



## eNeonatal Review

### Welcome to our third year of eNeonatal Review!

We're looking forward to bringing you another year of the latest research, best practices, issues currently under debate and concise, thoughtful reviews of relevant journal literature.

We're excited to announce that each issue of eNeonatal Review will now carry 1.0 CME/CE credits with a maximum of 12 credits a year for Physicians and Nurses. We are also developing a resource that will help our Respiratory Therapist participants determine how to satisfy their CE requirements using AMA PRA category 1 credits.

This promises to be our most engaging year yet, with new features and a new look to be unveiled in our October issue.

We thank you for your continuing participation and support.

### In this issue... Volume 3, Number 1

Spontaneous intestinal perforations (SIP) is a disease that predominantly affects our smallest and most vulnerable patients during their first two weeks of life. While dozens of important papers have been published on this topic over past half decade, the overall data may be narrowed down to a few well-repeated themes that highlight the essentials of understanding this condition.

In this issue, we review research designed to assist neonatologists in placing SIP within the bigger picture of neonatology by focusing on the differential diagnosis, risk factors, and ethical challenges associated with this disease.

#### → Commentary

Our guest editor opinion

#### → Differentiating SIP from NEC using clinical criteria

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### ▶ Recommend to a Colleague

### ▶ Post-test

### Learning Objectives

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CE activity.

#### At the conclusion of this activity, participants should be able to:

- Differentiate spontaneous intestinal perforation from necrotizing enterocolitis.
- Summarize the known risk factors for spontaneous intestinal perforations.
- Discuss the current research regarding harmful drug synergism in neonatal care.

### Program Information

#### CE Info

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→ **Glucocorticoids as an independent risk factor for SIP**

→ **Glucocorticoids + indomethacin: synergistic risk factors for SIP?**

→ **Managing SIP**

#### LENGTH OF ACTIVITY

1.0 hours

#### EXPIRATION DATE

September 15, 2007

#### NEXT ISSUE

October 15, 2005

#### Guest Editor of the Month



Reviews & Commentary  
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#### Guest Faculty Disclosure

**Phillip V. Gordon MD, PhD**

Faculty Disclosure: No relationship with commercial supporters.

#### Unlabelled/Unapproved Uses:

No faculty member has indicated that their presentation will include information on off label products.

## COMMENTARY

In 1963, when Patrick Bouvier Kennedy died of respiratory distress syndrome, his parents' anguish and the western world's purse spurred scientists on a 30 year quest to investigate and utilize surfactants. Respiratory distress syndrome (or the chronic lung disease that followed) was the primary cause of death in premature infants. Most neonatal scientists predicted that premature infants would be saved by surfactant. They were right; however, once opened, Pandora's Box could not be closed. With each passing year, as surfactant was administered to infants previously thought to be non-viable, the age of gestational viability was pushed farther and farther back. The result was an expanding population of extremely premature infants exhibiting a new form of chronic lung disease.

With no randomized trials to determine the best adjunct therapies, supportive treatments were simply extrapolated from one gestational age to the next. Practitioners, therefore, were soon administering steroids, COX inhibitors, and methyl xanthines to 2<sup>nd</sup> trimester fetuses *ex utero*. In an attempt to establish more effective protocols, researchers began to perform randomized trials that enrolled extremely low birth weight (ELBW) infants. Many of these earliest studies investigated early postnatal steroids as a means of preventing chronic lung disease. By 1997, three large and highly similar multi-center randomized trials were underway to definitively test the efficacy of dexamethasone prophylaxis.

The following year, I was trying to publish a cohort study demonstrating a relationship between early postnatal dexamethasone and this emerging disease known as spontaneous intestinal perforation (SIP).<sup>1</sup> There was little interest initially; however, after the dosage in Jay Garland's dexamethasone trial was reduced at the interim analysis because of the same findings<sup>2</sup>, the study was published. In my manuscript, I also noted a further increase in SIP incidence when infants received both dexamethasone and indomethacin together, and was the first to speculate that the two drugs might cause synergistic harm. Since that time, many steroid trials have been stopped or modified because of this apparent synergistic effect, and the relationship between indomethacin, steroids, and SIP has

become well recognized.

It was the stopping of Anne Stark's 2001 NICHD<sup>3</sup> and Kristi Watterberg's 2004 PROPHET<sup>4</sup> trials that essentially proved the harmful synergy between indomethacin and glucocorticoids. Moreover, Watterberg's meticulous analysis indicated that even high endogenous cortisol levels are sufficient to place indomethacin-exposed ELBW infants at risk for perforation. Together, these trials also revealed that SIP is multi-factorial in its origins. Like the new chronic lung disease, we've learned that SIP stretches beyond the common variable of prematurity to other acquired risk factors. These untoward influences warrant further study if we are to reduce the morbidity of extreme prematurity. Until such data are available, it is our eyes (looking for blue bellies, free air, and gasless abdomens) and our clinical acumen that we must depend on for diagnosis and development of the best individualized early postnatal management strategies.

1. **Gordon P, Rutledge J, Sawin R, Thomas S, Woodrum D.** [Early postnatal dexamethasone increases the risk of focal small bowel perforation in extremely low birth weight infants.](#) *J Perinatol.* 1999 Dec;19(8 Pt 1):573-7.
2. **Garland JS, Alex CP, Pauly TH, Whitehead VL, Brand J, Winston JF, Samuels DP, McAuliffe TL.** [A three-day course of dexamethasone therapy to prevent chronic lung disease in ventilated neonates: a randomized trial.](#) *Pediatrics* 1999;104(1 Pt 1):91-9.
3. **Stark AR, Carlo WA, Tyson JE, Papile LA, Wright LL, Shankaran S, Donovan EF, Oh W, Bauer CR, Saha S, Poole WK, Stoll BJ.** [Adverse effects of early dexamethasone in extremely-low-birth-weight infants.](#) National Institute of Child Health and Human Development Neonatal Research Network. *New England Journal of Medicine* 2001 Jan 11;344(2):95-101
4. **Watterberg KL, Gerdes JS, Cole CH, Aucott SW, Thilo EH, Mammel MC, Couser RJ, Garland JS, Rozycki HJ, Leach CL, Backstrom C, Shaffer ML.** [Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial.](#) *Pediatrics.* 2004;114(6):1649-57.

## Differentiating SIP from NEC using clinical criteria

**Pumberger W, Mayr M, Kohlhauser C, Weninger M.**  
*Spontaneous localized intestinal perforation in very-low-birth-weight infants: a distinct clinical entity different from necrotizing enterocolitis.*

*J Am Coll Surg.* 2002 Dec;195(6):796-803.

*(For non-journal subscribers, an additional fee may apply for full text articles)*



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**Okuyama H, Kubota A, Oue T, Kuroda S, Ikegami R, Kamiyama M.**

*A comparison of the clinical presentation and outcome of focal intestinal perforation and necrotizing enterocolitis in very-low-birth-weight neonates.*

*Pediatr Surg Int.* 2002 Dec;18(8):704-6.

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### **Reviewing two recent and representative case series help define the differential diagnosis.**

Both the Pumberger and Okuyama studies report on dozens of sequentially acquired cases of surgical necrotizing enterocolitis (NEC) and SIP, and then retrospectively compare their clinical presentation characteristics and outcomes. Of greatest value to the neonatal clinician is that these data translate immediately to the bedside.

Both trials defined SIP as perforation without pneumatosis on x-ray and without necrosis at

the time of surgery, and their findings are remarkably similar despite the studies being undertaken on opposite ends of the globe (Austria versus Japan). Both studies found that infants with SIP are of lower birth weight and gestation than those with NEC, with SIP generally affecting infants less than 1000 grams and below 26 weeks gestation. Likewise, both papers report that the timing of diagnosis was different for each disease, with SIP occurring earlier (generally around the 7<sup>th</sup> day of life) and NEC occurring later. In general, the evidence within the literature on this subject as a whole indicates that the timing of NEC seems to be center-dependent and probably correlates with variances in feeding protocols. Both studies also found markedly improved survival with SIP when compared to NEC.

While neither of these articles represents the best histopathologic comparisons or the largest cohort study of SIP, they are two of the most recent and best done comparisons of NEC versus SIP, and are representative of a growing body of literature that details both the clinical and pathologic differences between the two conditions. Further, they help define the differential diagnosis: that SIP occurs independent of feeding status and enteric colonization, occurs early in life (most cases occur within the first 14 days), predominately affects infants weighing less than 1000 grams, and is rarely (almost never) associated with pneumatosis or bowel necrosis.

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## Glucocorticoids as an independent risk factor for SIP

Gordon PV, Young ML, Marshall DD.

***Focal small bowel perforation: an adverse effect of early postnatal dexamethasone therapy in extremely low birth weight infants.***

J Perinatol. 2001 Apr-May;21(3):156-60

(For non-journal subscribers, an additional fee may apply for full text article)



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Halliday HL, Ehrenkranz RA, Doyle LW.

***Early postnatal (<96 hours) corticosteroids for preventing chronic lung disease in preterm infants.***

Cochrane Database Syst Rev. 2003;(1):CD001146

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### **Key data from meta-analyses examining steroid use in neonates**

Because results between insufficiently powered trials were conflicting, in 2001 my colleagues and I performed a meta-analysis seeking to determine, via a sufficiently powered cohort, if dexamethasone was significantly associated with SIP in randomized trials. Our focus was on the ELBW infant receiving early postnatal dexamethasone, and as such studied an extremely homogeneous pooled cohort consisting of 1382 infants. In contrast, Halliday's 2003 meta-analysis sought to determine if early postnatal corticosteroids of any type improved chronic lung disease. This meta-analysis included any randomized control trial enrolling preterm infants of any size and preterm gestational age that received steroids of any type within the first 96 hours of life; this patient pool consisted of 3072 infants who were then further stratified in sub-analyses that included SIP as a secondary outcome.

Both analyses found that early postnatal glucocorticoids were associated with an increased risk of SIP in ELBW infants. In our study, the best estimate of the number needed to harm by early postnatal dexamethasone was 19 patients treated. This value was not calculated by Halliday et al. for any early glucocorticoid exposure. Of interest, in our analysis dexamethasone was not associated with a significant improvement in chronic lung disease; the Halliday trial, however, did find a significant improvement in chronic lung disease with early steroids. The effect was small and so our cohort may have been under-powered or, more likely, because Halliday's cohort included older and larger infants, there may be a more positive effect of an early pulse of steroids on older gestation lungs. Halliday also

found adverse neurodevelopmental effects to be associated with dexamethasone exposure and thus could not recommend early use due to neurodevelopmental and intestinal complications.

The data from both these studies provides further evidence that early postnatal glucocorticoid exposure significantly increases the risk of SIP in infants weighing less than 1000 grams — and provides another reason why this therapy should not be used electively in this patient population.

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## Glucocorticoids + indomethacin: synergistic risk factors for SIP?

Stark AR, Carlo WA, Tyson JE, Papile LA, Wright LL, Shankaran S, Donovan EF, Oh W, Bauer CR, Saha S, Poole WK, Stoll BJ.

***Adverse effects of early dexamethasone in extremely-low-birth-weight infants.***

National Institute of Child Health and Human Development Neonatal Research Network. N Engl J Med. 2001 Jan 11;344(2):95-101

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Watterberg KL, Gerdes JS, Cole CH, Aucott SW, Thilo EH, Mammel MC, Couser RJ, Garland JS, Rozycki HJ, Leach CL, Backstrom C, Shaffer ML.

***Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial.***

Pediatrics. 2004 Dec;114(6):1649-57

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### ***Two randomized trials provide substantial evidence of harmful synergism between glucocorticoids and indomethacin when given in the first days of life.***

In 2001, Stark et al. first reported a causal effect of early dexamethasone on SIP in ELBW infants that was significantly increased by combination treatment with prophylactic indomethacin treatment for closure of the ductus arteriosus. In 2004, Watterberg et al. performed a gentler version of this trial by using hydrocortisone as a prophylaxis for presumed cortisol deficiency of prematurity in EBLW infants. The authors found a significant steroid effect, and that the incidence of SIP was also significantly increased in combination with early indomethacin exposure. Calculating the odds ratios for SIP in both trials for exposure to indomethacin and steroids combined (measuring infants exposed to the combination versus all others), the values are 5 and 6 respectively. Those are remarkably congruent values, and the two trials together provide fairly substantial evidence that there is a harmful synergism between these two drugs during the early postnatal period. Watterberg took the data one step further by also measuring endogenous cortisol values and found that even when SIP occurred in placebo patients, it was in patients with high endogenous cortisol levels.

The challenge with this data is in knowing what to do with it at the bedside. While discontinuing the use of early postnatal steroid exposure should be fairly obvious, it is not always that simple. Some ELBW infants are adrenally insufficient and others (as Watterberg showed) are replete and capable of generating enough cortisol to place themselves at risk when given indomethacin prophylaxis for ductal closure. That is the crux of the problem: all ELBW infants are not the same when it comes to the adrenal axis. One strategy that seems to be gaining currency in some of the nation's academic NICUs is to check cortisol levels on ELBW infants shortly after birth. In some cases, cortisol supplementation is unavoidable; however, indomethacin prophylaxis should be delayed or even aborted in infants who are so sick that they require hydrocortisone. In other cases cortisol levels will be markedly elevated due to the combination of stress and precocious adrenal competency — here similar abstinences should be considered. Finally, many infants will be in the

normal range, and proceeding with indomethacin prophylaxis might be considered to be an act with more benefit than risk in these particular patients.

The other variable that is implicit in both these papers is timing. With both steroids and indomethacin, the window of exposure occurs within the first 2-3 days of life, while the time of diagnosis for SIP is most frequently between days 7-10. The literature has been very consistent in reporting that it is early exposure to steroids and indomethacin that is associated with SIP; however, there is little or no evidence to suggest that later exposure to indomethacin carries the same risk. One hypothesis is that there may be a critical window during which the fetal intestine transitions into neonatal intestine. After that period the ELBW infant's vulnerability to SIP may be decreased, and so delaying indomethacin exposure to a later time of life may be another reasonable strategy for reducing the incidence of SIP.

Unfortunately, there is no way to know how long to delay to optimize safety — a few days? a week? ten days with serial ultrasounds to let as many PDAs close as possible? In the absence of more definitive data, these decisions must be the purview of the astute clinician, perhaps shared through informed consent with parents.

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## MANAGING SIP

Blakely ML, Lally KP, McDonald S, Brown RL, Barnhart DC, Ricketts RR, Thompson WR, Scherer LR, Klein MD, Letton RW, Chwals WJ, Touloukian RJ, Kurkchubasche AG, Skinner MA, Moss RL, Hilfiker ML.

*Postoperative outcomes of extremely low birth-weight infants with necrotizing enterocolitis or isolated intestinal perforation: a prospective cohort study by the NICHD Neonatal Research Network.*

Ann Surg. 2005 Jun;241(6):984-9

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### **Comparing surgical management strategies.**

There is considerable debate on the most effective initial management of SIP: whether immediate laparotomy or abdominal drainage is preferable. Practitioners in favor of drainage argue that it is less stressful on the infant during placement, less stressful on limited surgical resources, and results in comparable outcomes. Those in favor of laparotomy claim immediate and definite cure, improved evacuation of succus from the peritoneum, and faster recovery of intestinal function.

The study by Blakely et al is the first to prospectively compare these two surgical management strategies. However, the trial was less than ideal in that a) it was not randomized, and b) suffers by studying both NEC with perforation and SIP simultaneously. Therefore, it is under-powered to detect significant differences for each disease individually and instead compares the two management techniques within a combined cohort of NEC and SIP. In part, this was because the authors wanted to make sure that they could correctly diagnose each disease in a multicenter trial - while overall their diagnoses were accurate 95% of the time, they were less adept at diagnosing SIP (83% correct by surgical confirmation). In this first report focusing on surgical outcomes (a neurodevelopmental outcomes follow-up is currently being completed), the authors found no differences in mortality between the two techniques.

Examining the specific SIP mortality data, two findings become obvious. This first is that death from SIP was significantly reduced when compared to that of NEC. The second is that the incidence of death from SIP was twice as high in those treated with abdominal drain as those treated with initial laparotomy (45% versus 22%). This latter finding was not significant despite the impressive trend (the relative risk for death with SIP for laparotomy versus drain was 0.49 with a 95% confidence interval of 0.19 -1.2), confirming that the SIP

cohort sample size was not sufficient.

The data from this trial, unfortunately, cannot provide definitive conclusions with regard to the best surgical management of SIP; however, there are two randomized controlled trials currently underway to further address this issue. In the interim, the bedside clinician and surgeon are left with the conundrum of what to do with a 450 gram infant who acquires SIP. The answer — at least for now — lies in the skill of the surgeon's hands and the competency of the caregivers who will be providing postoperative support. As always, frank discussions with parents provide opportunities to seek direction when we must make decisions without adequate data.

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#### **Nurses**

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#### **Credit Designations · [back to top](#)** **Physicians**

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#### **Nurses**

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#### **Respiratory Therapists**

Contact your state licensing board to confirm that AMA PRA category 1 credits are accepted toward fulfillment of RT requirements.

#### **Target Audience · [back to top](#)**

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#### **Learning Objectives · [back to top](#)**

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- Discuss the current research regarding harmful drug synergism in neonatal care.

#### **Faculty Disclosure Policy Affecting CE Activities · [back to top](#)**

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presentation. The presenting faculty reported the following:

- Dr. Nogee has indicated a financial relationship of grant/research support with Forest Laboratories and has received an honorarium from Forest Laboratories.
- Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/material support from Nature Publishing Group as the Editor of the Journal of Perinatology.

All other faculty have indicated that they have not received financial support for consultation, research, or evaluation, nor have financial interests relevant to this e-Newsletter.

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