ABSTRACT & COMMENTARY

International Outbreak of Acute Hepatitis in Children — Putative Role of Adenovirus 41

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: Cases of acute hepatitis in children, tentatively ascribed to adenovirus 41 infection, while first reported from a single hospital in Alabama, are being seen internationally.


In November 2021, five children with acute hepatitis associated with viremia due to adenovirus were identified at a children’s hospital in Alabama, leading to a comprehensive investigation and to identification of an additional four cases. Despite issuance of a statewide advisory, no further cases were identified.

The median age of the patients was 2 years, 11 months; seven of the nine patients were female. None were immunocompromised or had significant comorbidities, and no epidemiological link between the cases was identified. Symptoms included vomiting in seven patients, diarrhea in six patients, and upper respiratory infection in three patients. Eight children had scleral icterus, seven had hepatomegaly, and one was encephalopathic. All had elevated serum transaminase concentrations with alanine aminotransferase (ALT) 603 U/L to 4,696 IU/L and aspartate aminotransferase (AST) 447 IU/L to 4,000 IU/L, while serum bilirubin ranged from 0.23 mg/dL to 13.5 mg/dL.

Three patients developed acute hepatic failure, and two, who were treated with cidofovir and corticosteroids, underwent liver transplantation.
All nine patients had recovered or were recovering at the time of the Centers for Disease Control and Prevention (CDC) report.

Adenovirus deoxyribonucleic acid (DNA) was detected in whole blood specimens of each at concentrations of 991 copies/mL to 70,680 copies/mL on initial testing. Sequencing was performed on the polymerase chain reaction (PCR) product in five cases, and adenovirus type 41 was identified in each. Subsequent testing of plasma samples in two cases was negative, while repeat testing of whole blood remained positive. Examination of liver biopsy specimens from six patients found evidence of hepatitis but did not find viral inclusions or immunohistochemistry evidence of adenovirus, and no viral particles were found on electron microscopy.

All tests for hepatitis A, B, and C, as well as a variety of other causes of acute hepatitis, were negative. Respiratory viruses were present in several patients. In addition, Epstein-Barr virus DNA was detected in the blood of six of the nine patients, but immunoglobulin M (IgM) antibody to this virus was negative in all five patients in whom the test was performed, suggesting this was the result of reactivated viral replication of latent infection.

**COMMENTARY**

This problem is not limited to a single Alabama hospital, and the number of cases continues to grow. On May 6, 2022, the CDC stated that they were investigating 109 possible cases in 24 states and Puerto Rico.1

On April 26, 2022, the World Health Organization (WHO) announced at a press conference that “at least 169 cases of acute hepatitis have been reported from 11 countries in Europe, and in the United States, in children aged from 1 month to 16 years.” Thus, in the United Kingdom alone, 163 cases of acute hepatitis of unknown cause in children with an identified etiology had been identified as of May 3, 2022, with 11 patients undergoing liver transplantation.1

Then the European CDC has reported that, as of May 10, 2022, there were at least 181 cases outside of Europe and the United Kingdom, with a total number of cases worldwide of approximately 450. Adenovirus has been detected in many of the cases in which its presence has been sought.

The association with adenovirus 41 seems relatively strong, although with some caveats. Of particular concern is the lack of morphologic, PCR, or electron microscopy (EM) evidence of virus in liver biopsy specimens. From a diagnostic standpoint, the need to test whole blood rather than plasma by PCR is unusual. These findings have led to suggestions that, while adenovirus is necessary to cause this illness, it is insufficient, and one or more cofactors are required.

First recovered from adenoidal tissue (hence its name) in 1953, there now are 88 known serotypes and seven species (A–G) of adenovirus. Adenovirus 41, along with adenovirus 40, which together comprise species E, most commonly causes diarrhea in children. Adenovirus is an uncommon cause of hepatitis, with most reported cases occurring in small infants with disseminated disease or in immunocompromised patients, with very few occurring in immunocompetent children.3 The diagnosis is confirmed by testing of hepatic tissue by PCR, immunohistochemistry, or thin section EM — each of which was negative in all the Alabama cases. ■

**REFERENCES**


ABSTRACT & COMMENTARY

Oral Tebipenem: A New Antibiotic for Multidrug-Resistant, Gram-Negative Complicated Urinary Tract Infections

By Richard R. Watkins, MD, MS, FACP, FIDSA, FISAC

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SYNOPSIS: A randomized clinical trial that compared oral tebipenem with intravenous ertapenem in patients with complicated urinary tract infection or acute pyelonephritis found tebipenem to be noninferior in efficacy. The safety profile was similar between the two drugs.


There are few oral options for a complicated urinary tract infection (UTI) caused by multidrug-resistant uropathogens. Tebipenem is an orally bioavailable carbapenem with broad-spectrum activity against multidrug-resistant gram-negative pathogens, including fluoroquinolone-resistant and extended spectrum beta-lactamase (ESBL)-producing Enterobacterales. Eckburg and colleagues compared oral tebipenem to intravenous (IV) ertapenem in hospitalized patients with a complicated UTI or acute pyelonephritis.

The study was a Phase III randomized, double-blind, double-dummy, noninferiority clinical trial conducted at 95 sites in Europe, South Africa, and the United States. Patients were included who were at least 18 years of age and hospitalized with a diagnosis of complicated UTI or acute pyelonephritis. Exclusion criteria included having confirmed or suspected infection with a carbapenem-resistant pathogen, a creatinine clearance of 30 mL per minute or less, receipt of more than one dose of a short-acting antibiotic within 72 hours before randomization, septic shock, severe hepatic impairment, pregnancy, immunocompromised status, and hypersensitivity to any beta-lactam antibiotic. The primary end point was overall response (a composite of clinical cure and microbiologic response) in the microbiologic intention-to-treat (ITT) population at the test-of-cure visit. Clinical cure was defined as a complete resolution or clinically significant alleviation of baseline signs and symptoms of complicated UTI or acute pyelonephritis, along with no new symptoms. Microbiologic response was defined as a reduction in the uropathogen level from baseline to < 10^3 colony forming units (CFU) per milliliter in a post-baseline urine culture, and a negative repeat blood culture if a blood culture was positive at baseline.

Eligible patients were randomly assigned in a 1:1 ratio to receive either tebipenem 600 mg (two 300-mg tablets) orally every eight hours plus a dummy ertapenem infusion every 24 hours, or ertapenem at a dose of 1 g IV over a period of 30 minutes every 24 hours plus dummy tebipenem tablets administered orally every eight hours. Both groups received treatment for seven to 10 days for UTI or pyelonephritis and up to 14 days for bacteremia. A dose adjustment of the tebipenem was made for patients with moderate renal insufficiency (baseline creatinine clearance > 30 mL/min to ≤ 50 mL/min).

There were 868 patients randomized in the microbiologic ITT population, of whom 449 received tebipenem and 419 received ertapenem. Demographic and clinical characteristics were well-balanced between the two groups. The mean age of the patients was 58.1 years, with 46.1% being 65 years of age or older. At the time of enrollment, 50.8% had a complicated UTI and 49.2% had acute pyelonephritis. Furthermore, 11.5% of the patients had bacteremia at enrollment. About 90% of the baseline pathogens were Enterobacterales, mainly Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, and Proteus mirabilis. In the microbiologic ITT population, 24.3% of the patients were infected with pathogens that met phenotypic criteria for ESBL-producing uropathogens, 39% with
fluoroquinolone-nonsusceptible uropathogens, and 43% with uropathogens resistant to trimethoprim-sulfamethoxazole.

Compared to ertapenem, tebipenem was noninferior with respect to the primary end point of overall response at the test-of-cure visit (61.6% vs. 58.8%, respectively). The overall response at the end-of-treatment visit was 97.3% in the tebipenem group and 94.5% in the ertapenem group. Both groups had similar safety outcomes. The overall incidence of adverse events was approximately 26%, with diarrhea, headache, and nausea the only events occurring in > 1% of patients in either treatment group. Most of the adverse events were mild or moderate in severity, with only one (0.1%) patient in the tebipenem group having an adverse event that led to discontinuation of the trial drug, compared to eight (1.2%) in the ertapenem group.

**COMMENTARY**

This randomized Phase III trial showed oral tebipenem to be safe and effective therapy for complicated UTIs and acute pyelonephritis compared to IV ertapenem. Having an oral antibiotic that can treat many UTIs caused by multidrug-resistant uropathogens will be an important advancement. It seems likely that the majority of post-therapy microbiologic persistence, which was evident in the overall response at the test-of-cure visit, represented asymptomatic bacteriuria. Indeed, clinical cure was observed in more than 90% of the patients in both treatment groups and was sustained in follow-up. It also was notable that oral tebipenem was as effective as IV ertapenem across all subgroups, including in patients with more severe disease (i.e., bacteremia). Tebipenem probably will be expensive, so it will be interesting to see how hospital antibiotic stewardship programs and payers respond once it is approved. Pharmacoeconomic analyses will need to be conducted that weigh the benefits of oral therapy (e.g., fewer IV-related complications) against the likely high cost of tebipenem.

The study had a few limitations. Patients were mandated to inpatient hospital stays of seven to 14 days to receive their course of antibiotic therapy, which is unrealistic in terms of standard medical practice for complicated UTIs and pyelonephritis in the United States. Patients were excluded who were immunocompromised or had severe renal impairment, conditions which commonly are encountered in clinical practice. Finally, the observed uropathogens and resistant patterns from the study sites may not be generalizable to other geographic areas.

Adding a new oral option for multidrug-resistant uropathogens to our antibiotic armamentarium is an exciting possibility. However, the Food and Drug Administration has asked for additional data prior to consideration, and the further development of the drug has been halted. Whether tebipenem will clear all the remaining hurdles on its path to approval remains to be seen, along with its price tag.

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**ABSTRACT & COMMENTARY**

**Who Can Get the Janssen/J&J (Non-mRNA) COVID-19 Vaccine Now?**

*By Stan Deresinski, MD, FACP, FIDSA*

Clinical Professor of Medicine, Stanford University

**SYNOPSIS:** The Food and Drug Administration recently limited the use of the Janssen COVID-19 vaccine.


On May 5, 2022, the Food and Drug Administration (FDA) restricted the use of the Janssen/J&J COVID-19 vaccine only to individuals ≥ 18 years of age for whom:

- the use of other authorized vaccines is not feasible; or
- it is the only available choice because they have elected its use and would otherwise not receive vaccination.

**COMMENTARY**

In contrast to the messenger ribonucleic acid (mRNA) vaccines from both Pfizer and Moderna, the Janssen/J&J vaccine contains recombinant...
replication-incompetent adenovirus 26 expressing the SARS-CoV-2 spike protein. It initially received emergency use authorization in February 2021, but its administration was paused three months later to allow the FDA to investigate six reported cases of thrombosis with thrombocytopenia syndrome (TTS) occurring after receipt of this vaccine. The hold was lifted just 10 days later at a time when a total of 15 cases of TTS occurred after approximately 8 million doses had been identified. Eight months later, in December 2021, the Centers for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices (ACIP) recommended the preferential use of mRNA vaccines over the Janssen vaccine and indicated circumstances in which it could be considered. These were basically identical to the current recommendation.

As of March 18, 2022, the FDA and CDC had identified 60 confirmed cases of TTS, eight of which were fatal. They calculated a TTS case rate of 3.23 per million administered vaccine doses, with a fatality rate of 0.48 per million.

The FDA provides the following as examples of individuals who still may be candidates for receipt of the Janssen/J&J COVID-19 vaccine. These include those with a history of an anaphylactic reaction to an mRNA vaccine and those who would not otherwise receive vaccination because they decline receipt of an mRNA vaccine because of personal concerns. The FDA has published a revised fact sheet for healthcare providers. For patients who fear mRNA vaccines, the Novavax vaccine, comprised of spike protein nanoparticles combined with an adjuvant, is under review at the FDA.

REFERENCE

SPECIAL REPORT
Updated Management of Malaria

By Philip R. Fischer, MD, DTM&H

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SYNOPSIS: Malaria is preventable and treatable, yet there still are hundreds of millions of cases of malaria each year. New guidelines encourage personal and community prevention. Treatment usually is with artemisinin-based combination therapy.


This year, the World Health Organization (WHO) released updated evidence-based guidelines for the prevention, diagnosis, and management of malaria. This article reviews key recommendations from the WHO report, supplemented with comments from the Centers for Disease Control and Prevention (CDC). The 220-page WHO paper is readily available for download, and it will be updated repeatedly at the WHO website.

Malaria is preventable and treatable. Nonetheless, 3 billion people live at risk of getting malaria, and there still are nearly 250 million cases of malaria around the world each year, with approximately 600,000 deaths.

There are more than 2,000 cases of malaria in the United States each year, and the number has been increasing during recent decades. More than half of U.S. cases result from exposures in West Africa, and more than two-thirds are caused by Plasmodium falciparum.

[There are more than 2,000 cases of malaria in the United States each year, and the number has been increasing during recent decades.]

PREVENTION
For individuals residing in areas where malaria is endemic, the use of pyrethroid-impregnated bednets is effective to reduce malaria transmission. Sleeping under nets is most useful, but there also is usefulness to having nets hanging in living areas during evening hours. In addition to blocking physical contact between mosquitoes and potential patients, these insecticide-laden nets also repel, disable, and/or kill mosquitoes.
Although the use of topical repellents can be effective for individuals, limited compliance with repeated applications of repellents makes community-wide use of topical repellents of dubious value.

Among residents of malaria-endemic areas of Africa, pregnant women should receive intermittent chemoprophylaxis with at least three monthly doses of sulfadoxine-pyrimethamine during the second and third trimesters of their first and second pregnancies. Children should receive sulfadoxine-pyrimethamine along with their second and third sets of routine immunizations.

In the Sahel region of Africa where there is seasonal transmission of malaria, children should receive monthly doses of amodiaquine and sulfadoxine-pyrimethamine during the malaria season for their first six years of life.

In parts of Africa with moderate to high transmission of malaria, a four-dose series of the RTS,S/AS01 malaria vaccine should be initiated for children at 5 months of age.

The WHO guidelines deal with population groups living in areas of malaria transmission. For travelers, the CDC provides detailed guidance for malaria prevention, noting the use of personal protective measures, geography-based risk, and anti-malarial selection.2

**DIAGNOSIS**
Patients with suspected malaria should have testing done, either with microscopy or with a rapid diagnostic test. Quality control of testing is essential.

The CDC malaria guidelines remind clinicians working in non-malarial areas, such as the United States, that the presenting symptoms of malaria are nonspecific. Thus, malaria should be considered in any febrile traveler who has been in a malaria-endemic area within recent months.

Thus, malaria should be considered in any febrile traveler who has been in a malaria-endemic area within recent months. Blood testing is necessary.

**MANAGEMENT**

Artemisinin-based combination therapy (ACT) is the mainstay of pharmacologic management of falciparum malaria. Other than for women during the first trimester of pregnancy, treatment of uncomplicated malaria may be with one of the following combinations:

- artemether + lumefantrine;
- artesunate + amodiaquine;
- artesunate + mefloquine;
- dihydroartemisinin + piperquine;
- artesunate + sulfadoxine-pyrimethamine;
- artesunate + pyronaridine.

The treatment should be for three days.

During the first trimester of pregnancy, uncomplicated falciparum malaria should be treated with seven days of quinine and clindamycin.

In regions of chloroquine sensitivity, non-falciparum malaria may be treated with chloroquine. If susceptibility is in doubt, artemisinin-based combination therapy should be employed. A 14-day course of primaquine may be given to prevent relapse of vivax and ovale malaria if the patient does not have glucose-6-phosphate-dehydrogenase deficiency.

The first-line treatment for anyone with severe malaria (even infants and pregnant women) is 24 hours of parenteral artemunate. When the patient can tolerate oral medication, artemisinin-based combination therapy may be used to complete a three-day course. The dose per kilogram of artemunate is higher in smaller children (specifically, those weighing less than 20 kg) than in larger children. In the United States, expert advice and access to intravenous artemunate, when not locally available, are available around-the-clock from the CDC.3

There is a rare but reported risk of post-artemisinin hemolytic anemia following the use of parenteral artemunate, possibly related to the initial degree of parasitemia.4 Thus, patients with severe malaria who receive intravenous artemunate should be monitored weekly for up to four weeks to promptly identify those who might be developing this rare complication.3

**REFERENCES**
COVID-19 Pre-Exposure Prophylaxis

By Stan Deresinski, MD, FACP, FIDSA

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SYNOPSIS: The combination of tixagevimab and cilgavimab (Evusheld) was demonstrated to be effective in the prevention of symptomatic COVID-19, but much remains to be learned as SARS-CoV-2 continues to evolve.


Levin and colleagues reported the results of an ongoing randomized trial evaluating the efficacy of a combination of monoclonal antibodies (tixagevimab and cilgavimab, marketed as Evusheld) in the prevention of symptomatic COVID-19 in adults. Subjects were judged to be at risk, either because of a likely inadequate response to vaccination or increased risk of exposure due to location (e.g., nursing home) or circumstance. A total of 5,197 patients were randomized (2:1) to receive tixagevimab-cilgavimab, 300 mg of each component, as separate intramuscular injections at the same visit, or comparable placebo injections. The study took place between November 2020 and March 2021 (pre-Omicron).

Polymerase chain reaction (PCR)-confirmed symptomatic illness occurred in eight of 3,441 (0.2%) tixagevimab-cilgavimab recipients and 17 of 1,731 (1.0%) in those who received placebo through day 183. The relative risk reduction was 76.7% (95% confidence interval [CI], 46.0 to 90.0; P < 0.001). With extended follow-up at a median of six months, the relative risk reduction was 82.8%. In addition, there were five cases of severe or critical COVID-19 and two COVID-19-related deaths, and all seven occurred in the placebo group. Adverse events, mostly mild, occurred in approximately one-third of subjects in each group.

Genotyping was performed on isolates from a total of 20 patients, including from seven asymptomatic monoclonal recipients and 13 symptomatic placebo recipients and, among variants of concern, one was a beta (in a tixagevimab-cilgavimab subject) while there were five alpha subvariants and five delta among the placebo recipients.

Pharmacokinetic analysis revealed that serum neutralization titers 29 days after administration were 16-22 times higher than reported in convalescent plasma in individuals recovering from COVID-19, and significant serum levels were seen at six months.

**COMMENTARY**

Tixagevimab and cilgavimab each bind to distinct sites within the receptor binding domain of the SARS-CoV-2 spike protein. This allows continued activity of the combination if resistance to only one of the epitopes emerges. The emergence of the Omicron variant led to the discarding of two available monoclonal combinations, bamlanivimab/etesevimab and casirivimab/imdevimab, because of markedly reduced activity against the Omicron BA.1 and BA.2 variants, and sotrovimab because of more modestly reduced activity against BA.2.

The emergence of mutants capable of escaping monoclonal antibodies became of concern with regard to tixagevimab-cilgavimab when data indicated reduced activity of one of its components against BA.1. The combination of its components, however, retains significant in vitro activity against BA.2 — although BA.2 breakthrough infections have been identified. The reduced activity against BA.1 had led the U.S. Food and Drug Administration, in February 2022, to recommend a doubling of the doses of...
the components to 600 mg each, with the purpose of overcoming modest reductions in activity. This remains the currently used dose. Betelovimab, which has emergency use authorization for treatment but not prophylaxis, remains active against both BA.1 and BA.2.

Furthermore, with a half-life of 90 days, serum monoclonal antibody levels persisted after tixagevimab-cilgavimab administration for as long as nine months, with levels likely to be protective against susceptible variants for at least six months. The extended half-lives of the monoclonal components of tixagevimab-cilgavimab are the result of modifications that reduce binding to the Fc receptor and C1q. The issue of when repeat dosing is indicated already is being raised in the clinic, and the answer remains to be seen. This first depends on whether, in dealing with a constantly evolving virus, it remains efficacious when that time comes.

When tixagevimab-cilgavimab first received emergency use authorization, it was in very short supply and, as a consequence, its use primarily was directed at patients with significant immunocompromise, such as those who were transplant recipients. However, in the clinical trial results discussed here, there were only a total of 198 patients with immunocompromise, with symptomatic infection occurring in 1/125 and 2/93 tixagevimab-cilgavimab and placebo recipients, respectively. Thus, we really do not know the degree of benefit that may be achieved in these patients, just as we do not know for certain its efficacy in an Omicron world.

ABSTRACT & COMMENTARY

HPV Vaccination in Adolescence Prevents Cancer More than 10 Years Later

By Rebecca B. Perkins, MD, MSc

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SYNOPSIS: This long-term follow-up study of three cluster-randomized trials of human papillomavirus (HPV) vaccination evaluated cancer protection over up to 11 years of follow-up. During this time, 17 HPV-positive cancers were identified in the unvaccinated group, and 0 were identified in the vaccinated group, indicating 100% vaccine efficacy at preventing HPV-associated cancers.


Human papillomavirus (HPV) infection is associated with six types of human cancers, as well as pregnancy complications, including preterm delivery.1-4 HPV vaccination has been recommended in more than 180 countries since 2006.5 Countries with high vaccination rates already have noted decreases in HPV prevalence, cervical precancers, and cervical cancers.6-8

A study from Australia also indicates reductions in preterm births and small-for-gestational-age infants as women vaccinated as adolescents begin to make up the majority of the pregnant population.9 Because HPV vaccination is recommended in early adolescence, more than a decade before most HPV exposures, concerns have been raised about duration of protection. In addition, the clinical trials were based on prevention of precancers, but did not have cancer outcomes.10

The study by Lehtinen et al examines the development of invasive cancers among randomized cohorts of Phase III clinical trials of bivalent and quadrivalent HPV vaccines.11 A total of 3,341 vaccinated women and 16,536 unvaccinated controls were followed by the Finnish Cancer Registry starting at trial cessation in either 2007 or 2009. Women were followed for the development of invasive cancer through 2019. Over 11 years of follow-up, a total of
17 HPV-positive cancers were identified, including 14 cervical, one vaginal, one vulvar, and one tongue cancer. All cancers occurred in unvaccinated women; none occurred in the vaccinated group. Intention-to-treat vaccine efficacy was estimated at 100% ($P < 0.05$).

**COMMENTARY**

This study indicates HPV vaccination confers long-term protection against a variety of HPV-related cancers. In the United States alone, nearly 44,000 HPV-associated cancers are diagnosed annually.\(^3\) The majority of these could be prevented with HPV vaccination in adolescence.\(^3\) However, HPV vaccination rates in the United States remain below national goals, and also are lower than rates for the other adolescent vaccines: tetanus-diphtheria-pertussis and meningococcus.\(^1,2\) Furthermore, adolescent vaccination, particularly HPV vaccination, decreased substantially during the COVID-19 pandemic.\(^3\)

Vaccine misinformation and anti-vaccination sentiment increased in prominence over the past decade, and the volume of misinformation has accelerated during the COVID-19 pandemic. The World Health Organization cites vaccine hesitancy as one of the top 10 threats to global health.\(^6\) The rise of social media has led to rapid promulgation of anti-vaccine misinformation through popular sites such as Facebook, YouTube, and WhatsApp.\(^7\) Unfortunately, public health messaging has not reached the same sophistication or success as anti-vaccine messaging. In fact, public health messages intended to educate on vaccine importance may unintentionally reinforce negative beliefs.\(^8\)\(^,9\)

Nonetheless, healthcare providers remain the most trusted source of vaccine information, and recommendations by healthcare providers are the strongest predictors of vaccine acceptance.\(^2\)\(^,\)\(^3\)\(^,\)\(^4\) To protect today’s adolescents from HPV-associated cancers in adulthood, it is incumbent upon all healthcare providers to ensure parents and adolescents receive high-quality vaccine recommendations. Yet, continuing to combat misinformation can be fatiguing to healthcare providers and lead to burnout.\(^25\)

The data from Lehtinen et al that HPV vaccination prevented all HPV-associated cancers more than a decade after vaccine receipt may be motivating for both clinicians and parents.

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Human Papillomavirus Infections: We Need to Improve Vaccination Rates

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: The prevalence of human papillomavirus infections and their sequelae remain high, although this is a problem that is preventable with available vaccines.


Tota and colleagues examined the prevalence of human papillomavirus (HPV) infection in sexually active human immunodeficiency virus (HIV)-negative men at the time of their enrollment in a global trial of a quadrivalent HPV vaccine. The following HPV types were included in the test system: HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 — the last five of which are in the 9-valent vaccine but are absent from the quadrivalent product.

The deoxyribonucleic acid (DNA) of one or more of these HPV types was detected in 455/3,463 (13.1%) heterosexual men (HM) and in 228/602 (37.9%) men who have sex with men (MSM). The seroprevalence (a measure of total exposure in this unvaccinated population) was 8.1% in HM from Europe and 29.9% in MSM from North America or Europe. The overall seropositivity risk was higher in MSM, with an adjusted odds ratio of 3.0 (95% confidence interval [CI], 2.4 to 6.4). Most HM and MSM were seronegative for all vaccine types, indicating continued risk. Multivariate analysis failed to identify independent risk factors for HPV DNA positivity in HM, but among MSM these were less frequent condom use, a greater number of receptive anal partners, and younger age at sexual debut.

Berenson and colleagues studied the prevalence of vaccine-type HPV DNA in the oropharynx of 9,437 individuals 18-59 years of age who were able to report their HPV vaccination status. The prevalence of oral HPV infection was 6.9% (95% CI, 6.1% to 7.9%) and was 3.5 times higher in males than in females, regardless of vaccination status. When the analysis was restricted to HPV included in available vaccines, HPV types in the quadrivalent vaccine and 9-valent vaccines were identified 5.5-5.6 times more frequently in males than females.

COMMENTARY

Of the 69,000 new diagnoses of HPV-related cancers in men in the world in 2018, 34,000 were oropharyngeal, 18,000 were penile, and 9,900 were anal. The frequency of oropharyngeal cancer is increasing at a rapid pace in the United States and occurs as much as five times more frequently in males than in females.

Evidence clearly indicates that many of these malignancies are potentially preventable with the use of available HPV vaccines. Although the uptake of such vaccination is increasing, vaccination of males remains limited. In their study of oropharyngeal cancers, the investigators concluded that the observation that males were more likely than females to be HPV positive, regardless of vaccination history, is most consistent with a lower frequency of males being vaccinated prior to their initiation of oral sex. Clearly, all the data point to the importance of vaccination and with improved targeting of males at a young age.
ABSTRACT & COMMENTARY

Need a Pig Heart? Beware Porcine Cytomegalovirus

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: The first recipient of a transplanted pig heart died with evidence of infection with a porcine cytomegalovirus.


On Jan. 7, 2022, a 57-year-old man, David Bennett Sr., with end-stage cardiac disease received a cardiac xenotransplant at the University of Maryland Medical Center. The donor was a pig with 10 genetic modifications. Among these were two human complement inhibitor genes (DAF and CD46), two immunomodulatory genes (CD47 and HO1), and deletion of a growth hormone receptor gene designed to prevent cardiac hypertrophy that had been seen in baboon recipients of pig hearts. There were deletions of genes encoding cell surface carbohydrate antigens, including blood cell antigens, making them suitable for universal donation.

The patient initially did well and, on day 34, an endomyocardial biopsy showed no evidence of rejection. However, as part of routine screening, next-generation sequencing of a plasma sample obtained on day 20 was marginally positive for the presence of porcine cytomegalovirus (PCMV). He developed fever and edema on day 45 (March 8) and, despite administration of cidofovir and intravenous immune globulin (IVIG), his illness rapidly progressed, and he died.

COMMENTARY

Although pig kidneys had previously been transplanted into humans on a few occasions, this was the first such transplantation of a pig heart. As noted, multiple genetic modifications had been implemented that were designed to, among other things, reduce the likelihood of organ rejection. There apparently was no evidence of rejection in this patient who was, of course, also receiving immunosuppressive therapy.

Despite its name, PCMV apparently is more closely related to human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7) than it is to human cytomegalovirus, and it is not known to be able to infect human cells. PCMV infection of porcine hearts transplanted into baboons is associated with reduced survival time of the transplant, and this was thought to be related to production of inflammatory cytokines as well as a pro-thrombotic effect in association with viral replication in the transplanted organ. This has led the clinicians involved in the human case to speculate that the observed illness, with fever and apparent capillary leak, was the result of a cytokine storm.

Pigs are uniformly infected with a variety of chromosomally integrated porcine endogenous retroviruses (PERV), but, although some of these viruses are capable of infecting human cells, there has been no evidence of transmission by transplantation of, e.g., pig islet cells. In addition to PCMV, other viruses affecting pigs to which attention should be paid are porcine circoviruses (PCV1-3), porcine lymphotropic herpesviruses (PLHV1-3), porcine reproductive and respiratory syndrome virus (PRRSV), Nipah virus (NIV), and hepatitis E virus (HEV). Of note is that university officials indicated that the donor pig had been screened for PCMV but “the tests pick up only active infections, not latent ones in which the virus may hide quietly in the pig’s body.”

REFERENCES

CME INSTRUCTIONS

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CME QUESTIONS

1. Which of the following is true regarding treatment of severe malaria?
   a. It is effective with artesunate alone.
   b. It is the same for pregnant and non-pregnant individuals.
   c. It frequently is associated with delayed post-treatment hemolysis.
   d. It requires seven days of quinine.

2. Which of the following is true regarding tebipenem?
   a. Tebipenem requires parenteral administration.
   b. Tebipenem is active against many extended spectrum beta-lactamase-producing Enterobacteriaceae.
   c. Tebipenem use is associated with significantly more serious adverse reactions than is etraphenem administration.
   d. Tebipenem received Food and Drug Administration approval in April 2022.

3. Which of the following is correct regarding tixagevimab-cilgavimab (Evusheld)?
   a. It must be administered intravenously.
   b. Its use is associated with a high risk of serious adverse reactions.
   c. It has been demonstrated clearly in clinical trials to be highly effective in severely immunocompromised patients.
   d. It is active in vitro against at least some subvariants of the Omicron SARS-CoV-2 variant, such as BA.2.

4. Which of the following is correct regarding human papillomavirus (HPV)?
   a. The only cancer caused by HPV is cervical cancer.
   b. HPV vaccination loses its efficacy after only two to three years.
   c. The prevalence of oral HPV infection is significantly higher in adult men than in adult women.
   d. The study by Lehtinen et al reported that the efficacy of HPV vaccine in the prevention of HPV-related cancers in women was approximately 56%.

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 latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests.
• Discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.