

# The derivation and validation of three novel sepsis molecular subtypes to help guide precision therapies

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## Background

Sepsis is defined as a dysregulated immune response, but no immunomodulatory therapies have been shown to decrease sepsis mortality. Despite its high clinical heterogeneity, sepsis is still treated as a single disease. Defining sepsis subtypes (or 'endotypes') based on the molecular immune response may allow for a precision medicine approach to match novel therapies to those sepsis patients that can benefit.

## Materials and Methods

We performed a systematic search of GEO and ArrayExpress for gene expression datasets of clinical studies in sepsis, as previously described [1]. We selected studies of bacterial sepsis, sampled within 48 hours of hospital admission, across a broad range of ages, severities, and geographic locations. We used a batch effect correction algorithm [2] to pool data from 14 bacterial sepsis transcriptomic datasets from 8 different countries (N=700). We then used a meta-clustering algorithm [3] to find conserved sepsis subtypes across the conormalized discovery samples. We derived a classifier for application in external datasets, and then validated our clusters in 9 independent datasets from 5 different countries (N=600). Clusters were evaluated for both clinical and molecular differences in both discovery and validation datasets.

## Results

Meta-clustering revealed three sepsis subtypes, which, based on gene ontology analysis, we termed Inflammopathic, Adaptive, and Coagulopathic. We derived a 33-gene classifier with an

overall 83% accuracy in leave-one-out re-assignment of the discovery data. We then applied this classifier to identify the same 3 subtypes in 9 independent datasets (N=600). Across both discovery and validation, we showed that the Inflammopathic subtype is associated with younger age, higher clinical severity and higher mortality; the Adaptive subtype is significantly associated with a lower clinical severity and lower mortality; and the Coagulopathic subtype is significantly associated with both older age and clinical coagulopathy. Further, these clusters are significantly associated with clusters derived by others in independent, single-study sepsis cohorts [4-8].

## Conclusions

We identified three sepsis subtypes (Inflammopathic, Adaptive, and Coagulopathic) associated with significant difference in mortality among sepsis patients. These sepsis subtypes may assist in the development of targeted therapies that would fail if applied to all patients with sepsis [6]. The consistent presence of the sepsis subtypes across a broad range of patients from multiple studies around the world suggests their potential for use as a single framework to better define heterogeneity in patients with bacterial sepsis.

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