posted within 4 weeks of the meal.

Of 294,000 restaurant reviews posted during the 9-month period, possible food borne illness was described in 983. Close scrutiny of these reviews by a food-borne epidemiologist winnowed this number down to 499, 468 of which were reported in a timely manner. A total of 129 reviews described illness in 2 or more people. This amounted to close review of 23 reviews per week on average, with a weekly average of 13 requiring further investigation. Only 15 (3%) of these had also been reported to the public health department hot-line.

From these 129 reviews, investigators were able to contact 27 (21%) restaurant patrons for more information. From these, the DOHMH identified 3 food-borne outbreaks at 3 different restaurants accounting for 16 illnesses, not previously recognized. Likely food items involved house salads, a shrimp and lobster cannelloni special, and macaroni and cheese spring rolls. The reviews were posted within 2-5 days of the meal. Investigations of the 3 restaurants identified multiple violations of public food safety code (in fact, a routine inspection a week earlier had already identified problems with one of the restaurants). Only 22% of the reviewers indicated awareness of the automated telephone system for reporting food borne outbreaks.

Restaurant reviews may be an excellent resource for public health departments looking for cases of food borne illness. Responses to PHDs could be enhanced by linking PHD websites to business review websites.

CME INSTRUCTIONS

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

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

CME QUESTIONS

1. Which of the following is correct regarding the updated CDC recommendations for HIV testing?

A. Initial testing should use a 4th generation immunoassay that detects HIV-1 p24 antigen as well as antibodies to both HIV-1 and HIV-2.

B. If the combination 4th generation assay is negative, a Western blot should be performed.

C. A Western blot test should routinely be used to confirm a positive combination 4th generation immunoassay.

D. Initial testing should include a Western blot.

2. Physician participants in the Pediatric AIDS Corps demonstrated:

A. high (> 90%) levels of compliance with malaria chemoprophylaxis

B. minimal (< 1%) risk of latent tuberculosis

C. significant (> 10%) risk of depression

D. low (< 10%) satisfaction with decision to participate in the program

3. New data from a multi-centered study show that:

A. antimicrobial prophylaxis prevents urinary tract infections in healthy children

B. antimicrobial prophylaxis prevents recurrent urinary tract infection in children with a previous febrile urinary tract infection

C. antimicrobial prophylaxis prevents renal scarring in children with a previous febrile urinary tract infection

D. antimicrobial prophylaxis prevents chronic renal failure in children with a previous febrile urinary tract infection

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

"In the early 1900s children routinely suffered and died from diseases now easily prevented by vaccines. Americans could expect that every year diphtheria would kill 12,000 people, mostly young children; rubella, 'German measles' would cause as many as 20,000 babies to be born blind, deaf or mentally disabled. Polio would permanently paralyze 15,000 children and kill 1,000, and mumps would be a common cause of deafness. Because of vaccines all of these disease have been completely or virtually eliminated. But now because more and more parents are choosing not to vaccinate their children some of these diseases are coming back."

-- Paul Offit, MD, Deadly Choices: How the Anti-Vaccine Movement Threatens us All