PEDIATRIC REVIEW

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An Update on Early-onset Group B Streptococcal Disease Prevention

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OBJECTIVES

At the end of this activity the participant should be able to:

1. Discuss the incidence and primary risk factors of early-onset Group B streptococcus (GBS) disease
2. Discuss the appropriate intrapartum antibiotic prophylaxis (IAP) for GBS-positive or preterm mothers
3. Describe the clinical presentation, diagnostic evaluation and management for infants at risk for early-onset GBS disease

INTRODUCTION

Group B streptococcus (GBS), an encapsulated gram-positive diplococcus, colonizes the genital and gastrointestinal tract of up to 40% of pregnant women. Despite mostly asymptomatic presence in moms, maternal colonization is a primary risk factor for neonatal sepsis. Vertical transmission to the infant can occur during labor and delivery, leading to early-onset invasive GBS disease. GBS disease has been one of the leading causes of neonatal morbidity and mortality since the 1970s. Routine screening of pregnant women has identified those at risk for transmission. Culture-positive women are 25 times more likely to deliver an infant with early-onset infection than are women with negative cultures. Guidelines for the prevention of perinatal GBS disease have been in place since 1996, with specific Centers for Disease Control and Prevention (CDC) recommendations for intrapartum antibiotic prophylaxis (IAP) for culture-positive women since 2002. This strategy has reduced early-onset GBS disease by an estimated 80%. Despite this, it still remains the leading cause of early-onset neonatal sepsis and meningitis in the United States. Healthcare providers who care for mothers and infants should be aware of the most recent evidence-based guidelines for GBS prevention.

INCIDENCE

The CDC began active surveillance for GBS in 1990. The incidence of early-onset disease (symptoms that present at birth up through the seventh day of life) declined from 1.8 to 0.5 cases per 1000 live births from 1990 through 2000. Since 2000, that rate has further declined to 0.28 cases per 1000 live births (**Fig 1**). There is, however, still a disparity among racial groups, with black neonates (both term and preterm) at greater risk than white neonates (**Fig 2**). The primary risk factors are: delivery at less than 37 weeks gestation, premature rupture of membranes, prolonged rupture of membranes (>18 hours), chorioamnionitis, GBS bacteriuria during current pregnancy, maternal temperature > 38°C or 100.4°F, sustained intrapartum fetal tachycardia, and prior delivery of an infant with GBS disease. Based on these risks, guidelines for IAP have been put forth by the CDC and have helped contribute to the overall decline of early-onset GBS disease.

PRESENTATION

Early-onset disease most frequently manifests as systemic sepsis, but can also present as pneumonia or meningitis. Signs are most often present within the first 24 hours of life. 80 – 85% will present as sepsis without a clear focus. Non-specific signs are irritability, lethargy, respiratory distress, temperature instability, hypotension, and poor perfusion. Laboratory findings concerning for early-onset sepsis are: low total white blood count (WBC < 5000), neutropenia (<1000 granulocytes), or a predominance of immature PMNs relative to total PMNs (ratio of 0.3 or greater). A normal or elevated WBC may also be seen. Thrombocytopenia can occur; however, it does not independently predict early-onset disease.

Late-onset disease also manifests most frequently as sepsis without a focus. However, meningitis occurs more often with late-onset GBS than with early-onset disease (7% vs. 30%). Other focal infections such as osteomyelitis, cellulitis, septic arthritis, or pneumonia are also more common with late-onset disease.

2002 GUIDELINE CHALLENGES

Previous CDC guidelines focused on term infants and missed a prevention opportunity for preterm neonates. Studies showed that 50% of preterm deliveries were screened prior to admission and only 18% were screened once admitted to the hospital if screening had not already taken place. Preterm mothers, therefore, were less likely to receive IAP when indicated. Also, the 2002 guidelines were not as specific with recommendations for Penicillin-allergic women. For those allergic, yet at low risk for anaphylaxis, only 14% were treated with Cefazolin, the recommended alternative agent.

Both the American Academy of Pediatrics (AAP) and the American College of Obstetrics and Gynecology (ACOG) as well as other agencies such as state health departments, microbiologists, and parent organizations reviewed relevant data in early 2009. Evidence-based guideline revisions were published in 2010.

OBSTETRIC PREVENTION STRATEGIES

Universal screening still is recommended for all pregnant women at 35 – 37 weeks gestation. IAP is still recommended for those who are GBS positive, had a previous infant with GBS disease, or have GBS bacteriuria in the current pregnancy. If GBS status is unknown at

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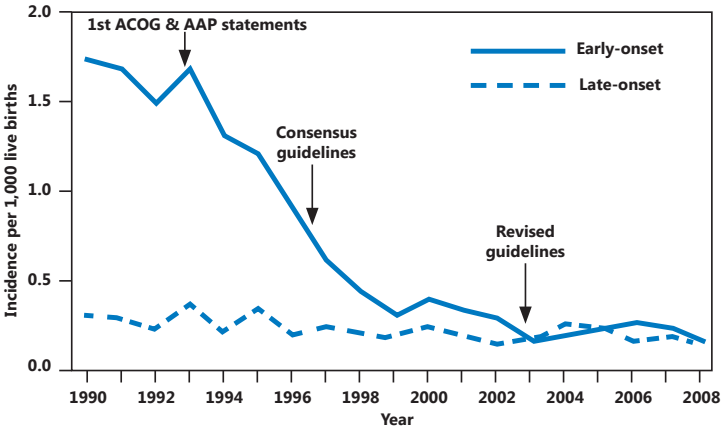

Fig 1. Incidence of early- and late-onset GBS disease

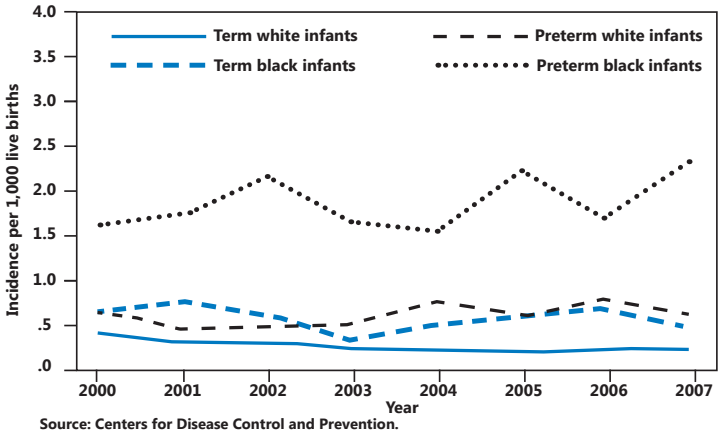

Fig 2. Incidence of early-onset GBS disease, stratified by race and gestational age

time of labor, IAP is recommended with any of the following: delivery < 37 weeks' gestation, rupture of membranes 18 hours or greater, or intrapartum fever of 100.4°F (38°C) or greater. Penicillin remains the preferred agent, and Ampicillin is an acceptable alternative. IAP is not indicated in the following circumstances: GBS colonization in previous pregnancy with negative screen in current pregnancy, GBS bacteriuria in a previous pregnancy, negative GBS vaginal/rectal culture during current pregnancy, or cesarean delivery performed before the onset of labor with intact amniotic membranes.

Important changes to the guidelines include:

1. **An expanded recommendation on laboratory techniques to identify GBS, with the preferred method still being culture.** For example, a nucleic amplification technique may be used if rapid identification is necessary in a mom presenting in preterm labor. Identification may also include chromogenic agars and DNA probes to allow for rapid results. The majority of infants with early-onset GBS are delivered to mothers with false-negative screens. Some false-negative cases are expected as testing is imperfect and timing is not always ideal.
2. **Clarification of the inoculums required for reporting GBS when detected in the urine of pregnant women.** Previously it was GBS in "any concentration." Now it states that growth should be at least 10^4 colony-forming units in urine collections.
3. **Updated algorithms for GBS screening and IAP for women with preterm labor (PTL) and preterm premature rupture of membranes (PPROM).** Women in PTL should receive a GBS culture. If it is felt that mom is entering true labor, IAP should be initiated and continued until delivery or results of culture are known. If not entering true labor, IAP should be discontinued. Culture results are valid for 5 weeks. Another culture is indicated if delivery does not take place during the subsequent 5 week period. Moms who have PPROM should be given IAP if thought to be in true labor until delivery. If not thought to be in true labor, IAP should continue for 48 hours or per protocol until infection excluded. IAP should be resumed if labor ensues either before results are available or if positive. Again, culture should be repeated 5 weeks after initial culture is obtained if delivery still has not taken place.
4. **Clarification of acceptable timing for IAP.** Antibiotic coverage should be initiated at least four hours prior to delivery. Penicillin-G remains the preferable choice for antibiotic coverage. An initial dose of 5 million units IV then 2.5 to 3 million units every 4 hours until delivery should be initiated. Alternatively, Ampicillin 2g IV initially, followed by 1g every 4 hours until delivery is an acceptable option.
    a. GBS remains susceptible to penicillin, ampicillin, and first-generation cephalosporins. Emergence of elevated minimum inhibitory concentrations to penicillin or ampicillin have been seen in 14 noninvasive isolates in Japan and 11 invasive isolates in the US from 1999 – 2005. Clinical significance is unclear however, as isolates were just at the threshold.
5. **Updated IAP regimes for women allergic to penicillin.** Erythromycin is no longer recommended under any circumstance. Cefazolin remains the drug of choice for penicillin allergy without anaphylaxis, angioedema, respiratory distress, or urticaria. Appropriate dosing is 2g initially, followed by 1g every 8 hours IV until delivery. Clindamycin (900mg every 8 hours until delivery) should only be used if sensitivity has been documented. Vancomycin (1g every 12 hours until delivery) should be used only in rare circumstances of serious allergy and a clindamycin-resistant GBS isolate.
    a. From 2001 – 2008, GBS resistance to Erythromycin has increased from 25% to 47.7% and resistance to Clindamycin rose from 11.4% to 24.8%.

Neonatal Prevention Strategies

The revised GBS guidelines via the AAP were designed to broaden the scope to include all neonates, to increase clarity of recommendations, and to decrease unnecessary laboratory evaluations and empirical antibiotics for infants at low risk.

The most sensitive indicator of sepsis is the presence of clinical signs. The presence of clinical signs has a sensitivity of 92% with a 99% negative predictive value. An abnormal CBC with elevated immature-to-total neutrophil ratio has sensitivity of 35% – 45% and 98% negative predictive value. It is for this reason that emphasis has shifted to "signs of neonatal sepsis" regarding evaluation **(Fig 3).**

1. All newborns with signs of sepsis should undergo a full diagnostic evaluation. This includes a CBC with differential, blood culture, a chest radiograph if respiratory symptoms are present, and a lumbar puncture if the patient is stable enough to tolerate the procedure. Sterile blood cultures are reported in 15% – 38% of infants with early-onset meningitis. However, if the provider feels the infant's signs are a result of a non-infectious condition (such as transient tachypnea) AND there are no maternal risk factors for sepsis in an otherwise well-appearing infant, the lumbar puncture can be deferred.
    a. Empirical antibiotic coverage remains Ampicillin plus Gentamicin and should be initiated promptly. Alternatively, Ampicillin and a third-generation Cephalosporin may be used based on local sensitivities.

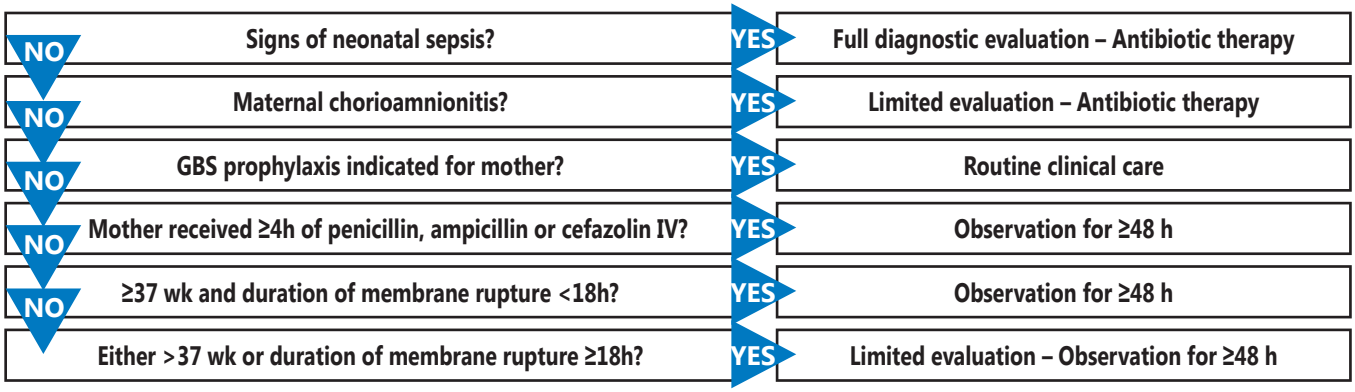

Fig 3. Algorithm for secondary prevention of early-onset GBS disease in the newborn.

2. Chorioamnionitis continues to be a significant risk factor for early-onset GBS sepsis in infants born to GBS-colonized women. All well-appearing newborns born to women with a diagnosis of chorioamnionitis should undergo a limited evaluation (CBC, blood culture) and should be started on empiric antibiotics.
   a. Delaying CBC until 6 – 12 hours of life improves its sensitivity.
   b. Empirical therapy should be discontinued as soon as clinical course and laboratory evaluation exclude sepsis, which differs from the previous complete seven-day antibiotic course.
3. In well-appearing newborns born to women without an indication for IAP, routine care is indicated unless signs of sepsis appear.
4. In well-appearing term infants born to mothers with an indication for IAP, emphasis is placed on observation without laboratory evaluation.
   a. If mom received appropriate IAP (Penicillin, Ampicillin, Cefazolin for at least 4 hours before delivery), newborn infants require only routine care and 48 hours of observation. Full term infants may be discharged as early as 24 hours if there is ready access to medical care and follow-up scheduled to take place within 48 – 72 hours.
   b. If mom received no IAP or inappropriate coverage (Vancomycin, Clindamycin, or Erythromycin) AND membranes were ruptured less than 18 hours, the infant should be observed for 48 hours with routine care.
   c. If mom received no or inappropriate IAP coverage and membranes were ruptured greater than 18 hours, a limited evaluation is recommended. This includes a CBC and blood culture. Infants should be observed in the hospital for at least 48 hours.
5. In well-appearing pre-term infants born to moms who received inadequate or no IAP, the neonate should undergo a limited evaluation and observation for at least 48 hours.

Conclusion

The 2010 GBS prevention guidelines continue to focus on universal screening of pregnant women and appropriate IAP for GBS-colonized women. The recommendations also include specific strategies for IAP for preterm delivery and premature rupture of membranes as well as antibiotic choice for penicillin-allergic women. Furthermore, the guidelines revised the neonatal algorithm to include all newborns. It emphasizes the infant's clinical presentation and close observation rather than laboratory tests and empirical antibiotics for low-risk newborns.

References

1) Centers for Disease Control and Prevention. Prevention of Perinatal Group B Streptococcal Disease. MMWR 2010;59 (RR-10):1-36.
2) Centers for Disease Control and Prevention. Trends in perinatal group B streptococcal disease—United States, 2000 – 2006. MMWR 2009;58:109-12.
3) Committee on Infectious Diseases and Committee on Fetus and Newborn. Policy Statement—Recommendations for the Prevention of Perinatal Group B Streptococcal (GBS) Disease. Pediatrics 2011;128:611–616.

CHILDREN'S HOSPITAL

DOCTORS' NOTES

Promoting Children's Hospital's medical advancements & achievements

Amanda G. Brown, MD, pediatric rheumatologist at Children's Hospital and assistant professor of rheumatology at LSUHSC, has been appointed to a three-year term on the American Academy of Pediatrics' PREP Editorial Board.

Anita Jeyakumar, MD, FACS, otolaryngologist at Children's Hospital and assistant professor of otolaryngology at LSU Health Sciences Center, had a presentation, The New Age of Hemangiomas, accepted to The Combined Otolaryngology Spring Meetings (COSM) in San Diego. Dr. Jeyakumar also had an article, Pediatric Enuresis, Sleep Apnea, and Adenotonsillectomy, accepted to Laryngoscope Journal. She also conducted a peer review on sensorineural hearing loss for the Journal of Otology & Neurotology's Encyclopedia of Otolaryngology.

Lawrence Simon, MD, otolaryngologist at Children's Hospital, has been elected to the board of governors, and also as vice president of the Young Physician Section of the Louisiana Medical Society.

Speech, Language and Audiology

The Speech, Language, and Audiology Department at Children's Hospital provides evaluation, management and consultation for patients from birth to 21 years of age.

Speech Pathology

Speech Pathology services include complete assessment and treatment as needed for the following areas/disorders:

- Dysphagia (Swallowing Disorders) and/or Feeding Difficulties: includes Modified Barium Swallow Study (MBSS), Clinical Feeding/Swallowing Evaluation, and Nippling Therapy.
- Oral Motor Deficits: includes assessment and treatment for weak or uncoordinated mouth muscles.

Speech Deficits:

- Articulation includes omissions, distortions, or substitutions of speech sounds
- Fluency of speech includes stuttering and/or increased rate
- Voice includes pitch, intensity, quality and resonance
- Motor speech disorders includes apraxia (difficulty sequencing speech sounds) and dysarthria (slurred, slowed speech)
- Language Delays/Disorders includes expressive and receptive language skills as well as Aphasia (language loss relating to brain injury)
- Cognitive/linguistic functioning includes problem-solving, memory, abstract reasoning
- Augmentative Communication includes an alternative form of communication (i.e. picture boards, electronic devices, etc).
- Tracheostomy

The speech-language pathologists collaborate with various departments and clinics, including Cleft Lip and Palate/Craniofacial Clinic, Down Syndrome Clinic, Ear, Nose, and Throat Clinics, Cochlear Implant Program, Psychology, Physical Therapy, Occupational Therapy, Music and Recreation Therapy, Radiology, and Rehabilitation Center.

The speech pathologists provide services to inpatients and outpatients. Our department may accept referrals from schools, physicians, other professionals and families. A physician referral/consult is required for all inpatients and patients with voice disorders and swallowing disorders.

Audiology

We provide comprehensive diagnostic hearing evaluations for patients from birth to 21 years of age and all developmental levels.

Risk factors for hearing loss include hospitalization in a neonatal intensive care unit (NICU), family history of hearing loss, meningitis or other illness with a sustained high fever, ear infections, chronic upper respiratory infections, ototoxicity, and speech and language delays.

Tests provided by the audiologist may include one or more of the following:

- Brainstem Auditory Evoked Response (BAER) testing with or without sedation
- Auditory Steady State Response (ASSR) with or without sedation
- Oto-Acoustic Emissions (OAE)
- Tympanometry Testing: both high and low frequency testing is available.
- Behavioral Observation Audiometry
- Visual Reinforcement Audiometry
- Pure Tone Audiometry
- Acoustic Reflexes
- Acoustic Reflex Decay
- Central Auditory Processing (CAP) Testing

Additional services provided include hearing aid evaluations and fittings. Medical clearance for amplification by the patient's physician is required.

The audiologists collaborate with various Children's Hospital of New Orleans departments and clinics, including Cleft Lip and Palate/Craniofacial Clinic, Down Syndrome Clinic, Ear, Nose, and Throat Clinics, Cochlear Implant Program, Psychology, Neonatal Intensive Care Unit (NICU), and Rehabilitation Center.

The audiologists provide services to inpatients and outpatients. Generally, a referral from the child's physician, teacher or parent for evaluation is accepted. A physician referral is required for all inpatients.

Cochlear Implant Center

The Cochlear Implant Center is a collaborative service between Children's Hospital and the LSU Department of Otolaryngology. The center works closely with a variety of resources to aid in providing services to children receiving cochlear implants.

A multidisciplinary team of otolaryngologists, audiologists, and speech-language pathologists will work together to assess a child's need for a cochlear implant and will help the child adjust to the cochlear implant following surgery. Cochlear implantation is a surgical intervention which is highly successful in restoring hearing, permitting mainstream education and full participation in academic, linguistic, social and economic advantages available to normal hearing children. A cochlear implant has two basic components: a surgically-placed internal implanted portion and an external component. While cochlear implants first became available in the mid-1980s, they have become an accepted standard of care for children who have severe to profound hearing loss.

For more information or to schedule an appointment, please call **(504)896-9551.**

Children's Hospital Specialty Clinics & Therapies

CLINICS IN NEW ORLEANS, METAIRIE, BATON ROUGE AND LAFAYETTE

Allergy/Immunology
Dimitriades, Victoria [M, BR] ..... (504) 896-9589
Ochoa, Augusto [M, L] ..... (504) 896-9589
Paris, Ken [M, L] ..... (504) 896-9589
Sorensen, Ricardo [M] ..... (504) 896-9589

Amputee Clinic
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Cardiology
Ascuitto, Robert [BR] ..... (504) 896-9751
Gajewski, Kelly ..... (504) 896-9751
Lilje, Christian ..... (504) 896-9751
Ross-Ascuitto, Nancy [BR] ..... (504) 896-9751
Sernich, Steffan ..... (504) 896-9751
Siwik, Ernest ..... (504) 896-9571
Stopa, Aluizio ..... (504) 896-9571

Cardiothoracic Surgery
Caspi, Joseph ..... (504) 896-3928
Dorotan, Jaime ..... (504) 896-3928
Pettitt, Timothy ..... (504) 896-3928

Children at Risk Evaluation (CARE) Center
Jackson, Jamie ..... (504) 896-9237
Wetsman, Ellie [BR] ..... (504) 896-9237

Cleft/Craniofacial
McBride, Lori ..... (504) 896-9568
Moses, Michael ..... (504) 896-9857
St. Hilaire, Hugo ..... (504) 896-9857

Clinical Trials ..... (504) 894-5377

Cochlear Implants
Arriaga, Moises ..... (504) 896-2141
Marks, Herbert ..... (504) 896-2141

Craniofacial/Genetics
Lacassie, Yves [M] ..... (504) 896-9857
Marble, Michael ..... (504) 896-9857
Zambrano, Regina ..... (504) 896-9857

Cystic Fibrosis
Levine, Stephen ..... (504) 896-9436
Pepiak, Derek ..... (504) 896-9436

Dental
Mobile Dental Program 34-BRUSH
Ritwik, Priyanshi ..... (504) 896-9580

Dermatology
Poole, Jeffrey ..... (504) 896-2888

Developmental/High Risk
Wong, Joaquin ..... (504) 896-9458

Diabetes
Chalew, Stuart ..... (504) 896-9441
Gomez, Ricardo ..... (504) 896-9441
Stender, Sara ..... (504) 896-9441
Vargas, Alfonso ..... (504) 896-9441

Down Syndrome
Lacassie, Yves [M] ..... (504) 896-9254
Marble, Michael ..... (504) 896-9254
Zambrano, Regina ..... (504) 896-9572

Endocrinology
Chalew, Stuart ..... (504) 896-2888
Gomez, Ricardo [M, BR] ..... (504) 896-2888
Stender, Sara ..... (504) 896-2888
Vargas, Alonso [M, BR] ..... (504) 896-2888

Epilepsy Surgery
McGuire, Shannon ..... (504) 896-9458

Feeding Clinic
Hyman, Paul ..... (504) 896-9534

Gastroenterology
Brown, Raynorda [M, BR] ..... (504) 896-2888
Hyman, Paul ..... (504) 896-2888
Keith, Brent ..... (504) 896-2888
Monagas, Javier [M] ..... (504) 896-2888
Noel, Adam [M] ..... (504) 896-2888
Rosenberg, Allan [M, BR] ..... (504) 896-2888

Genetics
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Marble, Michael [BR, L] ..... (504) 896-9572
Zambrano, Regina [M, BR] ..... (504) 896-9572

Gynecology
Wells, Lindsay ..... (504) 896-2888

Hematology/Oncology
Gardner, Renee ..... (504) 896-9740
Morales, Jaime [BR, L] ..... (504) 896-9740
Morrison, Cori ..... (504) 896-9740
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Hemophilia Clinic ..... (504) 896-9740

HIV Clinic/FACES
Wilcox, Ronald ..... (504) 896-9583

Hospitalists
Referrals ..... (504) 896-3924
English, Robin ..... (504) 896-3924
Hauser, Andrea ..... (504) 896-3924
Hescock, Jay ..... (504) 896-3924
Roy, Melissa ..... (504) 896-3924
Sulton-Villavasso, Carmen ..... (504) 896-3924

Infectious Disease
Bégué, Rodolfo ..... (504) 896-9583
Seybolt, Lorna ..... (504) 896-9583
Wilcox, Ronald ..... (504) 896-9583

International Adoption Clinic
Bégué, Rodolfo ..... (504) 896-9583

Kidney Transplant
Buell, Joseph ..... (504) 896-9238
Killackey, Mary ..... (504) 896-9238
Paramesh, Anil ..... (504) 896-9238
Slakey, Douglas ..... (504) 896-9238

Kidney Transplant Clinic
Vehaskari, Matti ..... (504) 896-9238

Metabolic
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Muscular Dystrophy
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Weimer, Maria ..... (504) 896-9283
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Weimer, Maria ..... (504) 896-2888
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Weimer, Maria ..... (504) 896-9859
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Vives, Tere [M] ..... (504) 896-2134

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Heinrich, Stephen ..... (504) 896-9569
King, Andrew ..... (504) 896-9569
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Patel, Prerana ..... (504) 896-9569
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Otolaryngology (ENT)
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Hagmann, Michael [M] ..... (504) 896-2888
Jeyakumar, Anita ..... (504) 896-2888
Kluka, Evelyn [M] ..... (504) 896-9532
Marks, Herbert ..... (504) 896-9572
Simon, Lawrence [BR] ..... (504) 896-2888

Physical Therapy ..... (504) 896-9557

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Kamps, Jodi ..... (504) 896-7272

Pulmonology
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Pepiak, Derek ..... (504) 896-9438

Rheumatology
Brown, Amanda [BR, L] ..... (504) 896-9385
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Scoliosis/Pediatric Spine
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Gonzales, Tony [BR, L] ..... (504) 896-9569
King, Andrew ..... (504) 896-9569
Patel, Prerana ..... (504) 896-9569

Spasticity
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Tilton, Ann ..... (504) 896-9283
Wong, Joaquin ..... (504) 896-9283

Speech & Hearing (504) 896-9551

Surgery
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Valerie, Evans ..... (504) 896-9756

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Seybolt, Lorna ..... (504) 896-9583
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Ortenberg, Joseph [BR, L] ..... (504) 896-2888
Roth, Christopher ..... (504) 896-2888

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Poole, Jeffrey ..... (504) 896-2838
Simon, Lawrence ..... (504) 896-2838

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CHILDREN'S HOSPITAL

200 Henry Clay Avenue
New Orleans, LA 70118
(504) 899-9511
www.chnola.org

In addition to Children's Hospital Main Campus, some physicians also hold clinics at other centers.

Children's Hospital	**(504) 899-9511**
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Please record your responses to the questions on the form below. Please circle the best possible answer. CME offer is good through May 2012.

1. All of the following pregnant mothers should receive IAP except:
   a. 40 weeks gestational age (WGA) mother with ROM 8 hours and positive GBS culture at 36 WGA
   b. 36 WGA mother with ROM 3 hours and unknown GBS
   c. 38 WGA mother with negative GBS culture and history of previous infant with GBS meningitis
   d. 40 WGA mother with positive GBS culture admitted for scheduled repeat C-section without onset of labor and intact amniotic membranes

2. According to the 2010 guidelines, all of the following antibiotics are considered appropriate IAP except:
   a. Penicillin
   b. Ampicillin
   c. Cefazolin
   d. Vancomycin

3. A healthy appearing 40 WGA infant is born to a GBS positive mother who received three doses of Ampicillin prior to delivery. The mother does not have a history of chorioamnionitis. Of the following, what are the most appropriate evaluation and treatment for this infant?
   a. Clinical observation only
   b. Limited diagnostic evaluation and clinical observation
   c. Limited diagnostic evaluation and empiric antibiotic therapy
   d. Full diagnostic evaluation and empiric antibiotic therapy

4. A healthy appearing 38 WGA infant is born to a GBS positive mother with rupture of membranes 22 hours prior to delivery. The mother received two doses of Clindamycin prior to delivery and did not have a history of chorioamnionitis. Of the following, what are the most appropriate evaluation and treatment for this infant?
   a. Clinical observation only
   b. Limited diagnostic evaluation and clinical observation
   c. Limited diagnostic evaluation and empiric antibiotic therapy
   d. Full diagnostic evaluation and empiric antibiotic therapy

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