

ADVANCES IN NEONATOLOGY

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A Care Bundle: Reducing Infant Mortality in Tanzania, a Low-Resource Country

Each year, some 9,500 premature infants die in Tanzania. This high neonatal mortality rate has remained unchanged for decades in this low-resource country. Among the major causes of death are birth asphyxia, respiratory failure, and infections. Tanzania has limited capacity to continuously monitor either heart rate or respirations and/or manage preterm infants with respiratory distress with any breathing support other than oxygen. In addition, antibiotics are only initiated when the preterm infant becomes symptomatic, which is too late to intervene.

Faced with these sobering facts, **Jeffrey M. Perlman, MB, ChB**, Chief of the Division of Newborn Medicine, Komansky Children's Hospital at NewYork-Presbyterian/Weill Cornell Medical Center, has marshalled efforts to facilitate a low-cost,



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evidence-based preventative strategy to combat infant mortality in the developing world. *(continued on page 2)*

Predictive Monitoring: Improving Application of Big Data in the NICU

In the intensive care setting, it is vital to assess hemodynamic status for optimization of end-organ tissue oxygenation and to decrease morbidity and mortality. "However, standard hemodynamic monitoring, such as heart rate and systemic blood pressure,



Dr. Rakesh Sahni

may only provide a crude estimation of organ perfusion during neonatal intensive care," says **Rakesh Sahni, MD**, Medical Director of the Neonatal Intensive Care Unit at NewYork-Presbyterian Morgan Stanley Children's Hospital, and Director of the Infant Physiology Laboratory at Columbia University.

"Recent technological advances in digital signal processing have allowed pulse oximetry to potentially fill this gap of monitoring tissue microcirculation," says Dr. Sahni. In a recent review of continuous noninvasive monitoring in the NICU published in *Current Opinion in Pediatrics*, Dr. Sahni provides an overview on the clinical use of pulse oximetry as a method for assessing end-organ oxygenation. He concludes that "noninvasive real-time continuous bedside monitoring with pulse oximetry has the potential to serve as a biomarker for early organ dysfunction and to predict adverse short-term and long-term outcomes in critically ill neonates. In the

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A Care Bundle: Reducing Infant Mortality in Tanzania, a Low-Resource Country (continued from page 1)

“I’ve been working in global health in Tanzania for about 12 years now,” says Dr. Perlman, a world-renowned expert in neonatal medicine. “We published a paper in 2013 in which we showed that by using a very simple educational program called Helping Babies Breathe, we were able to reduce mortality by 47 percent and, surprisingly, reduce stillbirths by 24 percent.”

Helping Babies Breathe, an initiative of the American Academy of Pediatrics in collaboration with the World Health Organization, and a number of other global health stakeholders, teaches healthcare workers in low-resource countries the basic techniques to resuscitate babies immediately after birth. “We were the first to publish on this and there have been numerous papers that have replicated our findings,” says Dr. Perlman.

Since then Dr. Perlman has targeted his efforts to save premature infants at 28 to 34 6/7 weeks estimated gestational age via the pilot implementation of a Premature Care Bundle. The bundle was tested at four Tanzania hospitals between July 2015 and June 2016 and includes:

- administration of antenatal corticosteroids to mothers in preterm labor to facilitate lung maturation
- administration of antibiotics to mothers when in active labor
- immediate stabilization/resuscitation of the newborn, including avoidance of a drop in body temperature $<36^{\circ}$ C, and
- administration of early neonatal antibiotics

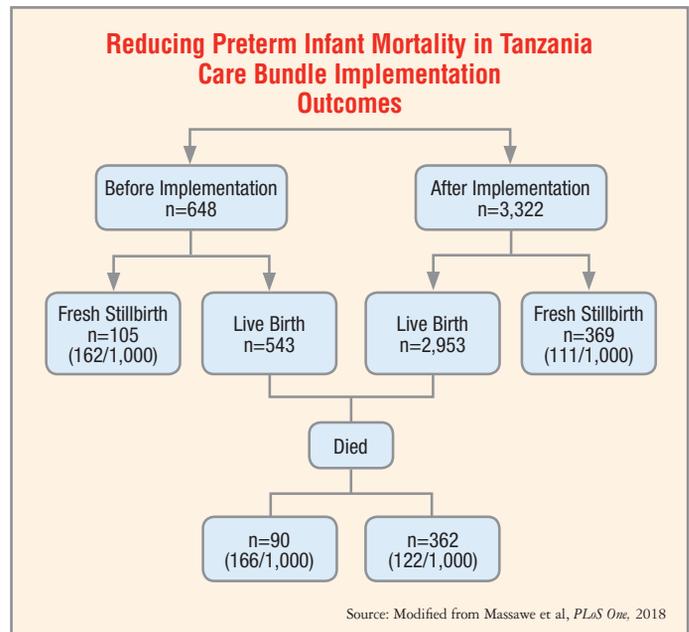


Dr. Jeffrey M. Perlman and some of the research team members in Tanzania

The care bundle reflected standard interventions undertaken in the United States. “This whole care bundle that we have developed costs less than \$7 per medication for both mother and baby,” says Dr. Perlman. “That’s about the cost of a large latté at Starbucks.”

“I’ve established a core group of investigators – all Tanzanians – at three university-affiliated hospitals and one district hospital that conduct research,” continues Dr. Perlman, who facilitated implementation of the care bundle.

The pre- versus post-implementation findings of the study, which were just published in the March 2018 issue of *PloS One*, saw an overall 26 percent reduction in neonatal mortality from 166/1,000 to



122/1,000 live births, and a 33 percent reduction in fresh stillbirths from 162/1,000 to 111/1,000. “By subgroup analysis, when we looked at the babies, 28 to 30 6/7 weeks, there was no reduction in mortality,” notes Dr. Perlman. “However, when we looked at the ‘bigger babies,’ i.e. 31 to 34 6/7 weeks, there was a 45 percent reduction.”

Dr. Perlman emphasizes that interventions that used a combination of medications, for example, steroids and neonatal antibiotics versus none, achieved a 70 percent reduction in mortality. “When steroids were used alone, it was associated with a non-significant increase in neonatal mortality, a finding similar to that reported previously in the low-resource setting,” he says. “We speculate this is because neonatal antibiotics weren’t used, which we think is extremely important. Babies at a lower temperature died more frequently compared to the survivors.”

At full implementation of the program, Dr. Perlman believes that some 4,000 lives can be saved each year in Tanzania. “This care bundle serves as a bridge between events during labor and the first postnatal ‘Golden Hour.’ Thereafter, other programs such as Essential Newborn Care and Saving Newborn Lives should be implemented.”

“The rewards for me are twofold. The first obviously relates to the positive outcomes, and the second relates to the development of a core group of Tanzanian investigators,” adds Dr. Perlman. “We have had spectacular results and that is attributed to the people on the ground. If these findings can be replicated in other resource-limited settings, the ability to further reduce the less than five-year mortality rates becomes enormous.”

Reference Article

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For More Information

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Battling Neonatal Infections Bedside and in the Lab

When Thomas A. Hooven, MD, is not saving young lives in the Neonatal Intensive Care Unit at NewYork-Presbyterian Morgan Stanley Children's Hospital, he is in the lab seeking ways to prevent their harm from a devastating infection – group B *Streptococcus* (GBS).

“Treatment of infection is a major part of my work, because babies, particularly preterm or other sick infants, are very susceptible to infections that generally do not affect healthy children and adults outside of the neonatal period,” says Dr. Hooven, a neonatologist in the Division of Neonatology and Perinatology, whose research focuses on using advanced genomic analyses to identify new drug or vaccine targets in an effort to eradicate neonatal GBS infections.

“GBS is a common adult intestinal and vaginal commensal that also causes neonatal sepsis, pneumonia, and meningitis,” says Dr. Hooven, who began his basic science research in infectious disease as a resident in pediatrics and then as a fellow in neonatology at Columbia. “GBS affects about 3,000 babies a year and is the leading cause of infectious neonatal mortality in the United States.”

According to Dr. Hooven, over the last 20 to 30 years, the accepted approach to preventing GBS has been to screen women between the 35th and 37th week of pregnancy. If they carry the bacteria on their skin or in the birth canal, they are given broad-spectrum antibiotics at the time of delivery. “From a public health standpoint, this is an effective way of limiting neonatal risk from group B strep, but there are definitely drawbacks in giving a million courses of antibiotics to women who are delivering babies every year,” he says. “In the last five to 10 years, we've learned an enormous amount about the significance of the microbiome and healthy bacteria, which are important during the neonatal period. These babies whose moms are treated with antibiotics basically have their microbiome wiped out the moment they set foot on the planet.”

Developing a Vaccine

What Dr. Hooven sees as a more targeted way to prevent serious bacterial infections is to develop a vaccine. “In order to develop a vaccine you need to know what target you're going after. So my research, in broad strokes, has been to use next-generation sequencing, bioinformatics, and computational approaches to understand how the bacteria manages to cause these infections, what genes are in the bacterial genome, and what proteins on the bacterial surface are needed for the bacteria to invade a newborn baby and cause these serious infections. I believe a protein product of those genes is likely to be the best target for new vaccine development.”

With funding from a four-year National Institutes of Health grant, Dr. Hooven's research is focusing on genes and gene networks that enable GBS to successfully colonize the maternal reproductive tract and to survive in amniotic fluid and blood during perinatal infection. Using a novel genome-wide screening technique based on next-generation sequencing of transposon-genome junctions from a saturated mutant library (Tn-seq), Dr. Hooven can accurately predict which GBS genes have the protein products necessary for bacterial growth under diverse experimental conditions. He is now using Tn-seq technology – in combination with *ex vivo* and *in vivo* models of colonization and invasion – to pinpoint these surface-localized GBS proteins whose functions are essential for pathogenesis. Once validated by targeted knock-out mouse models and antibody coinoculation experiments, those



Dr. Thomas A. Hooven

proteins identified as essential for pathogenesis will be purified and tested as candidate vaccines to prevent vaginal colonization, ascending chorioamnionitis, and early-onset sepsis in clinically relevant mouse models.

“The Tn-seq technology enables us to look at what GBS does in human blood, in human amniotic fluid, and in models of infection during late pregnancy in mice, and that has given us very large and interesting data sets of potential targets that are likely needed for GBS survival in each of those environments,” says Dr. Hooven. “The blood and amniotic fluid are particularly important models given that they provide environments in which fetal and early neonatal infection thrive.”

“There are still many steps between making a discovery in mice and translating it to the patient setting,” continues Dr. Hooven, “but we think we're on the right path and we are learning a lot about group B strep infection pathogenesis mechanisms as we go. When making small discoveries along the way, we never know which one of those discoveries is going to open up a whole new paradigm.”

While his investigations center on group B strep for now, Dr. Hooven believes that his work is transferable to the study of other organisms and diseases. “In some ways the pendulum is swinging back to an interest in vaccine prevention and development for neonatal protection,” says Dr. Hooven. “When I'm in the NICU, it's about saving one baby at a time. In the lab, I see that effort as amplified across the four million babies born in America each year – and someday all the babies in the world – to try to give them the best start possible and the best hope for a long and healthy life.”

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Predictive Monitoring: Improving Application of Big Data in the NICU *(continued from page 1)*

future, a combination of pulse oximetry with other noninvasive modalities, such as near-infrared spectroscopy, electroencephalography, ultrasound, and/or other imaging into single devices will provide comprehensive information of organ health through multi-modal monitoring.”

Moving Toward Predictive Monitoring

Predictive monitoring is an exciting new field involving analytics of physiological data to detect abnormal patterns associated with critical illness. In 2017, Dr. Sahni collaborated with colleagues at the University of Virginia in a federally funded retrospective study of 1,065 infants to determine how best to use vital signs and other clinical data for preclinical detection of sepsis or necrotizing enterocolitis. “Being able to collaborate with other institutions with the same goal enabled us to pool data equivalent to 131 infant years,” says Dr. Sahni. “One of the aims of our study was to be able to identify early on those infants receiving NICU care who contracted bloodstream infections or necrotizing enterocolitis, which can have catastrophic end results. Every neonatologist would be more than happy to know ahead of time what might be coming.”

The investigators focused on correlating continuous heart rate, breathing, and oxygen saturation data, seeking physiological signatures that could recognize critical illness before it became clinically overt. “We showed that cross-correlation of heart rate and oxygen saturation is altered significantly 24 hours prior to clinical suspicion of sepsis or necrotizing enterocolitis,” says Dr. Sahni. “Thus, the combined cardiorespiratory predictive algorithms may improve monitoring for earlier detection and treatment of potentially catastrophic illness in NICU patients. This growing and exciting science of ‘predictive monitoring,’ driven by the desire to transform the way

waveforms are analyzed, will improve the value of monitoring and thus improve quality and efficiency of care.”

Dr. Sahni and his colleagues have begun to apply this information to the NICU at NewYork-Presbyterian Morgan Stanley Children's Hospital. “We are now looking at various neonatal morbidities, such as retinopathy of prematurity, bronchopulmonary dysplasia, and intraventricular hemorrhage, retrospectively to determine if there were earlier physiological signatures that could predict these long-term problems,” says Dr. Sahni, who believes the answer lies in big data analytics and machine learning, i.e. being able to construct algorithms and make predictions based on data. “At Columbia, because we take care of such sick patients, we have the data to develop these algorithms. We have begun working with the Department of Informatics at Columbia, and our group includes neonatologists, an epidemiologist, a physicist, and a computer engineer. Continuing with our collaborators at University of Virginia, including their mathematicians, we can develop and bring the algorithms to the bedside for improving outcomes of ICU patients through early detection and prompt treatment of acute potentially catastrophic illnesses.”

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