Introduction

Current recommendations state that respiratory syncytial virus (RSV) prophylaxis should be initiated before the onset of RSV season, which typically starts in October or November and ends in March or April for most regions in the United States. The American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) recommend administering palivizumab (Synagis®, MedImmune Inc., Gaithersburg, MD) before hospital discharge to infants considered at risk of severe RSV infection. The 2003 AAP guidelines specify that initial immunoprophylaxis should occur 48 to 72 hours before NICU discharge during RSV season, with subsequent monthly treatment until the end of the RSV season. The 2006 Redbook guidelines have removed this recommendation. This subanalysis evaluated the timing and location of the initial palivizumab dose administered to infants who were admitted to the neonatal intensive care unit (NICU) before hospital discharge during the RSV season and were candidates for RSV immunoprophylaxis prior to the 2006 AAP guideline change. All infants came from the Palivizumab Outcomes Registry. This was a prospective, multicenter, US–based registry designed to characterize the population of infants and children receiving palivizumab for prophylaxis of serious lower respiratory tract disease caused by RSV.[1] Approximately 20,000 infants were enrolled and tracked over four consecutive RSV seasons.

Methods

The Palivizumab Outcomes Registry was conducted from 2000–2004 in 256 pediatrician offices and pediatric clinics across the United States. The design and method of data collection have been described in detail elsewhere.[1] In the present analysis of infants who received NICU care during each RSV season, those who were:

1. admitted to the NICU during birth hospitalization.
2. born or discharged after November 1 of the RSV season were considered candidates for an initial palivizumab injection before hospital discharge.

Data points assessed included gestational age, date and locale of initial palivizumab injection (hospital or outpatient), and NICU admission and discharge dates. If an infant did not receive the initial palivizumab dose...
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while in the hospital, the number of days to first outpatient dose was recorded as part of the prospective follow-up data collected at each clinical site. RSV hospitalizations were recorded after the first dose of palivizumab only; hospitalization data were not collected before the first outpatient injection.

Results

Overall, 19,458 subjects were enrolled in the 2000–2004 Palivizumab Outcomes Registry. Over the 4 seasons combined, 14.3% (2780/19,548) of total enrollees were identified as potential candidates for initial NICU dosing of palivizumab. The proportion of potential candidates ranged from 5.3% (331/6291 for 2002–2003) to 26.1% (553/2116 for 2000–2001) across the individual seasons. Across all 4 seasons, the rate of hospitalization among the entire population of NICU dose candidates was 2.3%.

Characteristics of NICU Dose Candidates: Across all 4 seasons, 94% of infants who were admitted to the NICU were born before 36 weeks’ gestation, and 88% had a birth weight less than 2500 g. Fifty-three percent of infants were male and 55% were Caucasian. Risk factors in NICU dose candidates included: child care attendance of the child or other household children (40%), followed by multiple birth (33%), and tobacco use in the home or in day care centers (20%). Histories of chronic lung disease (CLD) and congenital heart disease were documented in 18% and 7% of the infants, respectively. More infants who received initial hospital dosing of palivizumab were younger than 32 weeks’ gestation (47%), had a birth weight less than 2500 g (92%), or had CLD (21%) compared with those who received initial outpatient dosing (30%, 82%, and 13%, respectively).

NICU Dosing Analysis: Combining data across the RSV seasons, 42% (1172/2780) of NICU dose candidates received their first palivizumab dose in the outpatient setting. The percentage of NICU dose candidates who received their first palivizumab dose in the outpatient setting after hospital discharge increased from 33% in the 2000–2001 season to 37% in the 2001–2002 season, 51% in the 2002–2003 season, and 52% in the 2003–2004 season. Among infants receiving their first palivizumab dose as an outpatient, the overall mean and median times to receipt of first dose were 26 days and 23 days, respectively. The time to first outpatient dose ranged from 1 day to more than 4 months after hospital discharge (Figure 1). Because enrollment ended early for the 2002–2003 season, the upper limit of the range for that season was lower (66 days) compared with the 3 other seasons (95 to 120 days). Six percent of NICU infants received their first dose of palivizumab within 3 days after hospital discharge, whereas 32% received their first dose 30 days or more after discharge.

Of the potential candidates who did not receive the initial palivizumab dose in the NICU, 30% were born before 32 weeks’ gestation, 60% were born at 32 to 35 weeks’ gestation, and 10% were born at or after 36 weeks’ gestation. The delay in outpatient dosing was similar across these gestational age groups: 27 days, 25 days, and 31 days, respectively.

Discussion

To our knowledge, this study is the first to examine the actual timing of initial palivizumab dosing of NICU patients eligible for such therapy. The primary benefit of palivizumab immunoprophylaxis is the reduction in the rate of RSV-related hospitalizations among high-risk infants and children.[2,3] The majority of high-risk infants that did not receive a dose of palivizumab in the NICU prior to discharge in this study during RSV season experienced considerable delays in receiving RSV prophy-
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able population. The impact of reimbursement processes on the access and timing to immunoprophylaxis also needs to be reconsidered and more systematically evaluated to assess the potential consequences of delaying palivizumab prophylaxis protection to this high-risk group of babies.

References


US Child Health System Needs Total Overhaul

When it comes to health care for our kids, we live in a world that is only going to get tougher. That is the underlying message from three UCLA professors who are calling for a complete overhaul of the U.S. child health care system, which they describe as a "patchwork of disconnected programs, policies and funding" that lacks "clear accountability or performance goals."

In their report, which appeared in a recent issue of the Journal Health Affairs, Dr. Neal Halfon, director of the Center for Healthier Children, Families and Communities at UCLA's School of Public Health, and his co-authors argue that even as Congress, the nation's governors and the Bush administration debate federal spending on the State Children's Health Insurance Program, which covers low-income uninsured children whose families earn too much to qualify for Medicaid, our leaders are not tackling more fundamental challenges facing the nation's child health system.

According to the authors, the current system is failing to produce the kind of health outcomes that it could and should because it is powered by outdated logic, outmoded organization, and inadequate and misaligned finance strategies that were designed to be responsive to epidemiology and health goals more relevant to the early part of the 20th century.

"An increasing body of science now tells us that the scaffolding for our adult physical, cognitive and socioeconomic health is built in the early years of life," said Halfon, who prepared the report with Dr. Helen DuPlessis, UCLA adjunct assistant professor, and Moira Inkelas, UCLA assistant professor, both with the School of Public Health. "We know now that many health problems have their origins during childhood and simply compound over time."

"The most common diseases of the past were acute illnesses or infections, but today's children and youth face more chronic conditions that will impact them for the rest of their lives — diseases like asthma, diabetes and mental health problems like ADHD and depression," Halfon said. "These emerging health needs are simply not being addressed."

The authors call for ground-up reforms to the U.S. child care system that include:

- making transformation of the child health system a national priority.
- improving overall system performance by consolidating the fragmented array of programs scattered across various federal departments and agencies into a new national child health development agency that can take the lead in advancing the child health agenda.
- ensuring that all children have health care coverage that is responsive to their unique developmental health needs; that coverage is comprehensive and includes health promotion, as well as disease prevention services; and that coverage addresses the whole child, including physical, mental, behavioral and developmental needs.

The authors warn that transforming the child health care system is not only an ethical and social imperative but an economic one.

"The outmoded operating system and obsolete logic employed by the U.S. child health system is analogous to a modern business ignoring the Internet, Windows and new Pentium processors and running their operations using MS-DOS on separate and unconnected 286 machines," Halfon said. "It worked in the past, but it is not very effective and efficient for a competitive business, nor is it appropriate for a health system that needs to produce health outcomes that will help our children compete in the future."

For more information, visit www.ph.ucla.edu.

Joslin Researchers Discover a Surprising Culprit in the Search for Causes of Diabetic Birth Defects

Over the past several years, Joslin Investigator Mary R. Loeken, Ph.D., and her colleagues at Joslin Diabetes Center have unlocked several mysteries behind what puts women with diabetes more at risk of having a child with birth defects. Even though those risks have decreased significantly over the years, thanks in part to advancements at Joslin, women with diabetes still are two to five times more likely than the general population to have a baby with birth defects, especially of the heart and spinal cord, organs that form within the first few weeks of pregnancy.

In past work, Dr. Loeken and her research team were able to establish through their studies in mice that the mother's high blood glucose levels are the cause of these defects. This is one of the reasons why women with diabetes who are planning a pregnancy are encouraged to have their blood glucose levels under good control prior to conception. The Joslin researchers also have shown that the damage occurs because the extra glucose in the mother's blood inhibits the expression of embryonic genes that control essential developmental processes.

Now, in this latest study done in mice, Dr. Loeken and her colleagues have discovered that the protein called glucose transporter 2 (Glut2) makes it possible for the
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high concentrations of glucose to get into the embryonic cells efficiently when the mother's blood glucose concentrations are high. Also involved in the study was Rulin Li, Ph.D., a former postdoctoral fellow at Joslin. The study, supported by the National Institutes of Health, will appear in the March 2007 print edition of Diabetologia and was published online by the journal on Jan. 18, 2007.

"Glut2 is a gene that we wouldn't have expected to be switched on in early embryonic development," said Dr. Loeken, Investigator in the Section on Developmental and Stem Cell Biology and Associate Professor of Medicine at Harvard Medical School. "Yet our research in mice shows that the expression of this gene in the early embryo enables the cells to absorb glucose about two to three times faster when the mother's glucose levels are elevated, while other glucose transporters would be saturated at normal glucose concentrations. This makes the embryo very susceptible to the malformations that high glucose levels cause, such as neural tube defects."

Researchers so far have identified 14 different glucose transporters, a class of proteins that sit on the membranes of cells and enable the cells to absorb glucose. Each type plays a different role in glucose uptake and is found in different cell types. "We knew that the embryo expresses a variety of glucose transporters that bring necessary glucose into the developing cells," said Dr. Loeken, "but what caught my eye was that one of them was Glut2." This protein, Dr. Loeken explained, is what is known as a high-Km glucose transporter, that is, it works efficiently only when glucose levels are high. Low-Km glucose transporters, on the other hand, become saturated at these higher levels and no longer work efficiently to get glucose into the cells.

Low Km transporters can be thought of like a narrow doorway into a room that will only allow one person to pass at a time, whereas a high Km transporter is like a wide-open door that will allow several people to pass at a time, explained Dr. Loeken. When very few people need to get through the doors at a time, the narrow doors will work just as well as the wide-open doors, but if a crowd needs to get through the doors, the narrow doors will be saturated. The wide open doors will allow the people to go through at a high rate, and the concentration of people in the room will be very high.

"After birth, the Glut2 transporter is expressed on insulin-producing beta cells of the pancreas and in the liver, the tissues that receive blood carrying high concentrations of glucose absorbed from the intestine after a meal," said Dr. Loeken. "It makes sense that Glut2 would be expressed in the pancreas where the high glucose level signals the beta cells to release insulin, and in the liver, where it signals the liver to store the glucose. In a normal pregnancy, the glucose in the mother's blood that circulates to the uterus would never be as high as the blood that flows by the pancreas and the liver, and the embryo would not be exposed to high concentrations of glucose. Therefore, Glut2 won't work any better than the other glucose transporters to absorb glucose. But glucose concentrations can be very high during a diabetic pregnancy, and if this highly efficient glucose transport is functioning, the embryo cells act like a glucose sponge, absorbing glucose at a much higher rate than normal."

Using mice that lacked Glut2 genes, which were developed by one of the study's co-authors, Bernard Thorens, Ph.D., of the Center for Integrated Genomics at the University of Lausanne in Switzerland, Joslin researchers found that only embryos carrying normal Glut2 genes developed malformations when the mothers were diabetic, whereas embryos that lacked Glut2 genes were protected from malformations during diabetic pregnancy. "This shows that the high-transport Glut2 transporter was responsible for getting higher concentrations of glucose in the cell and causing the malformations." The embryos were examined on the 10th day of gestation. The time span in the mice, Dr. Loeken explained, is comparable to about the fourth or fifth week of a human pregnancy, which is about the time a woman may discover that she is pregnant.

The Joslin researchers were also surprised to find that there were fewer embryos recovered on day 10 of gestation if they lacked the Glut2 genes, whether or
The fourth annual Evidence vs. Experience in Neonatal Practices™ CME conference will be held in Chicago on June 22-23, 2007, providing physicians and other healthcare professionals with state-of-the-art information on the specialized management of preterm infants. A faculty of international thought leaders will participate in this exciting and informative program, describing and discussing the latest developments in the field, including cutting-edge treatments and their practical applications.

During the two-day event, sessions will include:

- “Necrotizing Enterocolitis and Nutrition of the VLBW Neonate,”
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- “Resuscitation and Stabilization of the VLBW Neonate,”
- “Protecting the Preterm Lung,” and ...
- “Newer Therapeutic and Monitoring Options for the VLBW Infant.”

Speakers will highlight issues such as feeding strategies in neonates, clinical practices in neonatal oxygenation, the Neonatal Resuscitation Program’s revised guidelines and their practicality, CPAP in the delivery room, lung protective ventilatory strategies, heat loss prevention, and indomethacin vs. ibuprofen for PDA – with an emphasis on research advances and clinical experiences.

Rangasamy Ramanathan, MD, of the Keck School of Medicine of the University of Southern California, will serve as chair of this stimulating program. In addition to the symposium’s other organizing committee members – Jatinder Bhatia, MBBS (Medical College of Georgia), Kris Sekar, MD (University of Oklahoma Health Sciences Center) and Istvan Seri, MD, PhD (Childrens Hospital Los Angeles) – the faculty will include leading neonatologists from the U.S. and Europe. The keynote address on the topic of “Surfactants: Past, Present and Future” will be delivered by Henry L. Halliday, MD (Queen’s University of Belfast, Northern Ireland).

The conference, which is returning this year to the city of its inaugural meeting, will take place at the InterContinental Chicago. The target audience for the event includes physicians, nurse practitioners, nurses and others caring for preterm infants. As in previous years, attendees will be encouraged to participate actively in the program, interacting with the expert faculty, offering their own clinical and research insights, and using an Audience Response System to help ascertain what they’ve learned.

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not the mothers were diabetic, suggesting that there is a survival advantage in having the Glut2 transporter. "Recent research by our collaborator, Dr. Thorens, has shown that Glut2 is also a transporter for glucosamine, an amino sugar that serves important functions in the synthesis of proteins," said Dr. Loeken. "Since glucosamine is synthesized in the liver, which the early embryo still lacks, it must get it from its mother's circulation. Although we don't know for sure, Glut2 could be needed by the embryo for glucosamine transport."

Putting these findings together, Dr. Loeken said, "The early embryo must express Glut2 for some reason, because fewer embryos survived early development if they lacked this transporter. Perhaps it is because it is needed to transport glucosamine. However, because this transporter, which works so well after birth to allow the pancreas to produce insulin and the liver to store glucose, also makes the early embryo take up glucose very efficiently when glucose concentrations are high, as can occur during diabetic pregnancy, this explains why the embryo is so sensitive to the mother's hyperglycemia."

"While it is too early yet to give any clinical recommendations to patients based on these new findings, the research does suggest that once the glucose reaches the concentration where the Glut2 transporter functions efficiently, that is probably sufficient to cause malformations," said Dr. Loeken. "The best we can do now to prevent malformations in diabetic pregnancy is to help a woman establish good blood glucose control before she becomes pregnant, so that she will be better able to make sure her glucose levels are as close to normal during pregnancy," she added.

For more information go to: www.joslin.org/754_880.asp
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