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Combining prognostic and predictive enrichment strategies to identify children with septic shock responsive to corticosteroids

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Christopher J. Lindsell: Developed the study, assisted with analysis, and edited the manuscript.

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Dr. Lindsell is named as a co-inventor in the above patent.
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Abstract

Objective—Prognostic and predictive enrichment strategies are fundamental tools of precision medicine. Identifying children with septic shock who may benefit from corticosteroids remains a challenge. We combined prognostic and predictive strategies to identify a pediatric septic shock subgroup responsive to corticosteroids.

Design—We conducted a secondary analysis of 288 previously published pediatric subjects with septic shock. For prognostic enrichment, each study subject was assigned a baseline mortality probability using the pediatric sepsis biomarker risk model (PERSEVERE). For predictive enrichment, each study subject was allocated to one of two septic shock endotypes, based on a 100-gene signature reflecting adaptive immunity and glucocorticoid receptor signaling. The primary study endpoint was complicated course, defined as the persistence of two or more organ failures at day seven of septic shock or 28-day mortality. We used logistic regression to test for an association between corticosteroids and complicated course, within endotype.

Measurements and Main Results—Among endotype B subjects at intermediate to high PERSEVERE-based risk of mortality, corticosteroids were independently associated with more than a ten-fold reduction in the risk of a complicated course (R.R. 0.09, 95% CI: 0.01 to 0.54; p = 0.007).

Conclusions—A combination of prognostic and predictive strategies based on serum protein and mRNA biomarkers can identify a subgroup of children with septic shock who may be more likely to benefit from corticosteroids. Prospective validation of these strategies and the existence of this subgroup are warranted.

Keywords

sepsis; corticosteroids; outcome; prognostic enrichment; predictive enrichment; prognostic enrichment; precision medicine; pediatrics

Introduction

Prognostic and predictive enrichment strategies are fundamental tools for enhancing clinical trials and embracing precision medicine [1]. Enrichment uses patient characteristics to select a study population in which a drug or intervention effect is more likely to be detected than in an unselected population. Prognostic enrichment strategies select patients with a greater likelihood of having a disease-related event. Predictive enrichment strategies select patients who are more likely to respond to an intervention or drug based on a biological or

physiological mechanism. Enrichment strategies are particularly effective when selecting patients for treatment trials in highly heterogeneous syndromes, such as septic shock.

We propose a prognostic and predictive enrichment strategy for pediatric septic shock. The prognostic enrichment strategy involves the Pediatric Sepsis Biomarker Risk Model (PERSEVERE), which uses a panel of protein biomarkers to estimate baseline mortality probability in children with septic shock [2]. The predictive enrichment strategy is based on endotypes of pediatric septic shock which, based on the mRNA expression profiles of 100 genes, reflect adaptive immune function and the glucocorticoid receptor signaling pathway [3].

We have previously applied these putative enrichment strategies independently in children with septic shock. Using PERSEVERE as a prognostic enrichment variable, we tested the hypothesis that the beneficial effects of corticosteroids are dependent on baseline mortality risk [4]. We did not detect a beneficial effect of corticosteroids in any PERSEVERE-based mortality risk strata. In our examination of the predictive enrichment strategy based on septic shock endotypes, we found that corticosteroids are independently associated with a four-fold increased mortality risk in endotype A patients; endotype A is characterized by decreased expression of genes corresponding to the glucocorticoid receptor signaling pathway relative to endotype B [3]. In the current study, we combine our prognostic and predictive enrichment strategies to test the hypothesis that there exists an identifiable group of children with septic shock who are more likely to benefit from corticosteroids.

Methods

We conducted a secondary analysis of previously published data [2, 3]. The protocol for collection and use of biological specimens and clinical data was approved by the Institutional Review Boards of each of the 18 participating institutions. Children ≤ 10 years of age admitted to a pediatric intensive care unit (PICU) and meeting pediatric-specific consensus criteria for septic shock were eligible for enrollment [5]. There were no exclusion criteria, other than the inability to obtain informed consent, which was obtained from parents or legal guardians. The consent allows for secondary analyses.

Blood samples were obtained within 24 hours of meeting criteria for septic shock. Clinical and laboratory data were collected daily while in the PICU. Organ failure data were tracked up to day 7 of septic shock using previously published criteria [5]. Mortality was tracked for 28 days after enrollment. Illness severity was estimated using the Pediatric Risk of Mortality (PRISM) score [6].

PERSEVERE and Endotype Identification

Baseline mortality probability was estimated using PERSEVERE, which is calculated from the biomarkers C-C chemokine ligand 3 (CCL3), interleukin 8 (IL8), heat shock protein 70 kDa 1B (HSPA1B), granzyme B (GZMB), and matrix metallopeptidase 8 (MMP8) [2]. Each study subject was classified as low, intermediate, or high risk. Because there were only 31 subjects in the high risk group, we combined this group with the intermediate risk group for analysis, thus generating an intermediate-high risk group (n = 93). Endotypes were assessed

from whole blood-derived RNA using a digital mRNA quantification platform [3]. Gene expression data for each study subject was depicted using gene expression mosaics and each subject was assigned to endotype A or B using computer-assisted image analysis and reference mosaics.

Data Analysis

The primary study endpoint was complicated course, defined as the persistence of two or more organ failures at day seven of septic shock or 28-day mortality [3]. We did not consider 28-day morality alone due to the low death rate in this cohort. We used logistic regression to test for an association between corticosteroids and complicated course, within endotype. We adjusted for PRISM score, risk category, and we tested for an interaction between risk category and exposure to corticosteroids. Since PRISM is based primarily on physiologic variables while PERSEVERE is based on biomarkers, and since the correlation coefficient between the two was low ($r = 0.292$), both risk variables were included in the analysis. Since the primary study endpoint was not rare, we converted the odds ratios generated by logistic regression to relative risk using the method suggested by Zhang and Yu [7]. Analyses used SPSS v 23.0 (IBM Corp, Armonk, NY).

Results

The study subjects were previously described in detail [3]. Among the 300 subjects included in the derivation and validation of the septic shock endotypes, 288 (96%) had PERSEVERE data and are included in the current analysis. Among the 112 endotype A subjects, 49 subjects (44%) had a complicated course. Among the 176 endotype B subjects, 37 subjects (21%) had a complicated course. Fifty-one endotype A subjects (46%) and 101 endotype B subjects (57%) were exposed to corticosteroids.

The Table shows the relative risks for complicated course derived from the logistic regression models. Among endotype A subjects, only the PERSEVERE risk category was associated with increased risk of complicated course, although there was a trend towards increased risk of complicated course with increased PRISM score. Among endotype B subjects, PRISM and PERSEVERE risk category were independently associated with increased risk of complicated course. Corticosteroid exposure was not associated with decreased risk of complicated course in endotype B subjects at low PERSEVERE risk, but in those at intermediate to high PERSEVERE risk, corticosteroids were associated with more than a ten-fold reduction in the risk of a complicated course.

Discussion

The role of corticosteroids in septic shock remains controversial despite decades of study. The importance of identifying subgroups of children with septic shock who may benefit from corticosteroids is highlighted by the suggestion of harm associated with corticosteroids [3, 4, 8]. In 2002, Annane and colleagues published a landmark study indicating that a corticotropin stimulation test could identify a subgroup of patients who benefit from corticosteroids [9]. This approach embodied the concept of predictive enrichment, but could

not be replicated in a subsequent trial [10]. This suggests that patient selection may be more complex than the information provided by corticotropin stimulation alone [11].

In the current study, we combine prognostic and predictive enrichment strategies to identify a subgroup of children with septic shock having a higher likelihood of benefitting from corticosteroids. Among endotype B patients with an intermediate to high baseline PERSEVERE risk, corticosteroid exposure was associated with reduced risk of complicated course. Because intermediate to high risk patients have a greater event rate, it becomes more feasible to detect an effect of corticosteroids; this is the concept of prognostic enrichment. Second, because endotype B patients have higher expression of genes corresponding to the glucocorticoid receptor signaling pathway than endotype A patients, it is biologically plausible that they are more likely to respond to corticosteroids. This is the concept of predictive enrichment.

We note the limitations of our study, including that it is a *post hoc*, secondary analysis of existing data. The subjects in the current study were originally included in the derivation and validation of both PERSEVERE and the septic shock endotypes [2, 3]. Finally, the prescription of corticosteroids was not under study protocol and was variable with respect to dosing, timing, and formulation [4]. All of these confounders increase the risk of a false positive finding. These important issues can only be addressed by a prospective study with an *a priori* goal of testing these enrichment strategies and their impact on corticosteroid responsiveness. We posit that the strength of the observed association suggests such a prospective study is warranted.

In conclusion, a combination of prognostic and predictive strategies based on serum protein and mRNA biomarkers can identify a subgroup of children with septic shock who may be more likely to benefit from corticosteroids. Further study is required to validate these strategies and the existence of this subgroup.

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References

1. Simon R. Clinical trial designs for evaluating the medical utility of prognostic and predictive biomarkers in oncology. Per Med. 2010; 7(1):33–47. [PubMed: 20383292]
2. Wong HR, Salisbury S, Xiao Q, Cvijanovich NZ, Hall M, Allen GL, Thomas NJ, Freishtat RJ, Anas N, Meyer K, et al. The pediatric sepsis biomarker risk model. Crit Care. 2012; 16(5):R174. [PubMed: 23025259]
3. Wong HR, Cvijanovich NZ, Anas N, Allen GL, Thomas NJ, Bigham MT, Weiss SL, Fitzgerald J, Checchia PA, Meyer K, et al. Developing a clinically feasible personalized medicine approach to pediatric septic shock. Am J Respir Crit Care Med. 2015; 191(3):309–315. [PubMed: 25489881]
4. Atkinson SJ, Cvijanovich NZ, Thomas NJ, Allen GL, Anas N, Bigham MT, Hall M, Freishtat RJ, Sen A, Meyer K, et al. Corticosteroids and pediatric septic shock outcomes: a risk stratified analysis. PLoS One. 2014; 9(11):e112702. [PubMed: 25386653]
5. Wong HR, Shanley TP, Sakthivel B, Cvijanovich N, Lin R, Allen GL, Thomas NJ, Doctor A, Kalyanaraman M, Tofil NM, et al. Genome-level expression profiles in pediatric septic shock indicate a role for altered zinc homeostasis in poor outcome. Physiol Genomics. 2007; 30(2):146–155. [PubMed: 17374846]
6. Pollack MM, Patel KM, Ruttimann UE. The Pediatric Risk of Mortality III--Acute Physiology Score (PRISM III-APS): a method of assessing physiologic instability for pediatric intensive care unit patients. J Pediatr. 1997; 131(4):575–581. [PubMed: 9386662]
7. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA. 1998; 280(19):1690–1691. [PubMed: 9832001]
8. Wong HR, Cvijanovich NZ, Allen GL, Thomas NJ, Freishtat RJ, Anas N, Meyer K, Checchia PA, Weiss SL, Shanley TP, et al. Corticosteroids are associated with repression of adaptive immunity gene programs in pediatric septic shock. Am J Respir Crit Care Med. 2014; 189(8):940–946. [PubMed: 24650276]
9. Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troche G, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002; 288(7):862–871. [PubMed: 12186604]
10. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008; 358(2):111–124. [PubMed: 18184957]
11. Atkinson SJ, Wong HR. Identifying critically ill patients who may benefit from adjunctive corticosteroids: not as easy as we thought. Pediatr Crit Care Med. 2014; 15(8):769–771. [PubMed: 25280145]

Table

Results of logistic regression to test the association between corticosteroids and complicated course using prognostic and predictive enrichment strategies.

Septic Shock Endotype	Variable	R.R. (95% C.I.)	P value
Endotype A	PRISM	1.03 (1.00 – 1.06)	0.052
	PERSEVERE	2.05 (1.76 – 2.18)	<0.001
	Corticosteroids	1.35 (0.81 – 1.81)	0.212
	PERSEVERE × Corticosteroids	1.03 (0.24 – 1.95)	0.957
Endotype B	PRISM	1.08 (1.04 – 1.12)	<0.001
	PERSEVERE	3.45 (2.40 – 4.15)	<0.001
	Corticosteroids	0.73 (0.32 – 1.51)	0.431
	PERSEVERE × Corticosteroids	0.09 (0.01 – 0.54)	0.007