Imprecise Medicine: The Limitations of Sepsis-3

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My fascination with sepsis and MODS began in my first month as a critical care fellow, in July of 1983 (ouch). My patients developed a highly lethal disorder that I hadn't previously noticed, a disorder that I didn't understand. I asked around, went to the library (a building, not something made of cDNA), searched the literature (using an antiquated instrument called *Index Medicus*) and read (in journals printed on paper). I found that not much was known and decided that I needed to get involved in research. That initial exposure to sepsis/MODS—'way back when"—shaped my career and, by extension, my life.

My friend and colleague Kevin Tracey tells a similar story–his own fascination with sepsis began with a single patient he managed as a surgery resident. Although Kevin is a neurosurgeon by training, his research has focused on inflammation and sepsis. (Parenthetically, by connecting inflammation and neurosurgery, Kevin was able to recognize and report on the vagally mediated inflammatory reflex [1].) Sepsis has that effect on the fertile mind–it's a captivating disorder, gnawing at the imagination, challenging the notion that there is order in nature, and disrupting closely held beliefs about adaptive responses and disease pathogenesis.

My reflections are in part stimulated by the recent publication of the "Third Consensus Definitions of Sepsis and Septic Shock (Sepsis-3)" (2). It was my privilege to serve as one of the co-chairs of this group, to work with Mervyn Singer as we sought insight and consensus among a group of brilliant–and brilliantly opinionated–experts. Each member was–at some point–forced to put aside at least one closely held viewpoint/belief so that we could fulfill our charge and arrive at consensus. As a result, there are concerns of importance to each task force member that Sepsis-3 left unresolved. I'd like to take this opportunity to inform critical care professionals about several issues that I believe to be particularly pressing.

1. **"Definition" versus "Clinical Criteria".** Of all the intellectual hurdles confronted during the task force deliberations, one in particular stood out–acknowledging that what we have long-called sepsis "definitions" were not really definitions at all. Somehow, the word 'definition' has become ill-defined in medical practice: many accomplished epidemiologists view a 'definition' as something inherently flexible–it is what they want it to be. But, per the *Merriam-Webster Dictionary*, a *definition* is "*a statement expressing the essential nature of something*" or, more simply, "*what something* ***is***". Essential implies immutable, and not subject to change based on convenience. It is relatively simple to define a myocardial infarction–cardiac muscle dies–or poliomyelitis–a specific pathogen attacks anterior horn cells. Both of these disorders have a discernable, verifiable biologic substrate. Sepsis, however, is quite different. We are a long way from being able to confidently state that something constitutes the "*essence*" of sepsis, what sepsis "*is*". This fact is both liberating and limiting. In defining sepsis, we can be quite flexible–"scientific license" allows us to be creative in our proposed definition simply because, at the present time, there is no way to prove that we are right or wrong. Therefore, our definition of sepsis, "*life-threatening organ dysfunction caused by a dysregulated host response to infection*", incorporates the latest information we have regarding sepsis pathobiology. Unfortunately, this definition isn't clinically useful. It doesn't provide a "gold standard" to which other, more clinically viable, approaches might be compared. This is a central problem for the clinician confronted with a sick patient and thus the need to know what the patient *has* in order to decide what to *do*.

The task force's solution was to derive *clinical criteria*–signs and symptoms, laboratory tests or images–that can be recognized by the practitioner at the bedside, and whose utility can be tested in the clinical realm. Yet absent a gold standard, we lack the ability to determine if our clinical criteria really do identify septic patients. The imprecision invokes what epidemiologists call *outcomes validity*–we determined what sort of outcomes might differentiate sepsis from uncomplicated infection (our choices–a long ICU stay or death), and, in several large clinical datasets, tested the ability of various clinical variables to identify those outcomes in patients with infection. This pragmatic approach provides something that is tangible and clinically useful, that can be tested both retrospectively using electronic medical records and prospectively moving forward. It does not, however, bring us closer to that elusive, immutable definition.

Practical consequences:

- Sepsis researchers, both bench and clinical, should consider how their findings might validate or invalidate the new definition;

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- Clinicians should determine if the clinical criteria are useful in their own practices and consider what additional elements ought to be tested;
- sooner rather than later.

2. **Dependent and Independent Variables.** Sepsis is defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection." It's useful to express this definition as if it were a mathematical function:

Sepsis = *f*[(life-threatening)(organ dysfunction)(dysregulated host response)(infection)].

If we consider *infection* as a constant (and we did exactly that by declining to address the definition of infection), we are left with three variables. But the manner in which we have constructed the definition indicates that they are not independent. Rather, the formulation implies a specific temporal relationship–infection provokes a host response that becomes dysregulated, causing organ dysfunction that can become life threatening. But there are also data that raise questions about this pathogenic sequence. For example, a MODS-like state can be experimentally induced by cardiac tamponade (3) and something like MODS can follow non-infectious conditions such as pancreatitis or aortic rupture (4, 5). Furthermore, it has long been postulated that the element of the host response that becomes dysregulated is immunological. Recent studies, however, suggest that dysfunction in the brain gives rise to the dysregulated host response by interfering with the anti-inflammatory activity of the vagus nerve (1) or by altering the hypothalamic activity that underlies abnormalities in other organs–in particular the cardiovascular and endocrine systems (6). It is similarly unclear if organ dysfunction is required for the syndrome to become life threatening. Seminal work on immunosuppression during sepsis suggests that mortality may arise from an inability to prevent secondary infection (7). Thus, the dysregulated (immune) response by itself may be life threatening, without the intermediate requirement for organ dysfunction.

Practical consequences:

- Don't assume that the sequence of events identified in the new definition reflects pathobiological reality, because no one really knows how things are ordered and connected;
- Don't assume that the predominant abnormality in sepsis is immunological–that hypothesis has dominated both mechanistic and therapeutic investigation for over two decades, and has yet to bear fruit.

3. **Appropriate comparators.** Sepsis is now defined in terms of a "dysregulated host response to infection." If that is correct, then the appropriate comparator would be a "regulated host response to infection." How do we design studies that compare the two responses–regulated and dysregulated–and identify the transition?

Those of us who conduct sepsis animal research rely primarily on cecal ligation and puncture (CLP) in rodents as a common model. The blood supply to the cecum (a stool-filled sac located where the appendix is found in humans) is ligated and the sac is punctured. Feces leaks into the abdomen. The control for CLP is sham operation, where a laparotomy is performed and the cecum is manipulated but neither ligated nor punctured. Is this an adequate reference? It may be a model of a regulated host response to (very mild) inflammation but it surely is not a regulated response to infection.

Experts align CLP and human sepsis using four **ordered** attributes–infection **leading to** dysregulated response **leading to** organ dysfunction leading to the life threat. Suppose the implied dependencies are imaginary? Putting aside "life-threatening" as a component, it could be that we require six (3 factorial, or 3 × 2×1) control groups–one with a "host response" but no organ dysfunction or infection and so on. Even if experimentalists exclude "infection" along with "life threatening", a control with (perhaps mechanical) organ dysfunction that doesn't include a dysregulated host response is still required.

Interestingly, clinical studies rarely use balanced inflammation as a control. Rather, septic critically ill patients are most often compared to non-septic critically ill patients. Perhaps the many failures of bench research on sepsis to translate into something that is clinically useful don't reflect a problem with the sepsis model itself but rather with the control that this model is compared with.

Practical consequences:

- We need to reconsider just what constitutes an appropriate control for sepsis research;
- At the very least, we ought to make sure that studies characterizing sepsis in animal models and in patients use similar controls.

And finally,

4. **What comes next**? How–and how soon–do we initiate Sepsis-4**?** I don't know–but let's not wait a decade and a half this time.

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