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Procalcitonin and Vesicoureteral Reflux in Children With Urinary Tract Infection

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In Reply.—

The comment by Zanardo et al is appreciated. Leukemoid reaction (LR) was observed in 26 extremely low birth weight (ELBW) infants in our study with an overall incidence of 17%, which is consistent with the incidence of 1.3% to 15% published in the recent studies of LR in term and preterm infants.^{1–3} We agree that there are multiple conditions known to present an excess of proinflammatory cytokines and are worth clarifying. In our study, we reported that there was no predictable relationship between these various perinatal and neonatal clinical characteristics such as sepsis, exposure to antenatal and postnatal steroids, or clinical chorioamnionitis and development of LR in ELBW infants.¹

The presence of histologic chorioamnionitis (HCA) is a very important prenatal condition that may affect the incidence or severity of LR in ELBW infants. We agree that exposure to prenatal inflammation, indicated as histologically diagnosed chorioamnionitis, may be associated with an increased incidence of LR and that patients with LR may exhibit a prenatal systemic inflammatory response.

Zanardo et al in their comment stated that “[o]f 61 preterm neonates with HCA, 8 (13%) developed LR, whereas 4 of 162 (2%) preterm infants without HCA developed LR.”

In our study, LR was detected in a significantly higher percentage of infants with HCA compared with the infants without HCA (30% [14 of 42] vs 11% [12 of 110]; $P < .001$). The percentage of infants with HCA was higher in our study (30%) compared with the percentage reported by Zanardo et al (13%). The infants in our study were ELBW with a gestational age of <30 weeks and birth weight of <1000 g, whereas the infants reported by Zanardo et al were premature infants with a gestational age of <32 weeks. Furthermore, we examined the postnatal age when the LR was detected in these ELBW infants. It was interesting to find out that the majority of LR was late onset and occurred after the first 7 days of life (17 of 26 [65%]), whereas early-onset LR (during the first 7 days of life) was detected in 35% of the infants with an LR (9 of 26). Of these 17 infants with late-onset LR, HCA was detected in 41% (7 of 17). The onset of early-onset compared with late-onset LR was at a significantly earlier postnatal age (4 ± 2 vs 18 ± 8 days; $P < .001$). The duration of LR was significantly longer (5 ± 4 vs 2 ± 3 days; $P < .007$), and the peak absolute neutrophil counts were significantly higher in early-onset LR (52 ± 23 vs $38 \pm 9 \times 10^3/\text{mm}^3$; $P < .03$). There was no difference between early-onset and late-onset LR infants in gestational age (26 ± 1 vs 25 ± 2 weeks), birth weight (797 ± 173 vs 730 ± 126 g), incidence of respiratory distress syndrome (78% vs 100%), ventilation days (30 ± 16 vs 40 ± 19 days), or the incidence of HCA (77% vs 41%). Therefore, we agree with Zanardo et al that different pathologic mechanisms other than HCA are involved in LR occurrence, especially late-onset LR. Neonatal LR was reported previously to be the result of a transient acceleration in neutrophil production and was associated with elevated serum granulocyte colony-stimulating factor in only 30% of the study infants.² We continue to believe that LR may be a manifestation of the immature inflammatory cascade activated in response to perinatal or neonatal insult and stress with an associated excess of proinflammatory cytokines including granulocyte colony-stimulating factor. We agree with Zanardo et al that additional new studies are necessary to better understand this phenomenon in premature infants.

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Procalcitonin and Vesicoureteral Reflux in Children With Urinary Tract Infection

To the Editor.—

We read with interest the article by Leroy et al¹ regarding procalcitonin as a predictor of vesicoureteral reflux (VUR) in children. The authors address an important issue: the prevention of unnecessary voiding cystourethrograms in children.

As they point out, the use of sterile bags to collect specimens for urine culture raises the possibility of selection bias in their study. We disagree with the authors, who state that selection bias does not explain their results. The specificity of bag urine specimens is poor and may lead to high false-positive rates, particularly in populations at low risk for urinary tract infection (UTI).² In children with VUR, especially those with high-grade VUR, an increased risk of parenchymal anomalies on renal scintigraphy after a diagnosis of UTI has been described.³ For a test of a given specificity and sensitivity, the positive predictive value improves when the prevalence of the disease increases in the population tested.⁴ Among children with UTI diagnosed with a bag specimen, the number of children without VUR falsely diagnosed with pyelonephritis is thus likely to be higher than in a population of children with high-grade VUR. Had urine cultures been performed through transurethral bladder catheterization or suprapubic aspiration in younger children, the number of false-positive urine-culture results, particularly in children without VUR, may have been lower, thereby decreasing the magnitude of the association observed between procalcitonin and VUR. In a prior study involving 37 children with abnormal renal scintigraphy after diagnosis of UTI, including 13 children with VUR, mean procalcitonin was similar in children with and without VUR.⁵ The association found between procalcitonin levels and VUR by Leroy et al may simply reflect the association between procalcitonin and renal lesions after UTI⁵ in a population diagnosed through a technique of poor specificity.

It will be essential in future studies of the same issue to diagnose UTI with the best technique available. Transurethral bladder catheterization or suprapubic aspiration, rather than bag specimens, should be used to diagnose UTI in young children, as recommended by the American Academy of Pediatrics² and the Canadian Paediatric Society.⁶ In the technical report supporting its 1999 guidelines, the American Academy of Pediatrics performed a decision analysis demonstrating that, when applied to a theoretical cohort of 100 000 children, the use of bag specimens to diagnose UTI led to 33 500 imaging work-ups. Comparatively, using transurethral catheterization reduced the number of imaging work-ups to 5000.⁷ These data demonstrate that, until the use of biological markers predicting the presence of VUR has been evaluated further, adopting appropriate methods for obtaining urine specimens remains an efficient strategy for reducing the needless use of voiding cystourethrograms.

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In Reply.—

We greatly appreciate Chevalier and Gauthier's interest in our article.¹ They suggest that the use of sterile bags for urine collection biased our results. They base their comments largely on a technical report² that support the American Academy of Pediatrics practice parameter on urinary tract infection (UTI).³ As stated in the discussion of our article,¹ we agree that the use of sterile bags for urine collection is not as specific as suprapubic aspiration or transurethral catheterization.

However, data concerning the specificity of sterile bags in non-toilet-trained children older than 1 month is scarce. The only valid method for ascertaining the specificity of sterile bags requires comparing urine specimens collected by this technique and by suprapubic aspiration or transurethral catheterization within a very close time frame in patients suspected of having UTI. What constitutes a positive bacterial culture of urine collected by sterile bags needs to be defined in advance for this comparison. In his 1999 technical report, Downs² reported that the specificity of sterile bags varied between 14% and 84% based on 4 published studies.^{4–7} Unfortunately, a careful analysis of 2 of these studies reveals that they do not provide data about the specificity of sterile bags.^{4,5} The specificity reported in the third study was based on pooled results obtained from 2 different urine-collection techniques (sterile bags and clean-voided midstream); it is not possible to calculate the specificity of sterile bags alone.⁶ Data from the fourth study did not permit calculation of the specificity of sterile bags either. Indeed, there were no available data about children with a negative culture of urine collected by sterile bags.⁷ As mentioned but not discussed in Downs' technical report,² Pytkkanen et al⁸ reported a specificity of sterile bags of 88% (95% confidence interval [CI]: 78–93) in a study of 272 children. The authors defined UTI as a positive bacterial monoculture of $\geq 10^5$ colony-forming units per mL for sterile-bag specimens. This threshold was also the one used in our study¹ (because it is recommended by the French Society of Pediatrics⁹), and it also was used in a recent study by the Pediatric Research in Office Settings' group.¹⁰ Other studies^{11,12} published before Downs' technical report support the results reported by Pytkkanen et al. For example, Benito Fernandez et al¹² reported in 1996 the comparison of sterile-bag collection with suprapubic aspiration in 48 children <1 year of age. The specificity of sterile bags was 89% (95% CI: 74–95) when using the same previously defined urine-culture threshold for bag specimens. It is unclear to us why

Downs' technical report² failed to cite and comment on those key studies. Thus, the level of evidence for the range of specificity of sterile-bag collection that he reported (and used in Chevalier and Gauthier's letter) is questionable. It may indicate room for a more systematic review.

Furthermore, if the relationship between vesicoureteral reflux (VUR) and high procalcitonin (PCT) was due only to the selection bias related to the use of sterile bags as Chevalier and Gauthier suggest, then (1) the prevalence of VUR would be higher in children with UTI diagnosed by suprapubic aspiration or transurethral catheterization than sterile bags, and (2) the external validation of this relationship would fail in other populations of children with UTI diagnosed by suprapubic aspiration or transurethral catheterization. As a matter of fact, we recently conducted a large multicenter validation study of 398 patients in 8 centers (5 using suprapubic aspiration or transurethral catheterization) in 7 European countries.¹³ The prevalence of VUR did not differ statistically ($P = .9$) according to the urine-collection technique used (26% in the centers using suprapubic aspiration or transurethral catheterization vs 25% in those using only sterile bags or clean-voided midstream). The relationship between VUR and high PCT remained strong and independent (adjusted odds ratio: 2.4; 95% CI: 1.4–4.1; $P = 10^{-3}$). High PCT sensitivity and specificity were very close to those found in our single-center study¹: the sensitivity was 75% for all-grade VUR and 89% for high-grade VUR, with a specificity of 43% in both cases.

We believe that the specificity of sterile bags as a urine-collection technique is not that poor, especially if febrile UTI is defined as the association of fever, positive urine monoculture ($\geq 10^5$ colony-forming units per mL), and positive biological inflammation, as it was in our study.¹ That is probably one reason, together with the adverse effects of suprapubic aspiration or transurethral catheterization (including pain and trauma), why many pediatricians in the United States,¹⁰ as well as in numerous European countries,^{9,14–16} use sterile bags. Our data also provide strong evidence that PCT is a powerful predictor of VUR in children with a first febrile UTI regardless of the urine-collection technique used for the diagnosis of UTI.

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