PTN POST
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Leading the Way

Herpes Simplex Virus in Infants

Nearly 90% of Americans will be exposed to one of the two types of herpes simplex virus (HSV) during their lifetimes. HSV type 1 usually causes small blisters on the eyes, in the mouth, or on the lips (i.e., cold sores); HSV type 2 generally affects the genitalia. For the vast majority of older children and adults, HSV causes little morbidity and almost no mortality. In infants, however, because newborns' immune systems are not fully developed, HSV infection can be severe, sometimes leading to death.

Most HSV infections in newborns are caused by HSV-2, which can be transmitted to the infant as he passes through the mother's birth canal. If the mother has an active genital herpes infection at the time of delivery, the baby is more likely to become infected during birth. Newborns sometimes contract HSV-1 through close contact with people who are shedding the virus in their saliva or who have an active cold sore outbreak.

Infected newborns may have mild symptoms initially, such as a low-grade fever or one or more small skin blisters. Herpes infection may spread throughout the body, however, and newborn infants with systemic herpes often become very sick very quickly. More severe symptoms include encephalitis, bleeding, breathing difficulties, jaundice, lethargy, poor feeding, seizures, and shock.

Newborns with HSV require treatment with intravenous antiviral medication lasting as long as 21 days. Acyclovir is the most common antiviral drug used for this purpose (see article below). Other therapies may also be needed to treat the effects of herpes infection, such as shock or seizures.

Luckily, transmission of HSV to newborns may be prevented through the use of precautionary measures. Pregnant women should tell their doctors about any history of genital herpes. If frequent herpes outbreaks are an issue, the mother-to-be may be prescribed acyclovir for use during the last month of pregnancy to prevent an outbreak around the time of delivery. Additionally, people with cold sores should avoid contact with newborn infants. Caregivers who have a cold sore should wear a surgical mask and wash their hands carefully before handling an infant to prevent transmitting the virus.

PTN Study: Pharmacokinetics of Acyclovir in Premature Infants

Acyclovir is approved by the U.S. Food and Drug Administration for HSV infections in infants. As described above, HSV is a very serious infection in this vulnerable group, often resulting in death or profound mental retardation. To date, appropriate dosing of acyclovir has not been adequately studied in preterm and term infants, meaning that their doctors must make educated guesses about how to use this potentially life-saving drug.

This PTN study is evaluating the safety and pharmacokinetics (PK) of intravenous acyclovir in preterm and term infants with suspected systemic HSV infection. Thirty-two infants <61 days of age participated in the study for up to 13 days at two centers. Acyclovir was administered to determine the levels of drug in each baby; such information will allow us to determine the appropriate dose of acyclovir in this understudied group.

On September 19, 2012, the PTN locked the database for this trial, meaning that all clinical trial data have been reviewed, queries have been resolved and issues addressed, and the database cannot be altered in any way. Preliminary findings from this trial should be available by spring of this year.

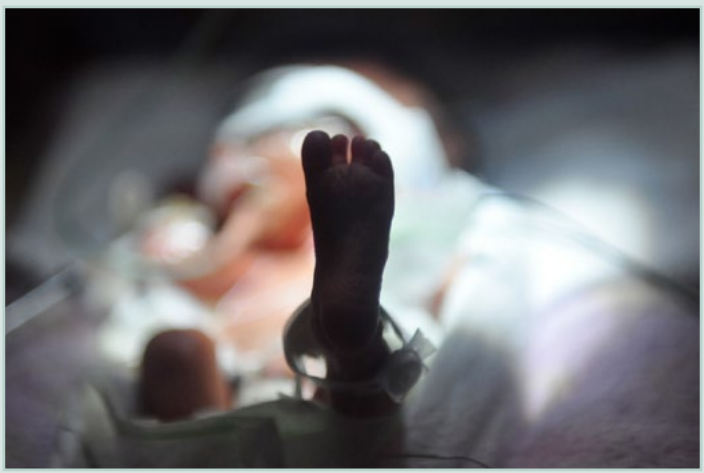
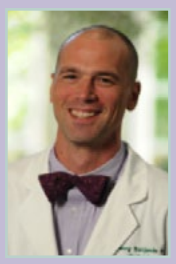


PHOTO BY MISS.LIBERTINE

A Message from the Lead Principal Investigator



Danny Benjamin, MD, PhD, MHS

Welcome to the fifth issue of *The PTN Post*, your bimonthly source for information about key issues in pediatrics and the work of the Pediatric Trials Network (PTN).

This month, we explore the devastating consequences of herpes simplex virus in infants, as well as the potential for its safe and effective treatment with acyclovir. As with many drug therapies, acyclovir has been shown to work well in adults and children, but data are lacking to inform its use in premature infants. We also check in with two PTN studies related to drug dosing in obese children, who comprise a growing and yet critically understudied population. The PTN's mission is to fill these critical knowledge gaps, making medicine as child-friendly as possible.

As always, we welcome your input about topics of interest for future issues. Please contact us with your suggestions via the PTN website (https://pediatrictrials.org/contact-info).

PTN Study: Safety and Pharmacokinetics of Clindamycin in Obese Children

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a leading cause of hospitalization among children and adolescents in the United States. MRSA infections typically start out as small red bumps that can quickly turn into deep, painful abscesses. Although infection may remain confined to the skin, it can also spread throughout the body, causing potentially life-threatening infections in bones, joints, and the cardiovascular system. Antimicrobial agents such as clindamycin are often employed as first-line therapies for the treatment of MRSA: use of clindamycin among children hospitalized with this disease increased from 21% in 1999 to 63% in 2008.

Over the same time span, rates of childhood obesity have also increased. National estimates suggest that one out of every five children in the United States is obese. These children are more likely to develop *Staphylococcus aureus* infections and to suffer from complications related to such infections. All too often, however, this population is excluded from pediatric trials of drugs used to treat this and a host of other diseases.

We know from studies in adults that the PK of drugs commonly used in the obese can be markedly different from that of their lean peers; as such, specific dosing recommendations for this population are often required. Similarly, clindamycin dosing guidelines based on weight may not be appropriate for obese children because the physiologic changes related to excess weight can alter the way that a child's body uses and excretes the drug. As a result, obese children are at greater risk of being over-dosed or under-dosed than their non-obese counterparts. This is concerning not only because it risks the health of the child but also because sub-therapeutic drug concentrations may increase the development of clindamycin-resistant MRSA organisms.

Currently, no PK data exist to guide clindamycin dosing in obese pediatric patients. This PTN study will evaluate the safety and PK of clindamycin in obese pediatric patients ages 2 – <18 years. To date, six sites have been selected. The study team anticipates holding the first investigators' meeting in May of this year, with patient enrollment to begin shortly thereafter. For more information about this study, visit **ClinicalTrials.gov**.

The PTN Obesity Informatics Web-Tool

As noted above, obesity can cause problems for drug dosing and safety, especially in children. PK parameters such as volume of distribution and drug clearance may be altered due to excess weight, making it difficult to predict what effect a drug will have. Because many drugs lack dosing information in kids, much less kids who are overweight or obese, the PTN is stepping in to help fill the knowledge gap.

For the PTN obesity informatics project, project staff scoured the existing literature on PK trials in obese patients, ultimately conducting two searches. Initially, the team looked for what PK data currently exist in obese kids; papers were found on about 20 drugs, many of which are uncommonly used in children (e.g., cancer drugs). Because of these limited findings, a second search was conducted based on a priority drug list comprising acute care drugs, antibiotics, and cardiovascular, gastrointestinal, neurological, and metabolic drugs. This time, the team searched the literature for all PK studies in both kids and obese adults. Among the PK studies in kids, those that included obese children were identified, and, when possible, obesity-specific PK data were extracted. All of these data were then combined into three deliverables:

1. A database containing obesity-specific PK data extracted from the studies in both searches
2. A web-tool that will present these data in a user-friendly way
3. A priority list that ranks drugs needing additional study

The Obesity Informatics Web-Tool is currently being finalized and will likely be hosted by a website under the auspices of the National Institute of Child Health and Human Development. Visit **our website** for updates on the web-tool's launch.

The Pediatric Trials Network (PTN) is made possible by the Best Pharmaceuticals for Children Act (BPCA). The BPCA, first enacted in 2002, provides mechanisms for studying on- and off-patent drugs in children. Visit us on the web at **www.pediatrictrials.org**.

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