Reply to the Letter to the Editor

Another Look: Is There a Flaw to Current Hip Septic Arthritis Diagnostic Algorithms?

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Received: 8 October 2013 / Accepted: 8 October 2013 / Published online: 22 October 2013
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To the editor,

I thank Dr. Yagupsky for his cogent and instructive letter.

It is important not to conflate two important, but distinct elements of the systemic review performed on septic arthritis diagnostic algorithms [9]. The limitations of such algorithms, identified in the form of modest samples sizes and too few episodes of septic arthritis to support a logistic regression analysis, persist notwithstanding the reliability of any putative gold standard. It is common for surrogate indices to be developed in lieu of any optimum test. This tends to be because either the gold standard is not readily available or cannot be accessed as expeditiously as necessary to be considered clinically useful.

This process in no way implies that the gold standard is faultless or infallible. In the present case, diagnostic algorithms have been described, matching as closely as possible

to the optimum methods of determining septic arthritis. This is because infection mandates emergency joint lavage. Waiting for the outcome of microbiology culture or DNA amplification would be too hazardous in cases of septic arthritis. To evaluate their performance, diagnostic algorithms must be compared to the gold standard. The statistical tools used for this process must be robust and their limitations appreciated. This is true irrespective of the quality of the gold standard.

Dr. Yagupsky does raise a valid point that there exists no ideal gold standard for the diagnosis of septic arthritis. I concur with this statement. Even culture is imperfect. In the only study evaluating the diagnostic ability of synovial fluid microbiology culture, Shmerling [7] reported sensitivities of 75%–95%, and specificities above 90% for this technique. This flaw led all the studies in the systematic review to select a “composite gold standard.” Therefore, children were deemed to suffer from septic arthritis if synovial fluid culture was positive or fluid cytology revealed a white blood cell count of greater than $50 \times 10^9/L$. This latter criterion introduces the phenomenon of “presumed septic arthritis” in instances where no pathogen is isolated. It minimizes the false negative rate, but increases the false positive rate. The magnitude of the latter effect may be quantified. Margaretten et al. [4] performed a meta-analysis in which they evaluated the predictive ability of various synovial fluid white cell concentrations at discriminating septic arthritis from other arthropathies in adults. The use of a threshold of a synovial white cell count of $50 \times 10^9/L$, as diagnostic of septic arthritis, creates a test with a likelihood ratio of 7.7 for a positive result. In the composite series of the systematic review, the preanalysis odds of septic arthritis were 2:5 (238:594). The postanalysis odds were 3:1 ($7.7 \times 2:5$). Using Shmerling’s figures, and imputing sensitivity for culture of 91% and a

(Re: Uzoigwe CE. Another look: Is there a flaw to current hip septic arthritis diagnostic algorithms? [Published online ahead of print Aug. 28, 2013]. *Clin Orthop Relat Res*. doi: [10.1007/s11999-013-3142-0](https://doi.org/10.1007/s11999-013-3142-0)). The author certifies that he, or any members of his immediate family, have no funding or commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

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specificity of 90%; the likelihood ratio of infection for negative microbial culture can be calculated at 0.1. Those with a synovial white cell count of greater than $50 \times 10^9/L$ who progress to yield a negative culture, carry an odds of disease ratio of only 3:10. This approximates to a probability of septic arthritis of only 25%. Therefore, potentially up to 75% of patients with a synovial fluid white cell count above the threshold but without an isolated pathogen will not have septic arthritis. However, researchers classed this group of 85 patients as suffering from septic arthritis. Inevitably, some will suffer from pseudo-septic arthritis. This is an acute aseptic inflammatory articular manifestation of noninfective connective tissue disorders and arthropathies. It, by definition cannot be distinguished from septic arthritis on the basis of history or laboratory investigation [3, 6]. However, to mitigate this effect, all of the studies in the systematic review excluded patients who were subsequently diagnosed with inflammatory arthropathies during the course of followup.

The synovial fluid white cell diagnostic threshold is understandably cautious given that the sequelae of septic arthritis are so grave. They include joint destruction or even loss of life. The hazards of misdiagnosis, combined with the inherent limitations of even the most sophisticated means of pathogen isolation, mean that it is difficult to imagine a situation in which the category of presumed septic arthritis will not exist; notwithstanding the false positive risk. Dr. Yagupsky correctly identifies this as a flaw of any “composite gold standard” into which this criterion is incorporated.

Dr. Yagupsky intriguingly speculates that some of the cases described as transient synovitis may actually be due to *Kingella kingae* infection. It is true that this pathogen has a wide pathogenic repertoire and is being increasingly recognised as the causative agent in paediatric infection [10]. However, the symptoms resolved with no medical intervention in the form of antibiotic therapy or joint lavage in all but 11 of the 594 cases of transient synovitis during the course of followup, according to the systematic review. This would be very unusual for septic arthritis. The condition does not typically follow a self-limiting course, but rather has an aggressive and complicated natural history even with medical intervention [2]. Having said this, in the work by Singhal et al. [8], there was a cohort of 11 patients who underwent arthrotomy, joint lavage, and antibiotic therapy. This cohort was classified as suffering from transient synovitis, as no pathogen was isolated [8]. It is conceivable that in this group there may have been some for whom *K kingae* septic arthritis was the true diagnosis.

Dr. Yagupsky argues that *K kingae* is elusive in presentation and diagnosis, and may have been overlooked entirely in all the studies of the systematic review. However, in his

own informative and comprehensive review [6], he demonstrates that the mean clinical parameters associated with *K kingae* infection fall within those that would raise clinical suspicion and result in a clinical diagnosis. Citing the work of Dubnov-Raz et al. [1], Yagupsky reports that the mean synovial white cell count following *K kingae* joint infection is $130 \times 10^9/L$. This would lead to a diagnosis of presumed septic arthritis even in the absence of a pathogen. Dubnov-Raz et al. [1] show that children with *K kingae* septic arthritis exhibit the predictors of septic arthritis identified in the systematic review with median values of temperature of $38.6^\circ C$, serum white cell count of $14.5 \times 10^9/L$, C-reactive protein of 32 mg/L and ESR of 48.5 mm/h. The management of *K kingae* does remain a challenge as it evades diagnosis by routine culture. Dr. Yagupsky is correct to bring this pathogen and its peculiarities to the attention of all who care for children, given that it is not well known.

Dr. Yagupsky's comments underscore the point that all diagnostic algorithms act only as guides. They do not obviate the need for independent thought and are not a substitute for clinical experience. In their review, Mathews et al. [5] suggested that the gold standard for septic arthritis should be the index of suspicion of an experienced clinician. In summary, I agree that a more reliable gold standard is required. Independent of this, techniques which aim to evaluate or correlate clinical parameters with the gold standard must be statistically robust. Finally, diagnostic algorithms should be formulated as a collaborative process with microbiologists.

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