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Identifying Sepsis Subtypes from Routine Clinical Data

The heterogeneity of sepsis is often cited as a key factor impeding the identification of new treatments (1). By lumping diverse patients with sepsis together in clinical trials, it is reasoned, we may fail to identify the benefit of therapies that help only a subset of patients (1). As a result, there is growing interest in identifying subgroups of patients with sepsis who may respond differently to treatments.

Recent studies have identified subtypes of patients with sepsis, defined by leukocyte genome-wide expression profiles, some of which are associated with differential response to hydrocortisone treatment (2). However, the optimal method to subtype patients with sepsis remains unclear, and different approaches may be necessary to identify responders to corticosteroids versus other therapies.

In this issue of the *Journal*, Bhavani and colleagues (pp. 327–335) sought to identify meaningful subtypes of infected patients on the basis of a readily available clinical parameter: temperature trajectory in the first 72 hours after hospital presentation (3). Hypothermia is known to be associated with sepsis mortality, whereas fever is protective (4). However, temperature is recorded repeatedly in nearly all hospitalized patients, and dynamic assessment may provide additional prognostic and theranostic information.

The study examined a cohort of 12,413 patients hospitalized for infection at the University of Chicago. Patients had a median of 20 temperature measurements during the 3-day study period, and abnormal temperatures were common. A total of 38% of patients were febrile, and 81% were hypothermic on at least one occasion.

To identify subgroups with different temperature trajectories, the authors used group-based trajectory modeling. This method is an extension of cluster analysis and identifies subgroups (or classes) based on changes in a characteristic over time. In contrast to hierarchical or growth curve models that estimate a mean trajectory and then measure variation around this mean, group-based trajectory models identify subpopulations, each with a different trajectory (5). These are not necessarily biologically distinct subgroups but, rather, a convenient way to describe the variation of trajectories seen in a population (5). Group-based trajectory models also assume that all variation is explained by the subgroups, and that there is no variation in trajectories among individuals within the same subgroup (5). However, this assumption is routinely violated in practice.

Group-based trajectory modeling was first developed to study developmental trajectories (6) (e.g., trajectories of antisocial behavior during adolescence and early adulthood), but has recently been applied to critical care research. The technique has been used to study functional trajectories before and after critical illness (7), quick Sepsis-related Organ Failure Assessment trajectory

in sepsis (8), and intracranial pressure trajectories in traumatic brain injury (9).

One of the most challenging and controversial aspects of group-based trajectory modeling is determining the optimal number of subgroups. Bhavani and colleagues tested models with up to four classes, and found that the four-class model best described their data (3).

The cohort was classified as 33% normothermic; 29% hypothermic; 23% hyperthermic, fast resolving; and 15% hyperthermic, slow resolving. In sensitivity analyses excluding patients who died or were discharged before 3 days, results were similar. Furthermore, the authors validated their findings in a separate cohort of 19,053 patients treated at Loyola University and found similar percentages of patients assigned to the four classes.

Clinical characteristics, processes of care, and hospital mortality differed across the temperature trajectory subgroups. Hyperthermic patients were younger with fewer comorbidities, whereas hypothermic patients were older with more comorbidities. Hyperthermic patients received antibiotics faster, whereas hypothermic patients were more likely to receive steroids and vasopressors.

In the derivation cohort, hospital mortality was lowest in the hyperthermic, fast resolvers (2.9%) and highest among patients in the hypothermic subgroup (9.5%). In the validation cohort, mortality was likewise lowest among hyperthermic, fast resolvers (3.0%), but was greatest among hyperthermic, slow resolvers (10.2%). Subgroup assignments remained associated with hospital mortality after adjusting for age, comorbidities, quick Sepsis-related Organ Failure Assessment score, and time to antibiotics.

The ultimate utility of temperature trajectory subgroups remains unclear and will need to be confirmed in future studies. Because the trajectories included 72 hours of data, they would not be useful for guiding initial management. However, most patients survive the acute phase of sepsis, so the bulk of sepsis-related mortality in occurs in the later phases of hospitalization (10) or posthospitalization (11) periods. One driver of these later sepsis-related deaths is secondary infection, which may occur, at least in part, as a result of persisting immune dysregulation after sepsis (12).

Hypothermia during the first day of sepsis has been associated with persistent lymphopenia, a feature of sepsis-induced immune suppression (13). And although 81% of patients in this study were hypothermic at some point, only 29% of patients were assigned to the hypothermic trajectory. It is possible that a hypothermic temperature trajectory may be a more specific marker of immune suppression. If so, it could help identify patients at increased risk for re-infection and enrich future studies of immune modulation in the later phases of sepsis.

In summary, Bhavani and colleagues show that four general temperature trajectories exist among patients hospitalized for infection, and that these trajectories are associated with mortality. The widespread availability of temperature measurements makes this an appealing means of subgrouping (particularly if physician assessment of temperature trajectory proves to be an accurate surrogate), and it also increases the feasibility of extending and validating these findings. Future studies are needed to determine both whether these findings extend to other populations (e.g., patients with sepsis in lower-income countries) and whether patients with different temperature trajectories respond differently to particular treatments. ∎

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