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Are We Correctly Diagnosing Adrenal Insufficiency or Are We Just Spitting into the Wind?

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Adrenal insufficiency continues to be a common and poorly understood associated feature of pediatric critical illness.(1,2) Incidence rates range widely from 30 to 88%. Part of the reason for this disparity is likely due to the variety of diagnostic strategies. Not only is there variability in the use of low- or high-dose corticotropin stimulation testing versus simple measurement of a baseline cortisol level, but the literature also points to the variance in results based on the use of total or free cortisol levels.(3,4) Normally 90% of cortisol is bound to cortisol binding globulin (CBG) or to albumin; however, the free form of cortisol is the active form. During critical illness there is a significant decrease in CBG and albumin leading to a drop in total cortisol, but not necessarily in free cortisol. The reduced total cortisol level may then inappropriately suggest adrenal insufficiency.(5)

In this issue of *Pediatric Critical Care Medicine*, Bhatia *et al.* report results comparing total, free, and salivary cortisol levels in a population of children admitted to the pediatric intensive care unit (PICU) to test their hypothesis that salivary cortisol levels are a more accurate and cost-effective assessment of adrenal insufficiency.(6) A total of 59 participants were enrolled in their trial, but they were only able to analyze data on 34 participants due primarily to incomplete cortisol level collection in the other 25. Of these 25, 21 of them were missing the salivary cortisol level. For the participants with complete data available, there was a strong correlation between their serum free cortisol levels and salivary cortisol levels. Of some concern, the Bland-Altman analysis did suggest this correlation was less robust at higher levels of cortisol. However, there were very few patients with high cortisol levels, so extrapolating the correlation of salivary and free cortisol values into higher ranges is problematic. Furthermore, from the low PIM2 risk of mortality and their demographic description of these subjects, this did not seem to be a very critically ill group of patients. Indeed, none were designated as being in septic shock at all.

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The question of how to accurately diagnose adrenal insufficiency is an important one. Like adults, children with adrenal insufficiency have been shown to have catecholamine-resistant septic shock.(7) Studies have been mixed, however, in their results regarding the efficacy of replacement therapies, with some showing no benefit and even potentially harm and others showing a reduction in vasopressor use.(1,8) This difference may in part be due to differences or errors in the diagnosis of adrenal insufficiency, perhaps by reliance on total cortisol levels, and has led to inconsistency in intensivists' and endocrinologists' approaches to diagnosing and treating adrenal insufficiency in this population.(9)

Serum free cortisol levels have been proposed as a more accurate assessment for adrenal insufficiency in critically ill patients given the decrease in protein levels, specifically CBG. Multiple studies have compared total cortisol level measurements with free cortisol levels in critically ill patients. Consistently the total cortisol levels have increased by a lesser amount with either stress or corticotropin stimulation testing than the free levels, suggesting that the diagnosis of adrenal insufficiency is being erroneously made when only total cortisol is measured.(3, 10,11) Despite efforts to simplify the lab process for free cortisol levels, most institutions still rely on total cortisol levels.(4)

Bhatia *et al.* propose the use of salivary cortisol levels to bridge this gap between accuracy of clinical diagnosis and an easily accessible laboratory technique.(6) Cortisol in saliva is unbound and may be more reflective of serum free cortisol levels. Studies in other populations at risk for adrenal insufficiency have shown that salivary cortisol levels may be more reliable than serum total cortisol levels, because the salivary level peaks were higher and exhibited lower inter-individual variability.(12,13) Although Bhatia *et al.* demonstrate a high correlation between serum free and salivary cortisol, the study is limited by the significant number of patients for whom they were unable to collect adequate salivary specimens. The authors state their data suggests a "learning curve" associated with this technique since they had more inadequate specimens earlier in their study. A previous study of adult patients in the intensive care unit demonstrated a similar problem with salivary collection.(14) Furthermore, we have had a similar issue with salivary cortisol collection in our research, suggesting this is not an isolated problem with their technique.(15) It is problematic to conceptualize salivary cortisol as a diagnostic alternative if its collection technique is so subject to inadequacy.

Given the literature demonstrating the significant negative impact of adrenal insufficiency in patients with critical illness, it is incumbent upon us to use the most accurate diagnostic method. Reliance on the total cortisol level appears inadequate. The high rate of insufficient sample collection for salivary cortisol levels and the low severity of illness of the patients studied by Bhatia *et al.* does not inspire confidence that salivary cortisol should be adopted readily in our patients. Still, Bhatia *et al.* have moved our field forward as we search for more reliable methods to truly assess the vital adrenal cortical response to pediatric critical illness. Based on the current study and those that precede it, it seems clear that we need to stop relying on total cortisol levels and move forward with defining the best practice to diagnose adrenal insufficiency.

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