Commentary

Modeling longitudinal data in acute illness

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See related research by Kyr *et al*., http://ccforum.com/content/11/3/R70

Abstract

Biomarkers of sepsis could allow early identification of high-risk patients, in whom aggressive interventions can be life-saving. Among those interventions are the immunomodulatory therapies, which will hopefully become increasingly available to clinicians. However, optimal use of such interventions will probably be patient specific and based on longitudinal profiles of such biomarkers. Modeling techniques that allow proper interpretation and classification of these longitudinal profiles, as they relate to patient characteristics, disease progression, and therapeutic interventions, will prove essential to the development of such individualized interventions. Once validated, these models may also prove useful in the rational design of future clinical trials and in the interpretation of their results. However, only a minority of mathematicians and statisticians are familiar with these newer techniques, which have undergone remarkable development during the past two decades. Interestingly, critical illness has the potential to become a key testing ground and field of application for these emerging modeling techniques, given the increasing availability of point-of-care testing and the need for titrated interventions in this patient population.

Critical care physicians titrate care of individual patients based on presumed diagnosis derived from available data and anticipated progression of disease. The problem of sepsis in the intensive care unit has proven particularly vexing because both components of the decision-making process are insufficiently characterized. The problem is compounded by the fact that interventions in severely septic patients are time critical, the data are complex, and there is at least theoretical potential for harming patients with immunomodulation of the host response to an infectious challenge.

In the previous issue of *Critical Care*, Kyr and coworkers [1] introduce a sophisticated statistical technique for modeling longitudinal data. Given baseline values of serum C-reactive protein (CRP) and patient characteristics, the models presented have the ability to predict future levels of CRP, across diagnostic categories and patient characteristics. The authors recognize their work to be exploratory, and limited by the small size of the cohort, lack of a validation group, and inability to include predictors in the models that could significantly enhance the applicability of the predictions to more refined subgroups or individual patients. However, the work is relevant to critical illness.

The critical care community's best effort to address sepsis is crystallized in the recommendations of the Surviving Sepsis campaign [2]. Despite conflicting reports on the efficacy of immunomodulation in sepsis, there is a prevailing view that future, decisive improvement in outcomes will result from targeted, biomarker-guided immunomodulation [3,4]. However, how the targeting should be achieved and how biomarker profiles should be interpreted remain open fields of inquiry. In this regard, the development of data-driven models that 'explain' the dynamics of markers of septic physiology may prove useful.

There are, however, two caveats. First, in view of observed variability between patients, how confident can one be when ascribing an individual patient to a specific disease subgroup, and how soon during the course of disease can this be accomplished? Such knowledge could help in selecting a therapeutic strategy that is most appropriate for the particular disease subgroup. The second caveat pertains to the assumption that disease modification is reflected in a longitudinal biomarker profile and, *vice versa*, that modification to this time course reflects disease modification. Whether this assumption is valid will in all likelihood depend on the mechanistic role played by the biomarker in the disease process. A corollary of this observation is that, in the absence of actual data describing the evolution of biomarker data in the presence and absence of treatment with a given therapeutic agent, it is unlikely that such models - in isolation - can direct titrated care. This would best be accomplished by a

CRP = C-reactive protein.

type of mechanistic model that 'understands' the drivers of disease progression.

These considerations may herald a more immediate usefulness of statistical modeling of longitudinal data in acute illness. We anticipate that knowledge-driven mechanistic disease models will be most useful in describing the molecular and physiologic manifestations of acute illnesses such as sepsis [5-8] and will be necessary to augment the rational design of upcoming clinical trials of immunomodulators in sepsis [9,10]. However, such models are difficult to design and to calibrate from existing data. Furthermore, the methods used to adapt mechanistic models to describe individualized disease progression are still under intense development [11]. There exists a definite complementarity between the class of models presented by Kyr and coworkers [1] and such mechanistic models. Statistical models that reliably segregate physiologic classes of severity [12] and quantify patient heterogeneity could assist in designing and calibrating relevant mechanistic models. Indeed, Kyr and coworkers [1] report that physiologic abnormalities take longer to resolve in patients with the most severe forms of sepsis, and that trauma and surgery are associated with more modest increases in CRP. These findings are clearly related to underlying physiologic mechanisms and represent predictions that must be made quantitatively by mechanistic models of sepsis [13].

The past few years have witnessed an increasing number of reports that employ sophisticated modeling techniques in the description and prognostication of acute illness, and in the rational design and interpretation of bench-top experiments. Access to these techniques will require the input of a greater number of quantitative scientists with an enhanced range of expertise. Similarly, this increased level of sophistication must not be a disincentive to editors of clinical journals to publish such papers. Rather, the current pool of reviewers of most clinical journals must be extended to quantitative scientists, as most senior editors have realized. The large scientific societies that represent critical care practitioners must play a leadership role by offering a forum for the quantitative and clinical scientists who are currently promoting these new modeling approaches, and who are much under-represented at international meetings. Smaller societies, such as the Society for Complexity in Acute Illness are pioneering in this field, offering a tantalizing forum for applications of new, sophisticated modeling methods in acute care [14] and a platform for computer scientists, engineers, statisticians, mathematicians, biologic scientists, and clinicians to share challenges and ideas [13]. Clinicians should not only be part of this wave, but they must lead in clearly communicating a research agenda that is of transitional relevance.

To conclude, sophisticated new statistical techniques of class identification and trajectory analysis promise to improve diagnosis, prognostication, and titration in critical care. These techniques are complementary to a growing array of mechanistic disease models, and will prove essential to the development of rational drug design and targeted care in critical illness.

Competing interests

GC is Vice President of the Society for Complexity in Acute Illness. GC is a minority shareholder in, and has received consulting fees from Immunetrics, Inc. (Pittsburgh, PA, USA), a biosimulation company.

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