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Identifying critically ill patients who may benefit from adjunctive corticosteroids: Not as easy as we thought

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Corticosteroid prescription for refractory shock in critical illness remains controversial among practitioners, who must weigh the potential for hemodynamic improvements against the potential side effects of corticosteroids [1, 2]. This controversy is personified by the variability among practitioner prescription of corticosteroids [3, 4]. Trials investigating corticosteroid use in critically ill adults have yielded conflicting results, and pediatric studies have yet to arrive at a clear consensus [5–7]. Although recent 2012 Surviving Sepsis Campaign guidelines for pediatric patients have a stronger recommendation for adjunctive corticosteroids than in previous years, they are still worded to allow for tremendous variability in practice and the basis of these recommendations has been questioned [8, 9]. Part of the reason for the varying recommendations is the inconsistent effect of corticosteroids on a patient-to-patient basis. With this inconsistency in mind, attempts have been made to identify those critically ill patients who stand to benefit the most from adjunctive corticosteroids.

One of the first subpopulations theorized to benefit the most from corticosteroid therapy for critical illness was patients with relative adrenal insufficiency. It stands to reason that patients who fail to mount a sufficient cortisol response to stress would benefit the most from corticosteroid supplementation. The landmark study by Annane et al. demonstrated that patients with septic shock who failed to mount an adequate cortisol response to adrenocorticotropin hormone (ACTH) stimulation testing had a survival benefit when administered hydrocortisone and fludrocortisone [10]. This study garnered much enthusiasm in the field of critical care medicine with the hope that a relatively simple test could identify a subpopulation of patients most likely to benefit from adjunctive corticosteroid

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administration; critical care medicine had entered the age of personalized medicine (theranostics). However, a subsequent, and larger, study could not replicate these data, thus making it clear that identifying such patients is much more complex than simply conducting an ACTH stimulation test [11]. Within pediatric literature, relative adrenal insufficiency has been shown to exist in critically ill populations, but no studies have demonstrated a benefit from adjunctive corticosteroid usage in this particular cohort [12, 13].

To further investigate the varying individual responses to corticosteroids, several investigators have started a search for alternative explanations based on other components of the hypothalamic-pituitary-adrenal (HPA) axis. For example, gene expression-based classification of septic shock patients has recently been validated and shown to correlate with subclasses of important phenotypic differences [14–16]. These studies identified a gene signature, comprised of a group of genes corresponding to the glucocorticoid receptor signaling pathway, which was repressed in patients with the highest mortality and organ failure burden. Another recent study demonstrated that critically ill patients have functionally important alterations in the pathways responsible for cortisol metabolism [17]. Collectively, these studies illustrate that the issue of cortisol-related homeostasis (or lack thereof) in critical illness is much more complex than the information provided by the ACTH stimulation test. This should not come as a surprise given the high level of complexity and heterogeneity intrinsic to critical illness.

This concept provides the foundation for a study in this issue of *Pediatric Critical Care Medicine* that identifies a single nucleotide polymorphism (SNP) within the noncoding region of the melanocortin 2 receptor (MC2R) gene (rs1941088) that may help explain the varying levels of cortisol production during critical illness [18]. The MCR2 gene has previously been shown as a receptor for ACTH within the zona fasciculata of the adrenal gland, the organ responsible for cortisol synthesis [19]. Mutations within the MC2R gene are responsible for familial type 1 glucocorticoid deficiency. Polymorphisms within the promoter region of the MC2R gene (other than the polymorphism in the current study) have been identified and associated with lowered sensitivity to ACTH [20]. These known mutations within the gene and promoter region support a relationship between the SNP identified in this article and cortisol production.

While promising and biologically plausible, one of the main limitations of this recent article is that the association between SNP rs1941088 and blunted cortisol responses was identified in patients with a PRISM score greater than seven. This cutoff of seven was derived based on convenience; the cutoff represented the median score within the study cohort and thus provided a statistics-based method for dividing the cohort into equal numbers, rather than a physiologically- or biologically-sound principal. This particular PRISM score has not been previously shown to be a crucial cutoff of particular relevance for illness severity within critically ill pediatric patients. Furthermore, PRISM was never designed, nor validated, to be used in this manner. Thus, while generally well conducted and intriguing, this study involving a small sample size must be interpreted with caution. Future adequately powered studies may find that further stratification of patients yields even stronger relationships between cortisol production and this SNP within specific cohorts. Ideally, the PRISM score

would be an independent, continuous variable within the analysis, but this study was underpowered to conduct that analysis.

Gene association studies should continue to be conducted within the critically ill population, and multiple studies surrounding the MC2R gene and its promoter in relation to cortisol production certainly lend the biological plausibility that prompts further investigation into these SNPs. It is important to note, however, that the MC2R gene is associated with the cortisol production in response to ACTH produced by the hypothalamus. While a SNP within this gene or its promoter could help explain why cortisol levels may vary among patients experiencing stress, it still does not address why corticosteroid supplementation fails to help all of these patients. In addition to gene association studies examining cortisol production, further studies exploring cortisol receptors and the varying hemodynamic responses may also prove fruitful in the future.

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