Impact of Steroids as Adjuvant Therapy in Acute Bacterial Infections of Childhood

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Two studies appearing in this edition of *Pediatrics* (Leszczynska et al[1] and Goenka et al[2]) have queried the impact of corticosteroids as adjuvant therapy for orbital cellulitis and retropharyngeal abscess (RPA) and parapharyngeal abscess (PPA), conditions that have traditionally been treated with antibiotics, with or without surgical drainage, on outcome of treatment. The subsidiary question that is raised by the design used by each study is whether administrative databases, such as the Pediatric Health Information System, are a viable approach to answering these questions.

The first consideration is the biological plausibility of using steroids as an adjuvant in any infectious disease and the clinical models that exist to suggest that steroids may be beneficial. The use of corticosteroids in patients with bacterial meningitis, including that caused by *Mycobacterium tuberculosis*, is often cited as an example of the benefits of steroids in infection. The specific rationale for use of corticosteroids is its antiinflammatory effects, which may result in decreases of swelling and/or edema to facilitate drainage, perfusion, reduction in pain, and healing.[3] However, the pharmacologic effects of steroids are myriad and complicated. Even in bacterial meningitis of childhood, the impact of steroids is variable; benefits (regarding diminution of hearing loss or improved survival) have been demonstrated for *Haemophilus influenzae* and *M tuberculosis*, although not for *Listeria monocytogenes* or *Cryptococcus neoformans*, reflecting the complexity of the antiinflammatory impact.[3,4] The potential beneficial effect of a decrease in inflammation must be balanced against any impact such an effect might have on the penetration of antibiotics into the cerebrospinal fluid, which is a critical determinant of effectiveness of antimicrobial agents in patients with meningitis.

Furthermore, there are well-known adverse consequences of steroid use, including the potential for masking the clinical course (by virtue of its positive antiinflammatory effect, thereby delaying appropriate therapy for unrecognized deterioration), as well as the possibility of immunosuppression, an especial worry when steroids are used in the management of infectious diseases. Any adverse consequences from long-term or chronic use of steroids are not a concern because the use of steroids is only short-term.

Leszczynska et al[1] were prompted to initiate their study because the existing literature on use of steroids in orbital cellulitis in children suggested a potential benefit in terms of length of hospital stay.[5–7] However, the studies are small, uncontrolled, and characterized by variance of corticosteroid dosing and

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heterogeneity of the patient population. Although the authors did not dwell on this issue, orbital cellulitis in children is particularly prone to heterogeneity because the term is often used clinically to describe a broad group of children who present with a swollen eye. Specific diagnostic criteria differentiating true orbital cellulitis from preseptal cellulitis (which is important in regard to likely outcome) include proptosis, impaired extraocular eye movements, and loss of visual acuity. In none of the existing studies were precise clinical criteria for inclusion stated. As expected, use of an administrative database, although dramatically increasing the size and geographic representation of subjects, did not permit the authors to close other important gaps that they identified, including assessment of severity at presentation, timing, route of administration and selection of steroid, timing and selection of antibiotics, use of protocols dictating length of stay, complications at baseline, and need for surgical drainage or other operative interventions.

Leszczynska et al[1] did not demonstrate a decrease in length of stay in patients treated with corticosteroids in the multivariate analysis after adjusting for age, presence of complicated orbital cellulitis, operative episodes for orbital cellulitis, and PICU visits during the first 2 days of admission. However, they did show a statistically discernable increased odds of both operative episodes after the second day of admission and readmissions within 30 days related to orbital cellulitis after adjusting for age, presence of meningitis and/or vision and/or abscess, and PICU visits during the first days of admission. Both observations suggest that children who received steroids may have been a sicker group of patients. To address this issue, the authors also conducted a sensitivity analysis by evaluating the association between corticosteroid prescription and length of stay in the subgroup of patients without PICU admission within 2 days of hospitalization. In this analysis, the lack of an association between corticosteroid prescription and length of stay was confirmed. Furthermore, a second sensitivity analysis was conducted by evaluating the associations between corticosteroid prescription and clinical outcomes after excluding patients for whom corticosteroids were prescribed only on the day of a surgical procedure. Additional sensitivity analyses to further minimize potential bias (eg, using propensity score matching) were not presented. A major strength of the study is the large sample size, which included 5645 patients from 51 hospitals. Unfortunately, the impact of steroids is ultimately unclear because of the retrospective nature of this study, with its inherent potential for bias due to unobserved confounders: were steroids prescribed more often when children were perceived to be sicker, or did they lead to a less good outcome?

In the study reported by Goenka et al,[2] researchers examined the association of corticosteroid use with surgical drainage procedures performed in children with RPA and PPA. This is also a retrospective study in which administrative data from the Pediatric Health Information System was used. The study included data from 2259 patients at 46 hospitals. The authors noted a trend toward increasing medical management compared with surgical management in cases of RPA and PPA. Patients receiving steroids as adjunctive treatment underwent drainage procedures substantially less often (22.2% vs 51.5%; $P < .001$), had less use of opioids, and decreased costs of hospitalization (probably because there were no surgical costs) compared with patients who did not receive steroids, as demonstrated in multivariate analyses after adjusting for age, severity index, and antibiotic regimen. Patients receiving steroids were more likely to visit the emergency department within 7 days of discharge but were not more likely to be readmitted to the hospital within 30 days. There was no significant association observed between steroid use and length of stay in this study. However, these results comparing health care use outcomes should be interpreted with caution because patients who started corticosteroids on or after the day of surgery were included in the noncorticosteroid group, resulting in a potential treatment effect overlap between the 2 cohorts. Sensitivity analyses by excluding patients receiving corticosteroids on or after the day of surgery would be informative but were not presented in this article. Although surgical drainage occurred more often on readmission of children originally treated with steroids, the total number of children undergoing surgery was still significantly less than in the nonsteroid group. The authors suggest a potential beneficial role for steroids in the medical management of children with RPA and PPA to reduce rates of surgical drainage. However, they also acknowledge the limitations of administrative databases that do not permit assessment of causality or details about intent or indications when prescribing steroids or ordering additional diagnostic tests.[8]

Both studies conclude that additional large, controlled, prospective clinical trials are needed to ascertain with certainty the impact of steroids and

the protocols that lead to the best outcome by standardizing the approach to diagnosis and management. Use of administrative databases are not optimal to answer questions related to outcome.

ABBREVIATIONS

PPA: parapharyngeal abscess
RPA: retropharyngeal abscess

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