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Minocycline and Pseudotumor cerebri: The Well-Known but Well-Kept Secret

Debra E. Weese-Mayer, Renee J. Yang, Jonathan R. Mayer and Zibute Zaparackas

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Letters to the Editor

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Minocycline and *Pseudotumor cerebri*: The Well-Known but Well-Kept Secret

To the Editor.—

Minocycline, a synthetic derivative of tetracycline, is the most widely prescribed oral systemic antibiotic for acne vulgaris because it does not appear to induce resistance in *Propionibacterium acnes* and can be administered only once or twice a day. Interestingly, minocycline is lipophilic and penetrates the blood-brain barrier more readily than other tetracyclines, thus attaining higher cerebrospinal fluid (CSF) levels. Despite its widespread use among adolescents, it does not appear that adequate prospective studies have been published to investigate its specific effects on the maturing teenager.

Recent personal experience allowed for more careful study of the effects of minocycline. Specifically, our then 12½-year-old son initiated minocycline (100 mg twice a day) by mouth for the treatment of moderately severe acne. Four weeks later, he was examined by a senior pediatric ophthalmologist for his annual assessment of myopia. An entirely normal examination (including pupil dilation and fundoscopic assessment) was documented, but 4 weeks later he complained of a global headache that was modestly relieved by an oral analgesic (day 1). The next day (day 2) he developed vomiting and diarrhea with a low-grade temperature. By day 3, the vomiting and diarrhea had improved, he had defervesced, but he began to complain of visual glare. Although he noticed slight double vision, he did not mention it until late on day 4. On day 5, he was seen by his pediatric ophthalmologist to assess the new symptoms of glare and the double vision. On examination he was noted to have right 6th cranial nerve weakness, bilateral papilledema with focal retinal splinter hemorrhages, and enlarged blind spots. A brain/brainstem computed tomography scan and magnetic resonance imaging the same day failed to identify a cause for the apparent increase in intracranial pressure; thus, a decision was made that minocycline accounted for the symptoms compatible with *Pseudotumor cerebri*. The minocycline was immediately discontinued. A spinal tap was deferred and Diamox (250 mg every 8 hours) was initiated. Within 24 hours of the last dose of minocycline, his headache was resolving and his double vision slightly improved. Because of sustained double vision 48 hours later, the Diamox was increased to 250 mg every 6 hours, and a potassium-enriched diet was initiated. Within 4 weeks of the diagnosis of *Pseudotumor cerebri* and discontinuation of the minocycline/initiation of Diamox, the papilledema had resolved, the blind spots had returned to normal size, and our son was virtually symptom-free (aside from the fatigue and shortness of breath with exertion induced by the metabolic acidosis effect of Diamox). The Diamox was tapered then discontinued over days 28 to 30, and the ophthalmologic examination followed closely with sustained normality documented over the next 6 months.

In the process of this alarming experience we made several observations. First, we noted that information about minocycline and *Pseudotumor cerebri* is lacking in common resources accessible to pediatricians. Specifically, *Pseudotumor cerebri* is not listed in the current edition of the *Harriet Lane Handbook* as a complication of minocycline—just nausea, vomiting, allergy, photophobia, injury to developing teeth, and vestibular dysfunction. The 2001 *Physi-*

cians' Desk Reference reports *Pseudotumor cerebri* as a rare complication in adults and notes that bulging fontanelle can occur in babies, but mentions nothing about children or adolescents. The *Pediatric Dosage Handbook* (commonly used by pediatric residents for medication dosages) does not even list minocycline. Finally, the package insert on the actual minocycline prescription from the pharmacy did not list *Pseudotumor cerebri* as a complication, nor did it provide an adequate symptom list that might equate with *Pseudotumor cerebri*. Second, we found that the literature is full of case reports or small series about minocycline and *Pseudotumor cerebri* (at least 19 reports were located) and tetracycline and *Pseudotumor cerebri* (at least 10 reports), but they are published primarily in the dermatology and ophthalmology literature. The first report of tetracycline/*Pseudotumor cerebri* in a child appeared in the *Journal of the American Medical Association* in 1971.¹ The first report of minocycline/*Pseudotumor cerebri* in a child appeared in *European Neurology* in 1978.² Yet, the only original report in the *Journal of Pediatrics* was a "Clinical Note" published in 1978 as a letter by Stuart and Litt³ regarding tetracycline, and then a letter to the editor citing previous publications.⁴ No reports were found in *Pediatrics*. The only large prospective study looking for the incidence of side effects of minocycline is in the dermatology literature⁵ and was based on symptom report and blood chemistries, without corroboration on physical or ophthalmologic exam. Finally, the rationale for performing the initial and serial spinal taps, with full recognition that more CSF would soon be produced, was less than clearly stated in the literature.

As a result of this first-hand experience, we have identified 3 key areas where we as pediatricians can prevent the above-described scenario. First, it is our responsibility as investigators to ensure that drugs to be used in children are studied prospectively before FDA approval. In the case of minocycline, an examination by an experienced pediatric ophthalmologist before the initial prescription and then every 2 to 4 weeks thereafter in combination with a patient questionnaire would be appropriate. Only then will the true incidence of *Pseudotumor cerebri* be known and its relationship to specific "side effects" be clarified. As initially proposed by Maroon and Mealy,¹ it is quite possible that *Pseudotumor cerebri* occurs more frequently than published reports would suggest. They proposed that many patients likely discontinue use of the offending agent when they experience the ill-defined side effects, before the symptoms progress to the full clinical manifestations. As a result, *Pseudotumor cerebri* would be unrecognized and therefore unreported. Further, even if the parent seeks medical attention, this would quite likely include examination by the dermatologist or pediatrician who could easily miss the subtle early signs of papilledema. Second, it is our responsibility as pediatricians to insist that all side effects, particularly the most serious ones, of widely dispensed drugs be clearly listed in detail on the package insert and in the texts commonly used by pediatric residents and pediatricians, with no room for ambiguity. If a serious side effect has been identified, this should be reported clearly in these locations with specific references provided. Finally, it is our responsibility as educators to ensure that each child and parent is instructed to look for specific symptoms and serious side effects of any drugs we prescribe before they leave our offices so that we can encourage parents to be knowledgeable and proactive and ensure

that the next generation will be well-educated in their own health and well-being.

DEBRA E. WEESE-MAYER, MD
Pediatric Respiratory Medicine
Rush Children's Hospital at Rush-Presbyterian-
St Luke's Medical Center
Chicago, IL 60612

RENEE J. YANG, MD
Northwestern University Medical School
Chicago, IL

JONATHAN R. MAYER
Latin School of Chicago
Chicago, IL

ZIBUTE ZAPARACKAS, MD
Department of Ophthalmology
Northwestern University
Chicago, IL

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Occult Bacteremia From a Pediatric Emergency Department

To the Editor.—

Regarding the report of Alpern et al,¹ given the low rate of adverse outcome to *Streptococcus pneumoniae* occult bacteremia and the risks associated with false-positives and hospitalizations for positive blood cultures, one should conclude that there is no utility to blood cultures in this setting and that close follow-up without blood cultures is more valuable.

JOHN DiTRAGLIA, MD
Portsmouth, OH 45662

REFERENCE

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In Reply.—

We would like to thank Dr DiTraglia for his thoughtful comment concerning our recently published article.¹ As pointed out in his letter, the main findings of our study highlight the low prevalence of occult bacteremia and subsequent very low risk of serious adverse outcomes. We agree that the high risk of contaminated blood cultures and subsequent medical care to evaluate patients at risk for occult bacteremia is concerning. Close follow-up is incontestably agreed upon in the care of patients at risk for occult bacteremia. In the emergency department (ED) setting, however, this follow-up is often difficult. Therefore, many practitioners may elect not to eliminate obtaining blood cultures. As we concluded in our study, a continuously monitored blood culture system may allow for early differentiation between contaminated and pathogenic cultures. The early recognition (94% within 18

hours) of true pathogenic cultures with the continuously monitored system may also allow for early and important follow-up of children with "known" occult bacteremia. This "red flag" may help focus urgent and immediate follow-up in the ED setting. Each practitioner should base medical practice on a clear understanding of the blood culture system available to his or her practice. As Dr DiTraglia points out, there is no substitute for close follow-up of patients at risk for occult bacteremia.

ELIZABETH R. ALPERN, MD, MSCE
EVALENE A. ALESSANDRINI, MD, MSCE
LOUIS M. BELL, MD
KATHY N. SHAW, MD, MSCE
KARIN L. MCGOWAN, PhD
Department of Pediatrics
University of Pennsylvania
Children's Hospital of Philadelphia
Philadelphia, PA 19104-4399

REFERENCE

1. Alpern ER, Alessandrini EA, Bell LM, Shaw KN, McGowan KL. Occult bacteremia from a pediatric emergency department: current prevalence, time to detection, and outcome. *Pediatrics*. 2000;106:505-511

To the Editor.—

I read with interest the article by Dr Alpern and colleagues on occult bacteremia in the pediatric emergency department (PED).¹ Their carefully collated experience reinforces earlier reports showing that occult bacteremia, along with its complications, continues to occur, although disease attributable to *Haemophilus influenzae* type b (Hib) has essentially disappeared.² I agree with the authors that most pediatricians do not encounter these complications very commonly. I believe, however, that several issues in this study merit clarification and/or further comment.

1. The authors report a prevalence of non-Hib occult bacteremia of 1.9% (95% confidence interval [CI]: 1.5%, 2.3%) in young febrile children evaluated in the PED, which is similar to that of previous large prospective studies on this topic (1.6%² and 2.7%³). The prevalence of occult bacteremia reported in the current study, however, likely underestimates the true prevalence in their population. This is because patients who were already receiving antibiotics at the time of blood culture, as well as those recently immunized, were not excluded from enrollment, in contrast to earlier studies.^{3,4}
2. The rate of adverse outcome (meningitis or death) of children with bacteremia in this study was 2 of 104 (1.8%; 95% CI: 0, 6.8%). Although the authors report that this is an "extremely low risk" in their conclusions, the 95% CI of this rate is consistent with the rates of development of pneumococcal meningitis reported in 2 large meta-analyses on the topic (2.7%⁵ and 5.8%⁶). Many clinicians would not necessarily consider this rate of meningitis to be low given the gravity of this complication. In the current study, however, 69 (66%) of 104 patients with occult bacteremia were treated with oral antibiotics, which may have diminished the rate of complications. The authors state that "a prior randomized clinical trial demonstrated that oral antibiotics do not affect the incidence of serious focal infections." The prospective study they reference, however, was not appropriately powered to make this conclusion.⁴ Furthermore, in the meta-analysis regarding empirical oral antibiotic treatment of children with occult pneumococcal bacteremia that the authors reference, significantly fewer serious bacterial complications developed in treated than untreated children.⁵ In addition, in that study only 3 (0.8%) of 399 patients with bacteremia who received oral antibiotics developed meningitis compared with 7 (2.7%) of 257 patients who did not receive empirical antibiotics, although this difference did not achieve statistical significance (the reported odds ratio [OR] for that comparison was 0.51, with a 95% CI of 0.12-2.09).⁵ From that study, one cannot conclude that oral antibiotics do not prevent *S pneumoniae* meningitis, because an eightfold reduction in the odds of developing meningitis for patients receiving oral antibiotics cannot be excluded (i.e., OR: 0.12, the lower end of the 95% CI). Two other large studies on this topic report that oral

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