When and how to use predictive biomarkers for corticosteroid treatment of septic shock

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The decision to give glucocorticoids to patients who have septic shock is difficult because of conflicting randomized controlled trial (RCT) level 1 evidence. Nonetheless, there is some evidence of overuse of corticosteroids in septic shock.

Early cohort studies found that there was an acquired corticosteroid deficiency in septic shock. A subsequent RCT [1] found that corticosteroids lowered mortality in patients who had an abnormal (i.e., inadequate) response to adrenocorticotropic hormone (ACTH) stimulation in septic shock. The ACTH stimulation test has false positives and false negatives and is not recommended for deciding whether or not to administer glucocorticoids in septic shock [2]. Two large multicentre RCTs of corticosteroids in adult septic shock had conflicting results; Anan
ee and colleagues [3] found significant benefit while Venkatesh and colleagues [4] found no effect of corticoste
roids on mortality. The most recent Surviving Sepsis Campaign (published prior to Annane [3] and Venkatesh [4]) used a cautionary tone, recommending against corticosteroid use in patients who have responded adequately to nor
epinephrine [5]. Similarly, but in a more positive tone, the recent Guidelines for the Diagnosis and Management of Critical Illness-related Corticosteroid Insufficiency (CIRCI) [2] recommend for corticosteroids in patients who do not respond to norepinephrine in septic shock.

One reason for conflicting evidence regarding responses to corticosteroids in septic shock is that different patients have different genomic, transcriptomic, and proteomic profiles that define different responses to corticosteroids in septic shock. Alder and colleagues recently made the hypothesis that peripheral leukocyte glucocorticoid receptor (GCR) expression and serum cortisol levels correlate with the response to glucocorticoids in pediatric septic shock (REF). They measured these biomarkers in a modest size prospective cohort (n = 164) of children who had systemic inflammatory response syndrome (SIRS), sepsis, or septic shock. The GCR expression levels were lower and the serum cortisol levels were higher in patients who had poorer outcomes. Where does this study leave the clinician who cares for patients with septic shock?

Finding predictive biomarkers—i.e. pharmacogenomic, transcriptional, and proteomic biomarkers that identify patients with improved responses to an intervention—is the holy grail of septic shock management [6]. We found that a novel combination of serum cytokine levels predicted improved responses to glucocorticoid administration in adult septic shock [7]. However, our study and others were made using cohorts of non-randomized patients who were treated with glucocorticoids or were simply observational cohorts such as Alder and colleagues (REF). Accordingly, despite the potential uses of predictive biomarkers in septic shock, the Surviving Sepsis Campaign [5] does not recommend any predictive biomarkers.

Transcriptomics—or expression profiling—is the study of RNA transcripts that are produced by the genome in specific conditions at specific times in specific tissues. So transcriptomics is more complex and more dynamic than genomics in that our genome is set at conception while transcriptomics change hour by hour in septic shock. Transcriptomics advocates cite that an advantage of transcriptomics is that they are even more specific than genomics and thus are better candidate predictive biomarkers. However, septic shock transcriptomics studies face barriers for robustness, such as which tissue to sample when—
septic shock is a very rapid process (leading to lead
time bias in clinical studies)—and even establishing a
gold standard for the diagnosis of septic shock [8].
Alder and colleagues used peripheral blood leuko-
cytes—which express the GCR but are a surrogate for
deeper tissues of interest—drawn within 24 h of onset
of SIRS, sepsis, or septic shock and then measured
GCR expression by conventional flow cytometry be-
cause they were studying a very limited number of
expression transcripts. Several groups [9] have evalu-
ated genomics or whole blood or specific leukocyte
gene expression as diagnostic and prognostic bio-
markers in septic shock. Transcriptomics has identi-
fied subtypes of acute kidney injury (AKI) [10], a
common complication of septic shock.

What are the next steps for validation of GCR ex-
pression as a predictive biomarker of corticosteroid
administration in septic shock? Corticosteroids need
to be evaluated in RCT(s) that are adequately pow-
ered to detect a significant interaction between (1)
GCR expression and (2) use—or not—of corticoste-
roids. Some would argue, in part because of the stor-
ied controversy of steroids in septic shock, for a
second confirmatory RCT to validate a GCR expres-
sion predictive biomarker. Recently completed RCTs
such as those by Annane and colleagues [3] and Ven-
katish and colleagues [4] are excellent choices for val-
idation because both were rigorous, yet the former
was “positive” while the latter was “negative”. I
suggest that if a GCR expression biomarker signifi-
cantly predicted which patients responded positively
to glucocorticoids in both RCTs, even steroid skeptics
would be interested.

After such confirmation and prior to widespread clin-
ical use, many would recommend regulatory approval of
a clinically validated GCR kit.

We and others have similarly addressed predictive
biomarkers such as genomics [11], cytokine levels
[12], and proteomics for use of vasopressin in septic
shock. This is relevant because vasopressin treatment
is also controversial in septic shock; the largest RCTs
[13, 14] of vasopressin in septic shock were “negative”
but there were suggestions of efficacy in patients who
had less severe septic shock [13]. Similarly, genomics
of the β1 adrenergic receptor could identify good re-
sponders to the first line vasopressor in septic shock,
norepinephrine [15].

Let’s actualize a future in which individual patient
baseline profiling of pharmacogenomics, mRNA ex-
pression (e.g., GCR), and protein levels (e.g., cyto-
kine and cortisol levels) could personalize treatment
with corticosteroids, vasopressin, and norepinephrine
in septic shock (Fig. 1) and even guide post-discharge care to decrease the readmission risk.
This future is not far off but requires focused
design, execution, and analysis of well-conducted
predictive biomarker studies in already completed
and future RCTs.

**Fig. 1** In the future, patients who have severe infection will have rapid pharmacogenomics (PGx), microbiomics, genomics, metabolomics, and
proteomics (‘omics) at presentation to guide acute management. Patients then die, have a partial or full recovery, and are discharged. After
discharge, patients will have follow-up in a precision medicine clinic or office where the results of the ‘omics will be discussed to select a diet,
exercise, and drugs profile for each patient. This will enhance the chances for full recovery and reduce the risk of a readmission for severe infection.
Abbreviations
ACTH: Adrenocorticotropic hormone; AKI: Acute kidney injury; CIRCI: Critical illness-related corticosteroid insufficiency; GCR: Glucocorticoid receptor; RCT: Randomized controlled trial; SIRS: Systemic inflammatory response syndrome

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Competing interests
Dr. Russell reports patents owned by the University of British Columbia (UBC) that are related to PCSK9 inhibitor(s) and sepsis and related to the use of vasopressin in septic shock. Dr. Russell is an inventor on these patents. Dr. Russell is a founder, Director, and shareholder in Cyon Therapeutics Inc. (developing a sepsis therapy (PCSK9 inhibitor)). Dr. Russell has share options in Leading Biosciences Inc. Dr. Russell is a shareholder in Molecular You Corp.

Dr. Russell reports receiving consulting fees in the last 3 years from: Asahi Kesai Pharmaceuticals of America (AKPA; developing recombinant thrombomodulin in sepsis); La Jolla Pharmaceuticals (developing angiotensin I1; Dr. Russell chaired the DSMB of a trial of angiotensin II; Dr. Russell is an inventor on these patents). Dr. Russell reports receiving consulting fees in the last 3 years from: Ferring Pharmaceuticals (manufactures leucyl/cystinyl aminopeptidase gene variants in septic shock). Dr. Russell reports patents owned by the University of British Columbia (UBC) that are related to PCSK9 inhibitor(s) and sepsis and related to the use of vasopressin in septic shock. Dr. Russell is an inventor on these patents. Dr. Russell is a founder, Director, and shareholder in Cyon Therapeutics Inc. (developing a sepsis therapy (PCSK9 inhibitor)). Dr. Russell has share options in Leading Biosciences Inc. Dr. Russell is a shareholder in Molecular You Corp.

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