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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Sofosbuvir and Ledipasvir combo Therapy for HCV: End game for interferon?

A sustained virological response even in patients with compensated cirrhosis

By Richard R. Watkins, MD, MS, FACP

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

SOURCE: Lawitz E, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): An open-label, randomized, phase 2 trial. *Lancet* 2014;383:515-523.

Hepatitis C virus (HCV) infection is an important global health issue that affects approximately 184 million people. Conventional therapy for HCV with interferon and ribavirin is associated with high rates of virological failure and severe side-effects. The recently introduced HCV protease inhibitors (i.e. boceprevir and telaprevir) also cause a high rate of adverse events. Novel direct-acting antivirals (DAAs) have been developed that make it possible to give interferon-sparing regimens. One of these is sofosbuvir, a nucleotide analogue inhibitor of the HCV NS5B polymerase and another is ledipasvir, an HCV NS5A inhibitor. A previous pharmacokinetic analysis found no significant interactions between the two drugs. Therefore, Lawitz and colleagues at the Texas Liver Institute investigated the efficacy of a fixed-dose combination tablet of sofosbuvir and ledipasvir with and without ribavirin, for 8 weeks and 12 weeks in both treatment-naïve and protease-inhibitor treated patients who

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failed to achieve sustained virological response (SVR) including those with compensated cirrhosis.

Eligible patients were over 18 years of age and had chronic genotype 1 HCV infection with a serum RNA concentration of at least 10,000 IU/mL. Patients with hepatic decompensation, low body mass index, or co-infection with HIV and/or hepatitis B virus were excluded. The researchers included treatment naïve patients (cohort A, n=60) and treatment nonresponders or relapsers (cohort B, n=40). Cohort A patients were randomly assigned to receive sofosbuvir plus ledipasvir for 8 weeks (n=20); sofosbuvir plus ledipasvir and ribavirin for 8 weeks (n=21); or sofosbuvir plus ledipasvir for 12 weeks (n=19). Cohort B patients were randomized to receive sofosbuvir plus ledipasvir for 12 weeks (n=19); or sofosbuvir plus ledipasvir and ribavirin for 12 weeks(n=21). In cohort B 22 patients (55%) had compensated cirrhosis. Deep sequencing of the NS3 and NS5A regions of the HCV RNA was done initially on all patients, 9 of whom were found to harbor NS5A resistance-associated variants (RAVs) and 33 had NS3 RAVs. This testing was repeated on patients with virologic failure at the time the failure was detected. Patients were followed for a total of 24 weeks. The primary endpoint of the study was the proportion of patients who achieved SVR at 12 weeks.

The results of the study were impressive. SVR was achieved by 97 patients at both weeks 12 and 24. Only 2 patients had virological relapse after receiving a full course of treatment. Of the three patients who failed to achieve a SVR at 12 weeks, none received ribavirin. All 33 patients with NS3 RAVs achieved SVR while 7 of the 9 with NS5A RAVs did. Deep sequencing at the time of virological relapse in one patient showed 3 new NS5A RAVs (Y93H, Q30L and L31V), while the other patient had the same RAVs detected at baseline and at the time of relapse (Q30L and Y93H). Adverse events were common but generally mild with 48 of 100 patients reporting at least one during the study. The patients in the ribavirin groups had the highest rates of adverse events (57% in both groups). The most commonly reported were nausea, anemia, upper respiratory tract infections and headache and were most often rated mild by the treating physician. Anemia was seen in 4 patients receiving ribavirin. The only serious events were delirium, an exacerbation of peptic ulcer disease, a spinal compression fracture, and one patient had anemia and suicidal ideation. No patient in any group discontinued therapy because of an adverse event. The investigators reported no high grade liver chemistry abnormalities or increases in creatinine. Patients receiving ribavirin developed mild increases in total bilirubin.

■ COMMENTARY

The combination of sofosbuvir and ledipasvir demonstrated a very high SVR with a favorable adverse event profile. However, this was a small, single-center study with a relatively short follow up, making it difficult to generalize the results to other settings and patient populations. For example, future studies will need to include patients co-infected with HCV/HBV and HCV/HIV in order to determine if a similar SVR is attainable. Another significant issue with the new DAA drugs in general and sofosbuvir in particular is their high cost. Sofosbuvir alone costs $84,000 for a 12 week course. However, this needs to be balanced by the huge burden on the health care system that comes

from decompensated cirrhosis, such as repeated hospitalizations and liver transplants. Indeed, further cost-benefit analyses need to be done to elucidate whether the upfront costs of these novel drugs are justified by potential savings in the future. A practical blueprint for these types of studies is already available from the HIV/AIDS epidemic, as are strategies for making the HCV DAAs available in resource-limited settings. It seems likely that interferon and probably ribavirin will go the way AZT has for treating HIV in the not too distant future. ■

ABSTRACT & COMMENTARY

CDC Messaging on MMR Vaccine Safety Paradoxically raises Parental Fears

By Hal B. Jenson, MD, FAAP

Dean, Western Michigan University School of Medicine, Kalamazoo, MI

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

SYNOPSIS: A national survey of parents found that information from the CDC about vaccines and adverse facts may not be effective in correcting parental misperceptions. Some attempts to heighten parental awareness about vaccine-preventable diseases and vaccine safety may actually be counterproductive.

SOURCE: Nyhan B, et al. Effective messages in vaccine promotion: A randomized trial. *Pediatrics* 2014;133:1-8.

A nationally representative 2-wave web-based survey was conducted in the United States in June-July 2011 among 1759 parents age 18 years and older having children age 17 years or younger. The first survey wave measured pre-intervention measures of health and vaccine attitudes. Parents were then randomly assigned to a control group receiving no information or to one of the four intervention groups that received information taken nearly verbatim from vaccine messages created by the Centers for Disease Control and Prevention:

(1) information explaining the lack of evidence that MMR vaccine causes autism;

(2) narrative information about the dangers of diseases prevented by MMR vaccine;

(3) images of children with diseases prevented by MMR vaccine;

(4) a dramatic narrative about an infant who almost died of measles.

The second survey wave measured perceptions about MMR vaccine, including adverse effects and intent to give MMR vaccine to their future children. None of the interventions increased parental intent to vaccinate their future children.

Among parents who were deemed from the first wave survey as having the least favorable attitude toward vaccination, the intervention providing information that refuted the link of MMR vaccine with autism successfully reduced this misperception about the vaccine (from 8.9% to 5.1%), However, it also decreased parental intent to vaccinate their children. Providing disease images increased the belief of a link between MMR vaccine and autism, and providing narrative information about the dangers of diseases prevented by MMR vaccine increased belief in vaccine serious adverse effects.

■ COMMENTARY

It is discouraging that no intervention using pro-vaccine messages created by the CDC increased parental intent to vaccinate their future children with MMR vaccine.

Informational messages aimed to inform

parents and correct misperceptions about vaccine safety and adverse effects may not always be effective, and may often be counterproductive. It appears that there is a danger-priming effect in which providing dramatic narrative information or images of sick children also increases misperceptions about the MMR vaccine. These results are consistent with other evidence that show that attempts by providers to scare parents with emotive information and stories may paradoxically increase concerns among parents who are hesitant to immunize their children.

The findings of this study confirm that there are significant challenges informing parents about topics that have been highly politicized, and that the lingering adverse effects of misinformation is strongly persistent and highly significant. In the instance of MMR vaccine, much of this parental misperception results from poorly worded or fraudulent reports in the scientific literature, such as the now-discredited publication in 1998 that putatively linked MMR vaccine with autism.

Parental resistance to persuasion even using factually correct information underscores the significant obstacle that health care providers face in educating parents about vaccines, especially with very limited time during office visits. ■

SPECIAL REPORT

Delayed-release Posaconazole Tablets Offer Increased Exposure in a Fasted State

By Caroline A. Lindsay, PharmD

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

Posaconazole oral suspension (Noxafil® oral suspension, Merck) has been, for several years, indicated for treatment of orophayngeal candidiasis as well as for prophylaxis of invasive Aspergillus and Candida infections in patients at risk. Posaconazole delayed-release tablets (Noxafil® delayed-release tablets, Merck) were recently FDA-approved for prophylaxis of invasive Aspergillus and Candida infections in immunocompromised patients 13 years of age and older.

Posaconazole works by inhibiting the fungal cytochrome P450 enzyme lanosterol 14α-demethylase which is the rate-limiting step in ergosterol synthesis. This results in a depletion of ergosterol which weakens the structural integrity of the fungal cell membrane and may also be associated with accumulation of toxic intermediates.

The new delayed-release tablets produce superior drug exposure when compared to the oral suspension when administered to patients under fasted conditions. Table 1 shows the pharmacokinetic parameters under fed and fasted conditions. In summary, under fasted conditions, the tablet form results in an AUC0-4 almost 4 times as high as observed with the oral suspension. Although, with the exception of a slightly higher Cmax, there is no significant difference in exposure between the tablet and oral suspension, the manufacturer nonetheless recommends that posaconazole delayed-release tablets be administered with a meal.

Dosing of posaconazole delayed-release tablets differs from that of the oral suspension. For fungal prophylaxis, the dose of the delayed-release tablet is 300 mg PO BID on the first day, followed by 300 mg

Table 1. Plasma pharmacokinetic parameters of 100 mg posaconazole							
Formulation	AUC0-t (ng*h/mL)	AUC0-∞ (ng*h/mL)	Cmax (ng/mL)	Tmaxb (h)	t1/2 (h)	CL/F (L/h)	V/F (L)
Under fasted conditions							
Oral suspension	2,970 (50)	3,420 (44)	84.0 (62)	4.00 (2.00, 8.00)	29.2 (31)	34.0 (38)	1,450 (54)
Tablet	11,400 (26)	11,700 (26)	385 (28)	5.00 (3.00, 6.00)	26.1 (28)	9.16 (29)	345 (45)
Under fed conditions							
Oral suspension	8,470 (25)	8,570 (24)	243 (18)	6.00 (5.00, 12.0)	25.1 (35)	12.1 (26)	427 (39)
Tablet	11,700 (24)	11,900 (23)	327 (23)	8.00 (3.00, 24.00)	23.7 (21)	8.97 (32)	305 (34)

[a] Data are means (percent coefficient of variation) for 16 subjects. AUC0 –*t*, area under the curve from time zero to the time of the final quantifiable sample; AUC0 –∞, area under the curve from time zero to infinity; CL/*F*, apparent total body clearance; *C*max, maximum plasma concentration; CV, coefficient of variation; *t*1/2, terminal-phase half-life; *T*max, time to *C*max; *V/F*, apparent volume of distribution

[b] Data are median (min, max)

PO daily. Duration of therapy is based on a patient's recovery from immunosuppression.

As with the oral suspension, posaconazole delayed-release tablet is hepatically metabolized, primarily via glucoronidation. It is also a substrate of P-glycoprotein and a strong inhibitor of cytochrome P450 3A4. It is contraindicated for concurrent use with the following agents, as posaconazole will increase the levels of these drugs:

- Sirolimus – can result in sirolimus toxicity
- CYP3A4 substrates such as pimozide and quinidine – can result in QTc prolongation
- HMG-CoA reductase inhibitors that are metabolized by CYP3A4 – can result in rhabdomyolysis
- Ergot alkaloids – can result in ergotism

In addition, posaconazole should be used with caution in patients taking calcineurin inhibitors (cyclosporine, tacrolimus) as posaconazole will increase the levels of these agents. Posaconazole has also been shown to prolong the QTc interval and cause Torsades de Pointes. Elevations in liver function tests can also occur, and may require discontinuation of posaconazole. Finally, posaconazole can prolong the hypnotic/sedative effects of midazolam, so patients should be monitored closely.

The most common side effects (>25%) in patients taking posaconazole delayed-release tablets 300 mg once daily were diarrhea, pyrexia, and nausea. Nausea was the most common reason for discontinuation of posaconazole (2%).

In summary, the delayed-release tablet has signicantly improved drug exposure under fasted conditions compared to the oral suspension. The delayed-release tablets should be used instead of the oral suspension, especially for patients unable to eat a full meal.

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ABSTRACT & COMMENTARY

Fever in African Children – More than Malaria

By Philip R Fischer, MD

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

SYNOPSIS: Most children presenting for care related to fever at two Tanzanian outpatient clinics had acute respiratory infections. Malaria accounted for "only" 11% of diagnoses and typhoid fever for 4%.

SOURCE: D'Acremont V, et al. Beyond malaria – causes of fever in outpatient Tanzanian children. *New Engl J Med* 2014;370:809-17.

One thousand five children — age two months to ten years — presenting with fever at two outpatient clinics in Tanzania (one rural, one urban) were evaluated extensively for etiologic diagnoses. Acute respiratory infection was identified in 62% of the children; 5% of those children had radiographic evidence of pneumonia. Twelve percent had viral upper respiratory infection without respiratory signs. Other diagnoses included malaria (11%), gastroenteritis (10%), urinary tract infection (6%), typhoid fever (4%), and meningitis (0.2%). Multiple concurrent diagnoses were common (23% of children), and only 3% of study subjects had no identifiable cause of the fever. Overall, 71% of children had viral disease, 22% had bacterial disease, and 11% had parasitic disease.

Among the 71% of children with viral disease, influenza virus, adenovirus, and rhinovirus were commonly seen. In addition, respiratory syncytial virus, bocavirus, coronavirus, picornavirus, enterovirus, metapneumovirus, and parainfluenza virus were also identified in children with acute respiratory infection. Human herpesvirus 6, parvovirus B19, cytomegalovirus, and other viruses were identified in children with systemic infections. Salmonella or Shigella was found in 14% of children with febrile gastroenteritis. Bacteremia, Rickettsia, and Leptospira were found in some children. Of children with radiologically confirmed pneumonia and with severe acute respiratory infection, approximately 90% had PCR evidence of pneumococcal infection.

■ COMMENTARY

Thirty years ago, pediatric care providers in East and Central Africa were taught that "Fever = Chloroquine" – meaning that the initial thought when facing a febrile child should be to give chloroquine. Obviously, the situation has changed. Chloroquine resistance emerged. And, even then — when half of febrile children in some areas were parasitemic with Plasmodium — those without malaria sometimes suffered poor outcomes because physicians and nurses did not consider other diagnoses.[1] Further, laboratory infrastructures expanded so that causes of pediatric fever could be more accurately diagnosed. Now, a new study from Tanzania shows that malaria is far less common than before and points us to other likely causes of fever in children.

While the relative importance of malaria as a cause of fever is declining in some areas of Africa[2] and childhood deaths due to malaria have dropped by 45% since 2000[3], malaria is still important. Eleven percent of febrile children presenting for care in Tanzania had malaria. Malaria still accounts for approximately 600,000 deaths of pre-school-aged children in Africa each year.[3] According to World Health Organization guidelines, children presenting with fever in malaria-endemic areas should be tested for malaria.[4]

In parts of Tanzania, at least, most children presenting with fever do not have malaria. The vast majority had viral infections. Obviously, neither antibiotics nor anti-malarials were needed for these children. Protocols can be used whereby febrile outpatient children are tested for malaria and treated if positive, while those with fever and tachypnea can be treated with an antibiotic effective against pneumococcus. Children with fever and bloody diarrhea might be presumptively treated for bacterial dysentery (realizing that hydration and nutrition are likely most important while antibiotics can also play a positive role in management). At the same time, clinicians must

also consider the possibilities of urinary tract infection, typhoid fever, and rickettsial disease. When a child is severely ill, hospitalization with presumptive treatment for malaria and bacteremia can still be reasonable.

Laboratory science has advanced dramatically, and only 3% of the children in the Tanzanian study had no etiologic diagnosis identified. Eventually, such detailed technology-dependent testing might become available throughout Africa, but we can already learn from studies like this that do extensive testing. We must remember that many children (23% in the Tanzanian study) are infected or colonized with multiple pathogens at the same time. Finding one pathogen (malaria, bacteria, or other) does not necessarily indicate that the identified pathogen is responsible for all or even part of the clinical illness. Clinicians must still interpret laboratory data in light of the clinical presentation. A recent Swedish study compared positive test results in children with acute respiratory illnesses and in healthy control children. Respiratory syncytial virus, metapneumovirus, and parainfluenza virus were associated with illness while some other potentially pathogenic respiratory viruses were identified equally in ill and well children.[5] Similarly, a review of metagenomic analysis reminds us that highly sensitive tests are easily capable of identifying colonizing pathogens unrelated to the symptoms.[6]

Thus disease frequencies are changing, and diagnostic strategies are expanding. While caring for children in Africa, we must continue to consider the possibilities of treatable life-threatening diseases such as malaria, pneumonia, typhoid fever, and bacteremia. We must remember to consider evaluation for urinary tract infection. We must consider covering with treatment for rickettsial infection in children with findings suggestive of this problem. But, at the same time, we must realize that the majority of febrile children in many areas — even in malaria-endemic developing countries — are sick with self-limited viral illnesses.

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ABSTRACT & COMMENTARY

Epidemiology of TB in Young Children

By Hal B. Jenson, MD, FAAP

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Dr. Jenson reports no financial relationship in this field of study.

SYNOPSIS: TB rates among pre-school aged children in the United States are 32 times higher in foreign-born children and six times higher in U.S.-born children with at least one foreign-born parent, compared to U.S.-born children with U.S.-born parents.

SOURCE: Pang J, et al: Epidemiology of Tuberculosis in Young children in the United States. *Pediatrics* 2014;133:e494.

A cross-sectional population-based study of TB in children was conducted in 2005-2006 among a consortium of 20 enrollment sites, primarily sites having statewide jurisdiction. The prevalence study included children <5 years of age diagnosed with TB and having at least one foreign-born parent. An observational study collected demographic and clinical information.

A total of 364 cases of TB were identified, which represented 49.6% of all TB cases among young children reported to the National TB Surveillance System in 2005 and 2006. More than 80% (n=303) of the children were born in the United

States, including 194 (64%) with at least one foreign-born parent and 76 (25%) with both U.S.-born parents. The parents' birth countries were unknown in 33 (11%) of the children.

Estimated TB rates per hundred thousand population for children <5 years of age were 2.57 for all children; 24.03 for foreign-born children; 4.81 for U.S.-born children with at least one foreign-born parent; and 0.75 for U.S.-born children of U.S.-born parents. More than one-half of the cases (53%) occurred among U.S.-born children with at least one foreign-born parent.

A total of 149 children were enrolled in the observational study from among 255 eligible children, including 27 (44%) foreign-born and 122 (63%) US-born. The median age was two years. Two-thirds of the enrolled children were Hispanic. A total of 149 children were enrolled in the observational study from among 255 eligible children, including 27 (44%) foreign-born and 122 (63%) U.S.-born. U.S.-born children with at least one foreign-born parent were more likely than foreign-born children to be diagnosed with tuberculosis as infants (30% vs 7%); Hispanic (73% vs 37%); diagnosed through contact tracing (40% vs 7%); and have an identified source case (61% vs 19%). Two thirds of children were exposed to tuberculosis in the United States.

■ COMMENTARY

Childhood tuberculosis remains an enormous global burden with approximately 530,000 cases of TB disease and 74,000 deaths estimated in 2012 among non-HIV infected children. Of the almost 10,000 cases of tuberculosis that occur annually in United States, more than 1000 occur in children. Two-thirds of cases in children and adolescents have at least one foreign-born parent.

The results of the study show that — compared to U.S.-born children with U.S.-born parents — foreign-born children in the United States have tuberculosis rates 32 times higher. U.S.-born children with at least one foreign-born parent have tuberculosis rates six times higher. Because of these relatively high rates of TB, U.S.-born children of foreign-born parents account for most cases of tuberculosis in the United States among children <5 years of age.

The basis of the increased risk for tuberculosis by having a foreign-born parent is unclear. This may be a marker for foreign travel, or for foreign visitors to the home who have undetected, active tuberculosis. Visitors to the United States are not screened for latent tuberculosis.

The results underscore two important points. First, tuberculosis in low-burden countries such as the United States cannot be eradicated until there is better control in the high-prevalence countries from which the U.S. receives many immigrants and visitors. It is only been since 2009 that children 2-14 years of age immigrating to United States are routinely tested for latent tuberculosis, though immigrants older than 14 years of age are not tested for latent tuberculosis. Second, the management of the adult source cases necessitates effective contact investigations that identifying young contacts, followed by targeted testing and treatment of latent tuberculosis infections in those children. ■

ABSTRACT AND COMMENTARY

Gene-Modified CD4+ T-cells Infused in HIV Patients may be a Promising Treatment

By Dean L. Winslow, MD, FACP, FIDSA

Clinical Professor of Medicine and Pediatrics Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, is Associate Editor of Infectious Disease Alert

Dr. Winslow is a consultant for Siemens Diagnostic

SYNOPSIS: Autologous CD4+ T-cells modified to delete CCR5 by Zinc-finger nuclease (ZFN) were infused into 12 HIV-infected patients. Cells survived in the circulation of patients and provided some control of viral replication

and immune reconstitution after interruption of antiretroviral therapy.

SOURCE: Tebas P, et al. Gene Editing of CCR5 in Autologous CD4 T Cells of Persons Infected with HIV. *N Engl J Med* 2014; 370: 901-910.

Twelve patients with aviremic stable HIV infection receiving antiretroviral therapy had lymphocytes harvested, had ex-vivo modification of the CCR5 genes performed in the CD4+ T-cells using ZFN, then had approximately 10 billion of those CD4+ cells reinfused (11-28% of which were shown to have undergone CCR5 modification). 6 patients underwent interruption of HAART 4 weeks after the infusion of the T-cells. Preinfusion CD4 counts were a median of 448 cells/uL At 1 week post infusion, the median total CD4 count was 1517/uL and median CCR5-modified CD4 count was 250/uL, constituting 13.9% of total circulating CD4 cells. The mean half-life of the genetically-modified CD4 cells was estimated to be 48 weeks. During treatment interruption and the resultant viremia, the decline in circulating CCR5- modified cells (–1.81 cells per day) was significantly less than the decline in unmodified cells (–7.25 cells per day) (P = 0.02). HIV RNA became undetectable in one of four patients who could be evaluated. The blood level of HIV DNA decreased in most patients. Infusion of cells was generally well-tolerated with only one patient experiencing a transfusion reaction.

■ COMMENTARY

In the mid-1990's the chemokine receptors, CCR5 and CXCR4 were identified as the major co-receptors for HIV on CD4+ T-cells. It was later demonstrated that the relatively common (in patients of Northern European genetic origin) 32 base pair deletion in CCR5 when present in homozygotes conferred almost complete resistance to infection with HIV. Heterozygous individuals who possessed one copy of this deletion per cell were often "long term nonprogressors" who maintained relatively preserved CD4 counts in the absence of antiretroviral therapy. Maraviroc, a small molecule, orally bioavailable inhibitor of CCR5/HIV-1 binding has demonstrated clear antiretroviral activity and is effective (as part of a HAART regimen) in the treatment of HIV infection in individuals who are infected with CCR5-tropic HIV. Finally, the "Berlin patient" (a man with chronic HIV infection who developed acute leukemia and received a bone marrow transplant from a homozygous CCR5 delta 32 donor) has had undetectable plasma and lymph node HIV-1 RNA and proviral DNA more than 4 years post-transplantation and off antiretroviral therapy. [1,2]

While the trial reported here does not represent a "cure" for HIV infection, the success in providing short-term immune reconstitution and partial suppression of HIV replication without HAART is exciting and may, eventually prove to be clinically beneficial. In addition, the use of other novel Zinc finger nucleases may prove to be useful in the treatment of other infections or non-infectious genetic diseases.

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

An old plague resurges in modern cities

Harper KN, et al. Syphilis: Then and now. *The Scientist* Feb 2014: http://bit.ly/1gMDIT6

Not a week goes by where I do not see at least one or two newly diagnosed cases of syphilis — and not just in my HIV+ MSM patients. Syphilis is beginning to appear in young heterosexuals as well. While most of these are identified based on screening serological studies, more patients than ever are presenting with signs

and symptoms of secondary syphilis. And an HIV+ patient at our county clinic recently presented with osteomyelitis of the carpal bones secondary to syphilis, something I've not seen in 20 years of ID/HIV consultation.

Two important questions remain, where did syphilis come from? And how did treponemal infection evolve into a sexually transmitted disease, from what was essentially a skin and skeletal disease passed on through close contact? Was it an old disease from the "New World", brought home to Europe by Christopher Columbus in the 15th century? Or is it older still? The "unifying diagnosis" postulates that a pre-Columbus, syphilitic-like organism causing infection in humans and/or primates in Africa or the Mediterranean was brought to the New World, where it morphed into yet another syphilitic disease, called Yaws. And then worked its way back to the Continent, possibly sailing home with Columbus to infect the "Old World" with a new variant trepemal disease, syphilis. But none of this has been proven.

Paleontologists have labored to trace the path of treponemal infection through skeletal findings. Syphilis can cause classical bone lesions, which, while not pathogenomic for treponemal infection, are highly suggestive. These include what are called "caries sicca" or clusters of shallow depressions in the external calvarium, surrounded by star-like cracks; and tibial swelling and regrowth, with shallow pits and ulceration on the shin bone — under a classical periosteal reaction — another tell-tale skeletal finding. Such skeletal evidence can be readily found in in the Pre-Columbus New World, but the search for similar bone lesions in pre-Columbus Europe has not been as rewarding. Bone lesions can be found, but they're either suspected to be from other diseases, such as leprosy, or carbon dating fails to provide conclusive dates pre-Columbus's voyage.

In 2008, microbiologists attempted to prove what historians and paleontologists could not. The first strain of "modern" *T. pallidum*, isolated from a patient 86 years earlier, was sequenced in 2008. Other strains of *T. pallidum*, as well as other human treponemal strains causing bezel and yaws were compared, creating a phylogenetic tree. Non-human primate strains of treponemes — which cause a contagious skin infection with bubos under the axilla and muzzle in West African monkeys — were also used. Unfortunately existing treponemal strains are too limited to provide much depth to the tree — but the data suggested that modern syphilis strains are most closely related to strains causing Yaws in Guyana, South America. (In fact, Christopher Columbus sailed to Guyana on this third voyage in 1498, encountering two major indigenous tribes of peoples, the Arawaks and the Caribs). The Governor of the West Indies in 1537 wrote in the "Historia General y Natural de las Indias", that a pre-existing but fairly benign skin disease in the area, which the Spanish called Bubas, was transmitted to the sailors of Columbus by indigenous women.

But why then did treponemal Yaws evolve into a sexually transmitted disease? Theories abound but the commonly held belief is that the sheer numbers of people living on the Continent, mostly in crowded cities, close quarters and loose mores quickly allowed for the spread of syphilis thru sexual means. A seminal event may have triggered the explosion of syphilis throughout the "Old World". When King Charles VIII of France invaded Naples in 1494-1498 with 25,000 troops, a nasty new infection broke out amongst the troops and accompanying prostitutes, with large boils and open weeping sores, and terrible joint pains. Those troops eventually returned to their homes, and from there, the infection spread rapidly throughout Europe. It is estimated by the 20th century, syphilis infected 10% of London residents, 15% of Parisians, and 20% of U.S. military recruits.

Another sentinel event in San Francisco may have triggered the ongoing resurgence of syphilis in the United States. It's a great story and demonstrates the ingenuity of the SF Public Health Dept. By the 1990's, syphilis had largely been beaten back in the United States. In 1999, the County of San Francisco reported only 17 cases of syphilis (remarkable when you consider the number of HIV cases in the city at that time). But a cluster of primary syphilis cases occurred in 7

gay men that year, 5 of whom were HIV+. The group was known for their sexual activity, finding anonymous partners through the internet. One individual alone estimated recent sexual contact with at least 47 "partners" found on the net, known only by their internet handles. The SFPHD reached out to AOL to assist in identifying and contacting these individuals but AOL declined, asserting that sexually transmitted disease exposure did not comprise a sufficient threat. The SFPHD reached out to enlist the help of "Planet Out", a local gay men's activist group, who alerted the gay on-line community to the possible outbreak through "chat rooms", where people were looking for partners. At least 50 contacts came forward for testing and treatment — but it was estimated that another 50-100 contacts slipped through the net. By 2003, SF county reported 595 cases of syphilis. Syphilis was back. ■

Wash your hands before eating !

Kundrapu S, et al. A randomized trial of soap and water hand wash versus alcohol hand rub for removal of *Clostridium difficile* spores from hands of patients. *Infect Control Hosp Epidemiol* 2014, 35(2):204-205.

These authors examined the frequency of hand contamination with C. difficile organisms and spores in hospitalized patients. Swab specimens were obtained from patients with *C. difficile* infection (CDI) as well as patients identified as asymptomatic carriers of *C. difficile* identified through surveillance techniques, before and after either hand washing with soap and water or after alcohol hand rubs. The specimens were cultured and colonies counted; isolates were also tested for cytotoxin production.

Specimens were obtained before and after a total of 62 hand washes and 59 alcohol hand rubs in 44 patients (2-4 hand hygiene events per patient). Before hand hygiene, 9 of 28 (32%) of patients with symptomatic CDI and 6 of 16 (38%) of asymptomatic carriers had positive cultures. Half of the 121 hand cultures were positive, with an average of 12 colonies per hand swab (range, 1-100 colonies per hand). All of the *C. difficile* isolates cultured exhibited toxin production.

Swabs taken after the use of alcohol hand rub showed little effect on colony counts. However, hand washing not only significantly reduced colony counts, cultures were negative from 90% of the hands after washing with soap and water.

We've instituted a program for hand washing before meals with a nice warm soapy wash cloth — brought with the meal tray – by the kitchen staff in a nice plastic bag — just like the airlines. It's a good practice — and this data suggests it could play an important role in reducing inoculation or re-infection with *C. difficile* organisms and spores. But I'd like to see more vigorous hand washing encouraged by patients throughout the day, especially before meals. ■

Wash your toys before sex!

Centers for Disease Control and Prevention. Likely female-to-female sexual transmission of HIV – Texas, 2012. *MMWR* 2014; 63 (10): 209-212.

The CDC has reported a rare case of sexual transmission of HIV during a 6-month exclusive relationship between two HIV discordant women, one of whom was known to be HIV+ and the other negative (a routine plasma donor). Sequencing of the viruses determined they were virtually identical, and the newly infected woman had no other recognized risk factors and believes the couple was monogamous.

Transmission of HIV between women during sex is highly unusual but has been previously reported. In large surveys of women presented for HIV care, virtually none of them presented with a sole risk factor of sexual contact with another HIV+ woman. This couple routinely engaged in unprotected sexual contact, had sexual contact during menses, and employed the use of sex toys. Their sexual play was described as occasionally "rough".

Although rare, HIV transmission may occur between discordant HIV+/HIV- women. Avoiding sex during menses, and the use of female condoms, especially during rougher sex, and cleaning toys between partners, may be helpful in avoiding transmission. ■

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 with regard to posaconazole delayed-release tablets?**

   A. Relative to the oral suspension, they have increased risk of drug-drug pharmacokinetic interactions.
   B. Relative to the oral suspension, its bioavailability (as determined by its AUC) is 25% greater.
   C. Relative to the oral suspension, its bioavailability (as determined by its AUC) is more than 2 times greater.
   D. It is a strong inducer of cytochrome P450 enzymes.

2. **Paradoxically, none of the pro-vaccine messages created by the CDC increased parental intent to vaccinate their future children with MMR vaccine.**

   A. True
   B. False

3. **In the Tanzanian study, which diagnosis was most common in febrile children?**

   A. viral respiratory infection
   B. malaria
   C. urinary tract infection
   D. typhoid fever

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

[IN FUTURE ISSUES]

Critically Ill Patients With Influenza A(H1N1) Virus Infection in 2014

Surgical site infections following ambulatory surgery procedures

Management of infections related to totally implantable venous-access ports: challenges and perspectives