Definitions for sepsis, septic shock, acute lung injury (ALI), and acute respiratory distress syndrome (ARDS) were developed by consensus conferences with the goal of achieving standardization of terminology and improved homogeneity of patient populations in clinical studies. Although such definitions have been useful in epidemiologic investigations, the criteria specified by the consensus conferences are broad and insufficiently specific to address the problem of heterogeneous mechanisms leading to clinical syndromes. An important challenge is to progress from clinical syndromes, as presently defined, to more specific entities that are delineated by alterations in specific immunologic or biochemical pathways. Such mechanistic definitions will provide more homogeneous groups of patients who can be identified at early stages of their clinical course. This approach encourages focused investigation of pathways leading to organ system dysfunction and death and, also, provides an efficient framework for the development of new therapies useful in critically ill patients.

**Key Words:** sepsis; acute respiratory distress syndrome (ARDS); acute lung injury; septic shock; cytokines; consensus conference; definitions; tumor necrosis factor-α; endotoxin; infection; organ dysfunction.

Multiple recent studies of patients with sepsis, septic shock, acute lung injury (ALI), and acute respiratory distress syndrome (ARDS) have not shown benefit with new pharmacologic therapies, including agents that inhibit endotoxin (1), cytokines (2-4), and cyclooxygenase (5). Although it is possible that the therapeutic agents examined were not effective, an alternate explanation is that the mechanisms leading to acute lung injury or other organ dysfunction in the patients studied were so heterogeneous that even though an agent may have had a positive therapeutic effect in a limited group, such benefit was diluted and not detectable in the overall study population.

The criteria for patient inclusion in these interventional trials were partially or totally based on
descriptive clinical definitions of sepsis, septic shock, ALI, and ARDS that were established by consensus conferences (6, 7). The consensus conference definitions, although useful in providing an initial clinical basis for identification of patients with injury to the lungs or other organ systems, do not refer to the underlying pathophysiology responsible for organ dysfunction. However, as understanding of the biochemical and inflammatory mechanisms that produce alterations in pulmonary and other organ function after infection, shock, trauma, aspiration, and other causes has increased, there is reason to believe that the use of such information in formulating new definitions may identify critically ill patients who are more likely to respond to novel therapies.

Early epidemiologic studies and therapeutic trials of sepsis, septic shock, ALI, and ARDS used a range of clinical definitions, which made it difficult to compare the results from one study with another. For example, definitions for ARDS were often complicated by different diagnostic criteria. Most definitions used indices of oxygenation, but the severity of hypoxemia was not the same. Also, there was no standard approach to interpretation of chest radiography or in the measurement of altered lung compliance (7). In an effort to achieve greater patient homogeneity in clinical trials, consensus conferences were held in which the clinically relevant characteristics for ALI, ARDS, sepsis, and septic shock were specified (Table 1 and Table 2). Unfortunately, the criteria specified in these consensus conference definitions may be too broad and insufficiently specific to account for the problem of patient heterogeneity. For example, the consensus conference definition for ARDS does not specify how the bilateral infiltrates on the chest radiographs are to be interpreted, the length of time necessary for the diagnosis of "acute" lung injury, or the specific clinical risk factors that are required.

Table 1. Consensus conference criteria for sepsis and septic shock

<table>
<thead>
<tr>
<th>Criteria for Sepsis and Sepsic Shock</th>
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</thead>
<tbody>
<tr>
<td>- Initial clinical signs</td>
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<tr>
<td>- Presence of infection</td>
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<td>- Organ dysfunction</td>
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</tbody>
</table>

Table 2. Consensus conference criteria for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)

<table>
<thead>
<tr>
<th>Criteria for ALI and ARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Bilateral infiltrates</td>
</tr>
<tr>
<td>- Hypoxemia</td>
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<tr>
<td>- Oxygenation indices</td>
</tr>
</tbody>
</table>

More than 12,500 patients meeting the consensus conference definitions of sepsis and/or septic shock have been recruited into studies of anti-inflammatory agents (8). Similarly, more than 1,500 patients with ALI or ARDS using consensus conference definitions have been enrolled in trials designed to investigate new ventilatory or pharmacologic therapies for these conditions (9). The National Institutes of Health ARDS Network recently demonstrated that the use of small tidal volumes (6 mL/kg) reduced mortality compared with conventional tidal volume ventilation. However, the study was directed toward ventilator-induced lung injury and not to the cause leading to ALI or ARDS. None of the multicenter trials has shown a clear beneficial effect on overall survival or other clinically relevant end point when treatment was aimed at a presumed cause of ALI, ARDS, or sepsis. It is certainly possible that this disappointing series of negative results may simply reflect the lack of efficacy of the new therapies in patients with acute inflammatory conditions initiated by infection or other noninfectious causes. However, because subgroup analyses in many of these studies suggest benefit in more rigorously defined patient groups (2, 3, 8), it is possible that the consensus conference definitions include patient...
populations that are too heterogeneous to demonstrate a therapeutic response to interventions aimed at a single step in the inflammatory process producing organ system dysfunction.

It was recognized in both the sepsis and ALI/ARDS consensus conferences that the definitions were descriptive, rather than mechanistic, and that the definitions described clinical syndromes, rather than specific pathophysiologic processes. The consensus conference definitions are based on clinical, laboratory, and radiologic abnormalities, without including any specific reference to the biochemical, immunologic, or pathophysiologic pathways that are activated to arrive at the point at which organ system dysfunction is clinically apparent. The lack of mechanistic homogeneity implicit in the all-encompassing consensus conference definitions is problematic because it results in heterogeneous patient populations. For example, patients with primary viral pneumonia will be classified the same as patients with Gram-negative septic shock or aspiration of gastric contents. This clinical classification may prevent appropriate evaluation of new therapeutic agents able to affect discrete mediators involved in biochemical or immunologic cascades activated in some, but not all, patients with severe infection and other conditions leading to subsequent organ system dysfunction, including acute inflammatory injury to the lungs.

PATHOPHYSIOLOGY OF SEPSIS AND ACUTE LUNG INJURY

Extensive animal and patient studies have examined the inflammatory cascades initiated by infection, trauma, burns, and hemorrhage (10, 11). These studies have demonstrated the complexity and multiplicity of pathways involved in these pathophysiologic processes, and they indicate that differences in the initial insult, combined with underlying conditions, can result in the activation of different inflammatory mechanisms. For example, neutrophils may be important in mediating acute lung injury from aspiration of gastric contents (12) and septic shock (13), but neutrophils may be protective in primary bacterial pneumonia (14).

Epidemiologic studies of sepsis, ALI, and ARDS have demonstrated similar variability between activation of inflammatory pathways and outcomes that depend on underlying conditions and risk factors leading to inflammatory lung injury and other organ system dysfunction (13, 15). For instance, alcoholics appear to be more susceptible (16) and diabetics less susceptible (17) to ARDS, even with similar pathophysiologic insults. Circulating adhesion molecules, such as intracellular adhesion molecule 1, are increased after sepsis in patients who develop ARDS, but the concentrations are not increased in trauma patients before the appearance of ARDS (18). Endotoxemia is often present in infected patients at risk for ARDS (19) but not in patients who have suffered major accidental trauma (20).

These preclinical and clinical data suggest that mechanisms of organ dysfunction in sepsis and ALI/ARDS may differ depending on the initial pathophysiologic event and the patient's underlying condition. Because of the heterogeneous mechanisms that lead to organ system failure, it would not be anticipated that all patients would respond to the same therapy. Even if specific groups of patients could be identified in which dysregulation of a particular mediator, such as tumor necrosis factor (TNF)-α, is known to play a role in the development of acute organ system dysfunction, the relative importance of that mediator compared with other cytokines is unknown. Future clinical studies of new therapies, therefore, must serve two purposes: a) to characterize the disease process more completely by showing that the specifically targeted biological mediator is producing organ dysfunction or death; and b) to test the efficacy of the drug's ability to modify the actions of the targeted mediator. The salient point that
emerges is that therapies that are more specifically directed at the inciting mechanism need to be given
early to patients who are more clinically, immunologically, and biochemically similar.

LIMITATIONS OF CONSENSUS CONFERENCE DEFINITIONS

The consensus conference definitions for sepsis and ALI/ARDS define syndromes, but they do not
include reference to the underlying pathophysiology. By eliminating references to the mechanisms that
cause organ failure, the intensivist is placed in a position somewhat analogous to that of the
rheumatologist who is examining cyclophosphamide for the treatment of rheumatoid arthritis but uses
joint swelling as the only entry criterion for the study. In this setting, many patients with osteoarthritis
would be included in the trial. In contrast, using indices of autoimmune activation as entry criteria would
permit identification of a more appropriate patient population that is likely to respond to cytotoxic agents.

In the case of ALI/ARDS, the consensus conference definition requires only the presence of two positive
criteria (bilateral infiltrates on the chest radiograph and arterial hypoxemia) and one negative criterion
(absence of clinical evidence of cardiogenic pulmonary edema). This definition permits inclusion of a
multiplicity of clinical entities ranging from autoimmune disorders, such as Goodpasture's syndrome,
Wegener's granulomatosis, and acute lupus pneumonitis to direct pulmonary injury attributable to causes
as diverse as pneumonia, aspiration of gastric contents, or smoke inhalation to indirect pulmonary injury
from bacteremia, hemorrhage/trauma, or pancreatitis. Treatment for most of these causes of ALI/ARDS
is only supportive at present. However, in some these conditions, such as typhoid fever (21), Wegener's
granulomatosis, and Goodpasture's syndrome, specific therapies, including immunosuppressive drugs,
can ameliorate the lung injury.

Although neutrophil activation, release of proinflammatory mediators in the lungs, or increased vascular
permeability may contribute to acute injury to the lungs, no specific reference to these or other
mechanisms is part of the consensus conference ALI/ARDS definition. Therefore, designing an
appropriate study to investigate an agent that affects one of the multiple pathways involved in producing
lung injury is difficult if many patients without activation of that pathway are included in the definition.
For example, the consensus conference definition of ALI/ARDS permits the inclusion of neutropenic
patients, but such patients would reasonably be excluded from studies examining antineutrophil agents.
Again, it is apparent that all-inclusive definitions that might be useful in clinical description and teaching
will not necessarily be optimal for testing new therapeutic agents that should have the greatest efficacy
when targeted to a specific pathophysiologic process that may exist only in a subset of patients.

The consensus conference definition of ALI focuses on pulmonary physiologic abnormalities to identify
patients. However, these physiologic abnormalities are not specific for clinical ALI. For example, a
recent clinical study (22) reported that a quantitative evaluation of oxygenation, compliance, level of
positive end-expiratory pressure, and extent of radiographic pulmonary infiltrates resulted in the same
physiologic score in patients who were being ventilated for hydrostatic pulmonary edema and patients
with clinical ALI. These two groups could be separated when physiologic markers for inflammatory lung
injury were examined because higher concentrations of protein and of a marker for collagen synthesis in
the lung, procollagen peptide III, were present in lung edema fluid from the patients with ALI (22).

Another important omission in the consensus conference definitions for ALI and ARDS is the failure to
specify the presence of nonpulmonary organ system dysfunction at the time of diagnosis. Several clinical
studies have reported the important prognostic significance of nonpulmonary organ system failure...
present at the time ALI is diagnosed (23, 24). For example, hepatic dysfunction is a major adverse prognostic factor in most studies.

Similar problems with cause and pathogenesis are present in the definitions of sepsis and septic shock. Organ system dysfunctions are defined by clinical variables, but there is no reference to the biochemical or immunologic mechanisms of injury operative in each patient. This has proven to be a significant problem in the anticytokine trials, because many patients without evidence of increased TNF or interleukin-1 were included, and, as might be expected, this lack of activation of the mediator of interest may have contributed to the negative results found in studies examining the effects of therapy with these agents (2). Similarly, the consensus conference definitions of sepsis and septic shock do not include consideration of the length of time that the infectious process has been present or of the anatomical source of infection, even though animal studies have shown different patterns of response to anticytokine therapy, such as anti-TNF-α monoclonal antibodies, for intra-abdominal infections compared with bacteremias and for rapidly initiated infectious processes, such as acute bacteremia, compared with more slowly developing infections, such as peritonitis (25). No microbiological classifications are used in the consensus conference definitions of sepsis or septic shock, even though responses to anti-inflammatory therapies may differ between Gram-positive and Gram-negative infections and anti-inflammatory therapies appear to be more effective in patients with documented infections, a factor not required in the consensus conference definitions (3, 26).

FUTURE DIRECTIONS

Understanding the range of pathways that lead to organ system dysfunction after endotoxemia, bacteremia, and localized infections permits classification of infected patients based on their underlying pathophysiology and may permit inclusion of appropriate patients into therapeutic studies earlier in their clinical course, before organ dysfunction develops. Such a classification scheme, in addition to allowing appropriate targeting of patient populations that may benefit from a specific therapeutic agent, would also mean that the development of clinically relevant organ system dysfunction can be used as an end point rather than as an entry criterion for clinical trials.

In this model, patients with clinical evidence of infection but without organ system dysfunction, and with alteration of the mediator of interest, such as TNF-α or activated protein C, would be eligible for study enrollment. Techniques that allow rapid measurement of endotoxin or cytokines are now available (27, 28) and can be adapted for the bedside, allowing increases of these mediators to be used as an entry criterion.

Increased homogeneity of patient populations may also be achieved by initially limiting the nature and site of the infection. Such an approach is currently being taken in trials examining treatment with the antiendotoxin agent bactericidal/permeability-increasing protein in patients with meningococcemia (29).

A similar mechanistic approach to achieve greater homogeneity in underlying pathophysiologic process can be adopted for what is currently defined as ALI but that, in fact, groups together a wide variety of pathophysiologic processes. Although reference still needs to be made to the physiologic severity of pulmonary dysfunction, such as abnormalities of oxygenation, more homogeneous patient groups can be identified using mechanistic markers. For example, measurement of procollagen peptide III in the air space of the lung may identify patients who are destined to develop fibrosing alveolitis with particularly
high mortality (22). As with sepsis, use of entry criteria that refer to the underlying mechanism will not only permit more accurate and earlier targeting of patient populations likely to respond to a particular intervention but also will allow the variables of lung injury, such as the need for mechanical ventilation or the development of infiltrates on the chest radiograph (now included as entry criteria for clinical trials) to be used instead as end points because they no longer define the entity being studied.

The use of mechanistic definitions to define patient populations at risk for developing inflammatory lung injury or infection-initiated organ system dysfunction lacks the reductionist simplicity of the consensus conference definitions of sepsis or ALI/ARDS, which generate large numbers of patients presenting with similar constellations of clinical findings. In contrast, mechanistic definitions will provide more homogeneous groups of patients at earlier stages of their clinical course with activation of similar immunologic or biochemical pathways. These patients should respond to interruption of inflammatory or other cascades if the mediators generated are truly important in contributing to the subsequent clinical course, particularly the development of organ system dysfunctions and patient outcome. Using more stringent definitions in clinical trials, of course, would restrict the numbers of patients eligible for a specific therapy until another study can examine a larger at-risk population. However, unless benefit can first be shown in a rigorously defined patient population in which there is specific evidence of mediator activation, there is little reason to anticipate that efficacy will be achieved in larger, more heterogeneous patient groups. Additionally, such mechanistic definitions, as opposed to the consensus conference syndromes, are hypothesis generating because new groups of patients will naturally evolve as our knowledge of pathophysiologic mechanisms grows. Such an approach will drive not only the development of new therapies for the critically ill patient but also will provide a structure for investigation into the pathways that lead to organ system dysfunction and death.

REFERENCES [Click here for reference links. (27 references linked.)]


