

Nature and nurture: the future of predictor variables

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The traditional approach to the severity of illness systems in the critically ill has relied on clinical variables. These systems, although increasingly refined and improved, continue to have difficulties. After the investigation of the pathogenesis of diseases in the critically ill it is becoming more apparent that patient response to disease and eventual outcome is strongly influenced by genetic predisposition. Although this ability is in the early stages of development, it may be possible in the future not only to predict patient outcome but also to preempt clinical management through knowledge of a patient's genetic susceptibility. *Curr Opin Crit Care* 2000, 6:166–170 © 2000 Lippincott Williams & Wilkins, Inc.

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Abbreviations

ICU intensive care unit
IL interleukin
TNF tumor necrosis factor

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Severity of illness adjustment scores for the critically ill were developed as a mechanism to evaluate systematically the quality and effectiveness of care in intensive care units (ICUs) [1]. These systems [2–6], developed over the last 20 years, determine the prediction of hospital outcome of patients in an ICU. The calculated predictions have been used as “gold standard” outcomes, and deviations from these have been touted as determining high- or low-performing ICUs [7,8]. The use of severity of illness adjustment systems has also been extended to clinical trials, whereby patients can be matched according to their severity of illness [9].

The ideal severity adjustment system

The ideal severity of illness scoring system must be developed from objective data that is not the subject of interpretation by the data collector [10] and independent of the type of therapy given to the patient that may be uniquely physician-dependent [11–13]. Data collection must be easy, simple, and without the involvement of complex variables such as hemodynamic calculations [14,15]. Any system that is developed must be highly sensitive and specific, must discriminate effectively between survivors and nonsurvivors (usually determined by the drawing of a receiver operating characteristic curve [16]) and must be calibrated across prediction bands [17].

Determination of patient outcome

In 1981 Knaus *et al.* [3] proposed that a patient's outcome was determined by four patient factors (type of disease, severity of presenting disease, physiological reserve, and response to therapy) and two treatment factors (type of therapy and skill and timing of therapy). To date no system accurately and easily accounts for all these factors.

Historical overview

The majority of the severity of illness systems used in the critically ill have been based upon the measurement of various physiological and biochemical variables. They measure the systemic response to injury or disease by assessing the impact upon function. The variables are then weighted according to the degree of derangement, and summed, resulting in a physiological score. In some systems these scores are then adjusted for the patient's admitting ICU diagnosis [2–4], age [2–6], previous chronic health [2–6], and source of admission [2–6]. After these adjustments, a prediction of hospital outcome is determined.

The earlier severity of illness systems that were developed required either the collection of large amounts of data [3], were complex and difficult to use, or required computer systems to operate [18,19]. Over the last decade there has been considerable fine-tuning with minimization of data collection [6], resulting in systems that are more sensitive and specific [4]. Refinement has incorporated the availability of a greater number of diagnostic categories available [4] (making it easier to categorize a patient according to his or her diagnosis), adjusting for the location of the patient before admission to the ICU [4], and the amount of time spent in the emergency department before admission [4]. Some systems have also reduced the number of variables collected and the time period over which they are collected [6].

Difficulties with severity of illness systems

No system perfectly adjusts for the patient's severity of illness in intensive care. In 1981 Knaus *et al.* [3] acknowledged six broad components affecting patient outcome (type of disease, severity of presenting disease, physiological reserve, response to therapy, type of therapy, and skill and timing of therapy) current systems address these only in part. There has been little attempt to design a system whereby the patient's response to treatment over time is observed and outcome prediction altered as a result.

Ongoing problems with the available systems include a continuing subjective element to data collection, resulting in lack of uniformity of data between units. The subjective elements of data collection are not only the determination of the level of consciousness (which can skew the physiological score considerably [20]), but also the categorization of a patient on admission according to admitting diagnosis. Other difficulties that arise include the number of variables that still have to be collected, and the fact that most systems require data collection over the first 24 hours after admission. This means that the calculation of prediction of hospital outcome does not occur at the time of the patient's admission, and data collection remains burdensome. It may also be true that the severity of illness systems do not account for or measure an important (yet unknown) variable that may significantly affect hospital outcome.

Severity scoring systems have failed to adjust for factors known to affect outcome, *eg*, system process (country, type of hospital, ICU, or treating physician) [21,22]. Indeed, there is no adjustment for the fact that "worst values" may have resulted from "worst care," which may or may not then accurately predict a patient's outcome. Equally, there is no adjustment for the care of the patient both pre- and post-admission to intensive care, which can equally have an effect on the eventual outcome of a patient [23–25]. To take these factors into

account, larger national databases will need to exist to determine the differences that various systems can have upon patients.

Novel concepts concerning prediction of outcome

Pathogenesis of disease and outcome

Subsequent to the development of all severity of illness scoring systems, there has been a determination to establish the pathogenesis of various diseases, including the development of sepsis and multiple organ failure, both common causes of morbidity and mortality in the ICU [26•]. In an attempt to elucidate the pathogenesis of disease, it has been important to distinguish between the markers of the disease and mediators of the disease. Markers can aid clinical decision-making and, ultimately, may be useful in the identification of appropriate candidates for phenotype-specific (and perhaps genotype-specific) interventions. However, mediators, by virtue of a causal relation, may be more effective guideposts toward effective and focused therapy. One approach to differentiating between mediators and markers utilizes a modern version of Koch's postulates: that is, that the mediator is detectable in all cases of the disease; that administration of the mediator reproduces the features of the disease; and that pharmacologic blockade of the mediator prevents development of the disease.

Tumor necrosis factor (TNF) (formerly called TNF- α or cachectin) has been shown to fulfill this triad of criteria in animal models of endotoxemia [27]. However, TNF is not detectable, at least in the plasma, of all patients with sepsis [28], and treatment with anti-TNF antibodies does not provide consistent protection against mortality in animal models of sepsis [29,30]. Thus, TNF presents an example of a substance that may be a marker rather than a true mediator, given that the Koch's triad of postulates have not been confirmed [30].

Circulating cytokine levels and relation with outcome

In addition to TNF, interleukin 6 (IL-6) and IL-8 concentrations have been associated with the development of multiple organ failure and nonsurvival [31,32]. Since the production of cytokines initiates many of the physiological disturbances that are used as predictor variables in scoring systems, measurement of the circulating cytokines would seem to have promise in further adding to the prediction of outcome in intensive care patients. However, a prospective study in London [33] was unable to demonstrate that there was a good correlation between plasma cytokine concentration and derangement of physiology and eventual outcome, but were able to find that the presence of bioactive TNF in plasma was an independent predictor of mortality. This study's inability to find convincing data may have

resulted from a number of problems, including a heterogeneous patient population, difficulty in standardizing the measurement of cytokines, issues concerning circulating versus bound cytokines, physiological modifiers of cytokines, and the occult effect of both drugs and food.

Genetic influences upon outcome

Advances in molecular genetic research are leading to an ever-expanding appreciation of the potential role of genetic variation in predisposition and subsequent outcome from specific diseases. Importantly, there has been enormous growth in the laboratory and information technologies being used to assess the genetic contribution to disease, such as DNA microarrays and sophisticated graphic representation techniques [34]. These techniques will likely offer powerful insight into complex patterns of DNA variance and gene expression.

Differences in DNA sequences between individuals, or genetic polymorphism, can be important or unimportant. Unimportant mutations can occur in areas of DNA not related to any gene, or in areas of genes or modulating regions of DNA that are not critical parts of the genetic message. Important mutations can occur if critical regions of coding for a gene (such as initiation or termination codes for protein synthesis) or modulator regions (such as a promoter region) are affected, thereby potentially disrupting effective translation or modulation of a specific gene. However, differences in DNA code between individuals associated with observable differences in gene function may be associated, but not necessarily be related in a causal manner. Modifications of unimportant regions of DNA located close to important modifications in a gene or regulatory region may be linked to phenotypic changes; thus, individuals with a specific functional change may all have a similar genetic change, even though the change discovered is not the causal or functional DNA difference.

Aside from the understanding of the structural differences of information (DNA) that could alter the response to disease (which could be known from birth and could be conceivably be transcribed onto a credit card-like information system), knowledge of the control upon gene expression (affect upon mRNA, and downstream signalling) will add further to the understanding of the pathogenesis of disease. These control mechanisms will be complex and probably not practical for use as a marker of prediction of outcome in patients in the near future

Hints of genetic predisposition to disease and outcome

Investigators of cytokine production and outcome in homogenous populations, such as patients with meningococcal disease, have found that there is a strong genetic link.

Westendorp *et al.* [35] studied the first degree relatives of patients who had had meningococcal disease, looking at their white cell production of TNF and IL-10 *in vitro* after stimulation by *Escherichia coli*. It was found that families with low TNF production had a tenfold increased risk for fatal outcome, whereas high IL-10 production increased the risk to 20 fold. Those families that had a combination had the highest risk for a fatal outcome. It is clear from this study that genetic influences upon response to disease plays a vital role in determining eventual outcome. However, the practicalities of performing such tests at the time of ICU presentation to determine outcome are too great and do not offer enough predictability to be of practical use.

Genetic susceptibility

A number of studies have identified polymorphisms within genes that influence the production of products important in the pathophysiology of inflammation and sepsis. In sepsis, differences in gene responsiveness are due to polymorphisms in promoter or regulator regions, rather than to changes in the actual coding for functional proteins. TNF-related polymorphisms have also demonstrated differential gene expression levels [36,37•]. *In vitro* studies demonstrate that gene polymorphisms cause differential gene expression levels and result in different levels of cytokine release. This may identify genetic loci that have some effect on gene regulation. The clinical impact of hypersecretory or hyposecretory tendencies may change in different clinical conditions [38]. Thus, clinical studies correlating polymorphism genotype frequencies to clinically important outcome are necessary to interpret the *in vivo* impact of these genetic differences.

Stuber *et al.* [36] investigated the genetic determinants, which may result in high or low TNF concentrations. They were able to discover that the bi-allelic *NcoI* polymorphism within the TNF locus was a genomic marker for patients with increased TNF- α response and poor prognosis in severe sepsis. TNFB2 homozygous individuals displayed an increased circulating TNF plasma concentration and a high mortality rate. The TNFB2 homozygous individuals were again found in trauma patients with severe sepsis [39]. However, it was concluded that it was possible that *NcoI* polymorphism may not be directly related to sepsis susceptibility but was serving as a linked major histocompatibility complex (MHC) marker because of its location in the class III region of the MHC.

In a large European study [37•], Mira *et al.* observed the frequency of the TNF2 allele in patients with septic shock and the relation to hospital outcome. They found that there was a significant increase in the incidence of

the TNF2 allele in patients with septic shock compared with controls (39% *vs* 18%). Patients who died from septic shock were more likely to have TNF2 polymorphism than those who did not die.

Other genetic studies are trying to elucidate individual differences in the quantity of mediator responses to septic challenges. Along with TNF, IL-1 has been implicated as a central mediator in the pathogenesis of sepsis. The working hypothesis is that individuals with severe sepsis producing large amounts of IL-1 receptor antagonist are afforded a greater level of protection than subjects producing lower levels. Consequently, Fang *et al.* [40] looked at IL-1 receptor antagonist polymorphism and found that there was a relation between a specific polymorphism (IL-1 receptor antagonist A2) and susceptibility to sepsis.

There is now much evidence in the literature that genetics play an important role in the development of disease and the subsequent response and outcome to disease. To use genetic predisposition usefully in the determination of outcome in patients that are critically ill, further research is needed to elucidate its sensitivity and specificity for outcome. It is also apparent that genetic susceptibility varies from disease to disease and possibly from population to population [41], making applicability to a general heterogeneous ICU population difficult. It is not clear whether knowledge of gene data will add to the severity of illness scores or be independent of them. It is likely that certain genetic predispositions will influence current variables that are collected and therefore may in the end be used in isolation. Only further examination of genetic predispositions and their relation to outcome will clarify how they can be used.

Genetic susceptibility will remain an important area of research for the prediction of outcome in patients in intensive care. However, before the literature and knowledge can be used usefully it is important to establish that the same rigorous principles are applied to genetic investigations as they are to any epidemiologic research into the pathogenesis of disease. This, however, is not always the case [42••].

Gender

No severity of illness system uses sex as a variable, although quite clearly there are diseases where sex is an important determinant of its development (ischemic heart disease and male gender). A challenging article from Eachempati *et al.* [43] recently looked at the influence of sex upon outcome in patients with sepsis. In their retrospective analysis of surgical patients with systemic inflammatory response syndrome, they found that female sex was an important independent predictor of increased mortality in critically ill patients with docu-

mented infection. Although this is interesting and should be examined prospectively, it is surprising that no other ICU database has been able to demonstrate a sex difference in outcome.

Race

Race and ethnicity or culture of a patient are also likely to influence the outcome of critically ill patients. Differentiating between underlying genetic influences and the environment that goes hand in hand with the patient's race is often impossible. There is evidence in the literature that certain races are more likely to be susceptible to certain diseases, but this is often as a result of moving from one culture to another, with the adoption of new ways of living.

Conclusions

The traditional approach to severity adjustment systems in the critically ill have relied upon clinical variables. These systems have been refined to such an extent that they can be used in ICU populations with reasonable amounts of confidence. However, they are not perfect and are particularly difficult to use upon an individual prediction basis and in certain (often small) cohorts of patients with specific diseases. The systems pay little attention to the effects of system processes, which quite clearly affect the care and outcome of the patient. It may be that hospitals, ICUs, and treating physicians have their own adjustment factor in the prediction of patients outcome.

Although probably now in the developmental stage, knowledge of genetic susceptibility to certain diseases may well be used in the future to identify patients at high risk of developing a disease and to undertake preventative measures. Indeed, it may be that everyone will have his or her own "credit card" describing genetic data with all the possible implications that may have upon response to disease and eventual outcome. This powerful knowledge would have to be used intelligently by the medical profession if it accurately predicted the outcome of a patient, to allow for the changes and improvements in treatment and hence eventual outcome.

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