Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination

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Abstract. The acute respiratory distress syndrome (ARDS), a process of non-hydrostatic pulmonary edema and hypoxemia associated with a variety of etiologies carries a high morbidity, mortality (10–90%) and financial cost. The reported annual incidence in the United States is 150000 cases, but this figure has been challenged and may be different in Europe. Part of the reason for these uncertainties is the heterogeneity of diseases underlying ARDS and the lack of uniform definitions for ARDS. Thus, those whose wish to know the true incidence and outcome on this clinical syndrome are stymied. The European American Consensus Committee on ARDS was formed to focus on these issues and on the pathophysiologic mechanisms of the process. It was felt that international coordination between North America and Europe in clinical studies of ARDS was becoming increasingly important in order to address the recent plethora of potential therapeutic agents for the prevention and treatment of ARDS.

Key words: ARDS – ALC, Acute lung injury – Consensus report – Clinical trial

The acute respiratory distress syndrome continues as a contributor to the morbidity and mortality of patients in intensive care units throughout the world, imparting tremendous human and financial costs. Widely reported figures place the incidence of ARDS at approximately 150000 cases per year in the United States alone, although this figure has frequently been challenged and

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Lausanne, Switzerland. *3) Risk factors, prevalence and relevant outcomes of ARDS.* Chairpersons: L.D. Hudson, MD, University of Washington, Seattle, WA and J.R. LeGall, Paris, France. Members included: T. Hyers, St. Louis University, St. Louis, MO; W. Knaus, George Washington University, Washington, DC; R. Matthay, Yale University; M. Pinsky, University of Pittsburgh, Pittsburgh, PA. *4) Mechanisms of clinical study coordination.* Chairpersons: R. Spragg, University of California, San Diego, CA, and K. Falke, Berlin, Germany. Members included G.R. Bernard, Vanderbilt University Medical School, Nashville, TN; R.C. Bone, Rush Medical College, Chicago, IL; C. Bosken, NIH, NHLBI, Division of Lung Diseases, Bethesda MD (the views of Dr. Bosken are her own and do not necessarily represent those of the NIH/NHLBI); W.G. Johanson, New Jersey School of Medicine, Newark, NJ; K. Lewandowski, Berlin, Germany; J. Repine, University of Colorado Health Sciences Center, Webb Waring Institute for Biomedical Research Denver, CO; R. Rodriguez-Roisin, Hospital Clinic Barcelona, Spain; C. Roussos, Evangelismos Hospital, Athens, Greece. *Other contributors:* M.A. Antonelli, University degli Studi, Rome, Italy; S. Beloucif, Paris; D. Bihari, Guy's Hospital, London, UK; H. Burchardi, University of Göttingen, Germany; F. Lemaire, Paris; P. Montravers, Paris; T.L. Petty, University of Colorado Health Sciences, Center, Denver, Co; J. Robotham, Baltimore, MD; W. Zapol, Massachusetts General Hospital, Boston, MA

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may be an overestimate [1 – 4]. The published mortality rate of patients with ARDS varies from 10% to as high as 90%. The difficulty in determining the incidence and outcome of ARDS is largely due to the heterogeneity and lack of definitions for the underlying disease processes, the lack of definition for ARDS, the non-uniformity of therapy, and the failure to define the population within which ARDS patients are identified [4]. Thus, those whose wish is to know the true incidence and outcome of this clinical syndrome are stymied [5 – 11].

Under the auspices of the American Thoracic Society and the European Society of Intensive Care Medicine, a series of meetings were held in conjunction with the American Thoracic Society Annual Meeting on May 15, 1992 in Miami, Florida and with the European Society of Intensive Care Medicine Annual Meeting on October 26, 1992 in Barcelona, Spain. The American-European Consensus Committee on ARDS was formed in an attempt to bring clarity and uniformity to the definition of Acute Lung Injury and ARDS. In addition, an attempt was made to add a degree of order to the issue of incidence, to focus on the rapidly evolving knowledge of the pathophysiologic mechanisms of the process and to establish guidelines for the conduct and coordination of clinical studies. Special impetus to form this committee was provided by the desire to enhance international coordination between North American and European scientists in the conduct of clinical studies and to better deal with the ever-expanding plethora of potential, but still unproven, therapeutic approaches and agents for the prevention and treatment of ARDS.

The members of the Consensus Committee were divided into subcommittees, each of which were charged with discussing and developing a position paper on at least one aspect of the problem. These position papers were presented to the entire Committee for comments and discussion. When the committee reached agreement, specific modifications were made to the position papers. The following subcommittee reports are a result of this consensus process.

Subcommittee I: definitions

Background and controversies

The subcommittee appointed with defining ARDS had perhaps the most difficult task and its recommendations were met with the greatest discussion by the parent committee. Some participants suggested that ARDS be defined differently for the purposes of research, epidemiology, and individual patient care; ultimately, however, it was decided that one definiton should apply for all of these areas.

Early on it was decided that there should be a return to the original term *acute* (rather than *adult*) respiratory distress syndrome in recognition of the fact that ARDS is not limited to adults [12]. In this report, 1 of the 12 patients reported was 11 years old. Confusion over the term can be traced to an article appearing in 1971 in which "adult" was used as part of the term [13]. This creeping of "adult" into the term is now regretted by at least one of the authors (T.L.P, personal communication). Second, it was recognized that the clinical spectrum of presentation included a continuum of arterial blood gas and chest radiograph abnormalities and that the cut-off point for any definition of ARDS would be arbitrary. It was agreed, however, that the term *acute lung injury* (ALI) could be applied to a wide spectrum of this continuum of pathological process so as to acknowledge and define it. It was felt that the term ARDS should be reserved for the most severe end of this spectrum. Thus all patients with ARDS have acute lung injury but not all patients with acute lung injury have ARDS.

Although they may present with similar abnormalities, patients with hypoxemia and pulmonary infiltrates caused by volume overload and/or heart failure (left atrial hypertension) were not considered to have ALI or ARDS although, such patients may also have ARDS in addition to hydrostatic edema. Mechanical ventilation support was not considered a requirement in defining ALI or ARDS because both ventilator therapy resources and physician practice patterns vary considerably. Also, there are many cases in which mechanical ventilation is intentionally withheld due to patient request or a determination that aggressive support is futile. It was recognized that for clinical studies it may sometimes be desirable to exclude non-mechanical ventilated patients to allow for better assessment of pulmonary parameters. Finally, the committee recognized that since ALI and ARDS are not specific disease entities, any definitions would be compromised by the necessity of imposing somewhat arbitrary threshold limits.

Recommendations

The Committee recommends that acute lung injury be defined as a syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiologic, and physiologic abnormalities that cannot be explained by, but may co-exist with, left atrial or pulmonary capillary hypertension. It is associated most often with sepsis syndrome, aspiration, primary pneumonia, or multiple trauma. Much less common associations include cardiopulmonary by-pass, multiple transfusion, fat embolism, pancreatitis and others. ALI and ARDS are acute in onset, and persistent, e.g. lasting days to weeks, are associated with one or more known risk factors, are characterized by arterial hypoxemia resistant to oxygen therapy alone, and are associated with diffuse radiologic infiltrates. Chronic lung diseases such as interstitial pulmonary fibrosis, sarcoidosis and others which would technically meet the criteria except for the chronicity are excluded by this definition. Specifically, the recommended criteria for ALI and ARDS are as follows:

Acute lung injury criteria

● Timing: Acute onset
● Oxygenation: $PaO_2/FiO_2 \leq 300$ mmHg (regardless of PEEP)
● Chest radiograph: Bilateral infiltrates seen on frontal chest radiograph

- Paw: ≤18 mmHg when measured or no clinical evidence of left atrial hypertension

ARDS criteria (same as acute lung injury except)

- Oxygenation: $PaO_2/FiO_2 \leq 200$ mmHg (regardless of PEEP level)

Considerable discussion centered around the cut-off between ALI and ARDS with regard to the PaO_2/FiO_2 with many suggesting that the level defining ARDS should be < 150 rather than < 200. Although it was easily accepted that some patients would readily be called ARDS but have a PaO_2/FiO_2 above 150 mmHg, serious concerns were raised over the possibility that the more liberal definition may allow the inclusion of processes associated with altered gas exchange but not considered to be in the realm of ARDS. Recent data from a large registry of ARDS patients defined as above but using a PaO_2/FiO_2 limit of 250 mmHg, indicate that greater than 98% of these patients ultimately met the ARDS criteria used in clinical trials in ARDS, but did so 1 to 7 days earlier than would have been the case if the lower ratio were used [14–16]. Thus, the cut-off < 200 was accepted with the expressed caution that careful exclusion of other disease processes be carried out in order to minimize the chance of including non-ARDS related illnesses.

It was also recognized that PEEP can have a profound influence on pulmonary shunt fraction, however, response to PEEP is not consistent. Furthermore, effects of PEEP are often time dependent, i.e., a certain amount of PEEP applied for 5 min does not necessarily have an equal effect as the same level of PEEP applied for 2 h. For these and other reasons, PEEP was left out of the oxygenation criterion. It was felt that chest radiographic infiltrates should be bilateral, should be consistent with pulmonary edema and importantly these infiltrates could sometimes be very mild. Some panelists suggested that in occasional cases the radiograph may be clear for a period of time prior to the development of infiltrates and others suggested that patients with severe unilateral disease should be included but there was not a clear consensus on these latter issues. Pulmonary artery wedge measurement was not considered essential for diagnosis in all cases but was recognized as clearly useful in some cases, especially where cardiac pulmonary edema is a distinct clinical possibility.

As mentioned in the introduction to this report, the incidence of ARDS is still controversial and studies need to be done to determine the true incidence by utilizing ICU, hospital, regional, and national databases where incidence data on ARDS are kept. Based on recent studies by Thomsen et al. [4], the incidence of ARDS may be lower than originally estimated [1]. Determination of incidence of acute lung injury and ARDS will be affected by their definitions. Since increased pulmonary microvascular permeability is considered a hallmark of ALI, research into methods of quantifying altered pulmonary permeability is encouraged. There was consensus that many patients are given the diagnosis of ARDS and managed as such clinically even though they do not meet most published definitions of ARDS. In this regard, the com-

mittee hoped that the broader definition of acute lung injury would quantitate more accurately the impact of this clinical entity on society in general and the health care system specifically.

Subcommittee II: mechanisms of acute lung injury

Background and controversies

Acute lung injury should include injury to both the lung endothelium and the epithelium and should be defined pathophysiologically in quantitative terms whenever possible. It is important to note that clinical lung dysfunction sufficient to cause respiratory failure may occur with injury exclusively to one or the other barriers, though at present, there is no clinical means to make this determination. Scientific questions which remain relatively uninvestigated or controversial relate to interactions among organs, factors which determine whether host responses are pathologic or homeostatic, the phenomenon of tolerance, reasons for species differences in responses to toxins, relationships between perfusion and lung cellular injury, and factors determining whether responses are directed toward increased injury or toward repair.

The committee noted that there are many accepted causes (etiologies) of acute lung injury. In general, it is useful to think of the pathogenesis as consisting of two pathways – the direct effects of an insult on lung cells and the indirect result of an acute systemic inflammatory response. The clinical correlates of these processes are described in the report from subcommittee III below.

The inflammatory response includes both cellular and humoral components. The cellular response involves neutrophils, macrophage/monocytes, and lymphocytes. Cellular events which may have a role in the process include adhesion, chemotaxis/chemokinesis and activation. These latter processes include the expression of cell adhesion molecules (integrins and selectins).

Events in the inflammatory response include alterations which occur in plasma independent of cells (complement system, coagulation/fibrinolysis and kinin systems), the mediators generated by cells (cytokines, lipid mediators, oxidants, proteases, nitric oxide, growth factors and neuropeptides) and induction of protein synthesis such as activation of NFkB, an early step in the production of cytokines. These factors were generally considered to be responsible for cell injury and defects of surfactant balance, ventilation-perfusion matching, etc. In spite of considerable effort, the committee could not reach a consensus on the order of events in the pathogenesis of acute lung injury. In fact, many participants felt that the pathogenesis is different for different precipitating causes of acute lung injury and that our current level of knowledge is neither sufficient to allow an intelligent conclusion about the precise sequences of events nor sufficient to allow a determination of which of these putative mechanisms are more important.

Recommendations

The consensus was that the emphasis of future investigations should be placed on relating cellular and humoral

events to physiology and to measures of clinical outcome. Several desired characteristics of experimental studies should be emphasized: 1) A definition of the time course of pathogenetic events: there is certainly a sequence of pathogenetic events and the time course is critical to understanding the overall process. 2) Mediators or any other factors studied should be measured quantitatively. 3) Relationships between amounts of mediators at different sites (e.g. blood vs airspaces) and the pathogenetic significance of localization of mediators are probably important variables. 4) The presence of mediators should be correlated with quantitative measurements of pathophysiology.

Subcommittee III: risk factors, prevalence and relevant outcomes

Background and controversies

The clinical risk factors for ARDS and the outcome of the process have been described in detail elsewhere [17–18] but little is known about acute lung injury in this regard. Therefore, the discussion for this subcommittee was limited primarily to ARDS. There was general consensus that risk factors should be categorized into direct and indirect. There was considerable discussion regarding the sepsis syndrome category with some participants wishing to use the category of systemic inflammatory response syndrome (SIRS) recently proposed by a consensus conference on sepsis [19]. However, the majority of the participants felt that the criteria for SIRS were so liberal as to include a large number of patients who would not be at significant risk for ARDS resulting in a very low incidence. The specific sepsis syndrome definition was not discussed and the description given below reflects criteria employed in several clinical research settings [16–20]. The incidence of ARDS identified with these various definitions ranges from 25–42% and appears to be increased when sustained hypotension is present as part of the syndrome.

There was controversy regarding diffuse lung infection. The question is: If a pulmonary infection becomes diffuse and severe enough to meet ARDS criteria, should it be included under the ALI and ARDS definitions? The consensus was that pulmonary infection, e.g., pneumocystis carinii pneumonia, should be considered ALI/ARDS when the physiologic criteria listed above are met, although this was not a unanimous decision.

The prognosis for ARDS, as determined at the time of either hospital or ICU admission, is based on a variety of key factors such as the acute underlying diagnosis (e.g., head trauma, metastatic cancer, etc.); etiology (e.g., aspiration, sepsis, etc); severity of illness as measured by pulmonary and non-pulmonary factors, (e.g., Apache II/III, SAPS, SAPS II); physiologic reserve, as measured by chronologic age; co-morbidities and pre-existing conditions such as AIDS, leukemia, or other disease that affect the patient's immune status [21–24]. The available scoring systems (Apache II and III, SAPS I and II, MPM 85, 87 and 92, and others) give either a score or a risk of death. They can be useful to stratify and compare groups

of patients. For maximal usefulness in clinical decision making, a scoring system should include only those measurements and observations which are readily available, widely acceptable, objective and easily quantifiable. Because the knowledge base is constantly changing and because of the need to compare studies, it is preferable that the raw data be retained in the score. Clearly, more work needs to be done in this area.

Once treatment and patient support has begun, prognostic factors relate to serially obtained data that measure the patient's response to therapy. There are published data suggesting that while oxygenation (PaO_2/FiO_2) is an unreliable prognostic factor at the onset of ARDS, it does appear to be predictive of outcome when examined at 24 to 48 h after onset [8, 9]. These prognostic factors relate to pulmonary as well as non-pulmonary systems and physiology (e.g., development of multiple organ system dysfunction). The development of secondary diagnoses and/or complications (e.g., acute myocardial infarction, or single or multiple organ failure) have a profound impact on the ultimate outcome. Based on autopsy studies, the persistence of clinically unrecognized secondary sepsis is thought to be particularly indicative of a bad prognosis [25].

The major categories of ARDS risk discussed by the subcommittee were as follows:

I. Direct injury:
   A. Aspiration
   B. Diffuse pulmonary infection (e.g., bacterial, viral, Pneumocystis infection and others)
   C. Near-drowning
   D. Toxic inhalation
   E. Lung contusion
II: Indirect injury
   A. Sepsis syndrome, with or without clinically significant hypotension, e.g. (systolic blood pressure ≤ 90 mmHg), with or without evidence of infection outside the lung. This syndrome can be described as having both signs of systemic inflammation, (i.e. by abnormalities of body temperature, heart rate, respiratory rate, and white blood cell count) and signs of organ system dysfunction including, but not limited to, pulmonary, hepatic, renal, central nervous system, and the cardiovascular system.
   B. Severe non-thoracic trauma as indicated by:
      1) Clinical description
      2) Scoring systems such as the injury severity score (ISS) or Apache II/III.
      3) Treatment interventions, such as the Treatment Intervention Scoring System (TISS)
   C. Hypertransfusion for emergency resuscitation.
   D. Cardiopulmonary bypass (rare).

Recommendations

The long term outcome can be measured in a variety of ways. Hospital mortality or 30-day mortality are still the primary endpoints in most studies but other endpoints such as 2 and 6 month survival are important. The quality of life in survivors, as determined by such indices as

the sickness impact profile (SIP), Nottingham, and other quality of life scales is also important. These quality of life scales have only recently begun to be applied to acute lung injury [26].

In order to capture the information needed to interpret outcome, a minimum data set should include the following: screening criteria, etiology/risk factor, severity (both pulmonary and non-pulmonary), age, gender, co-morbidity, time from clinical risk (etiologic event, e.g. sepsis) onset to ARDS onset, complications during illness, time of extubation, and death. Short term outcome predictions require data on changes in gas exchange, lung or thoracic compliance, sequence of organ system dysfunctions, changes in physiology, and risk of death over time. Decisions to limit or withdraw therapy should also be considered as short term outcomes. One objective would be to relate short term outcomes such as changes in gas exchange to long term outcomes such as functional status and mortality.

Subcommittee IV: mechanisms that promote clinical study coordination

Background and controversies

The committee recognized the value of a clinical environment that provides the best possible ethical clinical care while at the same time providing reliable data capture and control of therapy. Also recognized was the fact that standardization of any aspect of clinical trial design, while providing uniformity, reduces flexibility. But it was agreed that uniformity should be given priority in protocol design because resultant noise reduction is the best way to deliver significant results from clinical trials. Sometimes standardization is reduced because flexibility in trial design is required to allow multiple centers and individuals to participate in collaborative efforts.

Definition of standard therapy. Substantial discussion took place regarding the value and feasibility of defining standardized care and employing these definitions in clinical trials. In principle, it would be ideal to obtain consensus on standardized therapy and to use this as a gauge against which new interventions could be measured. Historically, it has been difficult to impose standard approaches to the treatment of ARDS on multiple practitioners within an institution, let alone on practitioners in wide-spread diverse institutions. Nonetheless, standardized approaches are becoming increasingly acceptable as evidenced by a recent report describing the success of standardizing one of the most difficult areas in intensive care, mechanical ventilation [27]. The committee felt strongly that this process of standardization for the conduct of clinical trials should continue in cases where strong data exist which support certain clinical methods.

Several therapeutic methods are believed to be so uniformly accepted that, although they have not been formally tested, they may be considered as standards. These include: supplemental oxygen, PEEP/CPAP, mechanical ventilation (if required to support gas exchange), avoidance of fluid overload, and delivery of care in the ICU setting. The committee acknowledged that, although variations exist in how these elements of care are delivered, there are few data to substantiate the advantage of one method over another. This leaves a clear way for the ethical standardization of care for research purposes. In this vein, the Committee endorsed the goal of defining boundaries to interventions and patient management so as to minimize variability. During a specific study, it may be important to define which elements of care must be rigidly defined and/or kept constant and which may vary. Major variables in treatment must be identified and stratified (e.g. use of ECMO or various pharmacologic interventions).

Approaches to testing novel interventions. The committee made several observations in this regard. First, approval to proceed with the study of an individual patient should be facilitated in every way possible while protecting the rights of that patient. Informed consent from the patient or, much more commonly, from next of kin or other appropriate surrogate decision-maker is desirable even when interventions with a high benefit/risk ratio are used. The committee felt strongly that consent from the patient's next-of-kin should be accepted in most clinical trials. Consent/assent should be implied if the patient is unable to give consent and a good-faith effort to reach the next-of-kin is unrewarding. Assent, specifically and directly from the next-of-kin or legal guardian becomes more desirable for studies with a lower or less certain benefit/risk ratio.

Second, the design of studies was discussed in some detail. While specific design recommendations cannot be provided at this point, there was a strong sentiment that pivotal (FDA-Phase III) studies require the prospective randomization of patients into study and control groups. Studies that use historical controls may be effective for hypothesis generation, endpoint selection, sub-population identification, and/or dosing, but are inappropriate for statements of efficacy.

Several investigators have attempted to study ARDS prospectively in groups of patients identified as being at risk for developing the syndrome. Prospective identification of patients who subsequently develop ARDS is made difficult by rapid development of the syndrome. In addition, some disorders (risk factors) that preceed the development of ARDS have a low incidence of the syndrome. A maximal incidence of approximately 25% may be expected and this incidence is seen in hypotensive septic patients. Thus, prospective studies that use such high-risk groups must expect to include large numbers of patients. Longitudinal studies of patient groups may provide clinical models of ARDS and are to be encouraged. Such groups may include patients undergoing aortic aneurysm resection, or pulmonary artery thromboendarterectomy.

The design of studies may be inclusive or exclusive depending on the questions being asked by the study. In general, the patient population to be studied should be defined as narrowly as possible relative to the intervention's expected mechanism of action. For example, surfactant supplementation should only be studied in a pop-

ulation known to have surfactant dysfunction or which is at high risk of developing dysfunction.

Stratification of severity. Accurate stratification of patients into clinical studies will depend on definitions that provide information on the degree of disease severity — not just on the presence or absence of disease. Additional stratification by predisposing cause is currently desirable, though not always achievable due to the limited numbers of patients in subcategories. Althoug stratification by disease mechanism is not now possible, this could become a reality in the near future. Stratification of ARDS severity along the lines suggested by Murray et al. [28] may be useful. At this point, such a definition of ARDS severity serves mainly to assign a numerical score to various abnormalities which make up the syndrome. If subsequent studies show that this score is in some way predictive of final outcome, it, or one like it, should be used in addition to the more general scores (e.g. Apache) in clinical studies of ARDS patients. Scores that maintain the quantification and identify of the raw data used to produce the score would be superior to those in which the raw data quantities are lost in a composite. For example, a score which identifies key components, e.g. PaO_2/FiO_2 and lung compliance as well as quantifying severity would likely be more useful than a composit score combining several variables such that severity quantification of the components is lost.

Data collection. Several general principles can be stated about a given database, particularly if it is related to a multicenter trial performed in collaboration with industry. There should be prospective definitions of: (a) ownership of the database; (b) access to the database; and (c) the time-line for access to the database. Because of the potential conflict of interest, ownership of the database by industry sponsors is to be discouraged. However if industry retains ownership, it is strongly encouraged that information within the database be disseminated to workers in the field after appropriate analysis and reporting. This should be accomplished in a timely fashion. Within a database, there is a need for descriptors of: (a) the patient's baseline status, including the underlying etiology; (b) the evolution of the disease process; and (c) the treatment modalities.

In the routine screening of patients for clinical studies, all sequential patients discovered through the particular screening plan for a given study who meet study inclusion criteria must be accounted for in the database. This is not to imply that screening must include 100% of patients in a given hospital. For example in many centers only one ICU (e.g. surgical ICU) is actually screened. If the patient identified as meeting study criteria is later excluded, appropriate documentation of reasons for the exclusion and the patient outcome, should be included. The point of this type of reporting is to give a clear idea of the entire screened population that meets this study definition and not just the enrolled patients.

Assessing success. Clinical outcome must be the final arbiter of success in interventional clinical studies of ALI.

Mortality remains the desired efficacy endpoint, especially for pharmaceutical studies that will later be presented to the United States Food and Drug Administration to obtain drug approval. However, tenacious adherence to this endpoint makes the development of adjunctive therapies more difficult. Since mortality is a dichotomous endpoint and since mortality in ALI is only partially due to the pulmonary process, the use of mortality as the only endpoint for all interventional clinical studies of ALI is problematic. For pilot studies performed to gain information rather than prove efficacy, it is important to identify physiological and/or biochemical endpoints. Such endpoints should also be employed in pivotal studies wherever possible. As more experience is gained in the systematic study of patients with ALI, it seems likely that these surrogate endpoints may be identified.

Recommendations and future studies

I. The following is a list of goals for clinical coordination efforts:
   1. Design studies to provide long-needed information on the incidence of ARDS.
   2. Provide for the rapid evaluation of clinical interventions and promote widespread availability of the data. Discourage private ownership of large databases.
   3. Develop a database of centers interested in and capable of performing clinical studies so that large populations of patients are accessible for the investigation of disease mechanisms and therapeutic interventions that relate to ALI.
   4. Conduct all clinical trials for efficacy of agents or therapies in a controlled prospective fashion; exceptions may be those with limited endpoints such as pharmacokinetics evaluation.
II. Mechanisms that would help to achieve these goals:
   1. Development of a mechanism for organized and efficient information clinical specimen sharing between multiple centers.
   2. Development of standardized clinical management protocols to improve the signal to noise ratio of clinical studies and to allow for direct comparison of data between studies. Computerization of protocols would likely aid in this process.
   3. Development of randomization procedures which balance major variables, e.g., PaO_2/FiO_2, Apache II Score, etc, or on major clinical interventions known at baseline such as extracorporeal membrane oxygenation.
   4. Development of standardized informed consent procedures emphasizing the next-of-kin's role and other methods of surrogate consent when appropriate.
   5. Acquisition of study populations that are as homogeneous as possible recognizing that this will require more multicenter collaboration.
   6. Establishment and standardization of quality assurance procedures so that objective evaluation of the quality of information generated by clinical studies can be accomplished.

7. Routine inclusion of fully independent data and safety monitoring committees in the design of large scale clinical trials.

III. Routine data collection should include certain elements the collection of which are considered to be imperative:

1. Age, height, weight, race, gender, residence address with zip code.

2. Vital signs.

3. Chest radiograph findings.

4. Information pertaining to pulmonary function and oxygen delivery:

a) P_aO_2, P_aCO_2, pH, and hematocrit.

b) Ventilatory parameters including peak, mean, and plateau pressures; PEEP/CPAP; tidal volume; minute ventilation; F_iO_2; and mode of ventilation; inspiratory to expiratory ratio; respiratory rate.

c) Cardiac output when monitored.

5. Additional descriptors of organ systems function (including circulatory, renal, hepatic, etc.). The date and time of onset, as well as the resolution of these major organ system dysfunction/failure should be noted; precise criteria for each organ system dysfunction or failures are needed.

There are additional data whose collection the committee felt would be desirable, although not imperative. These data include the central hemodynamic measurements made available when a pulmonary artery catheter is in place, additional data describing the day to day level of major organ function, and data provided by bronchoalveolar lavage. The timing of data collection will need to be tailored to the therapeutic interventions under examination.

The collection of plasma, pulmonary edema fluid (if present), and other bodily fluids is desirable. Mechanisms for collection, processing, and storage of these fluids should be standardized. Samples should be made available to qualified investigators when adequate supplies exist:

Broader View of Coordination mechanisms. The committee believes that this process of developing mechanisms for performing clinical studies in ALI and ARDS should be expanded beyond the boundaries of this Conference. A small working group of representatives from the American Thoracic Society, American College of Chest Physicians, American Heart Association, European Society of Intensive Care Medicine, European Respiratory Society, Society for Critical Care Medicine, National Institutes of Health and other interested parties should be identified. These representatives could facilitate additions and/or amendments to this document, could help with the standardization of therapy for clinical study purposes, and could act as monitors of clinical trials and other studies of patients with ALI.

Summary

This consensus committee, like others that have convened in the past, had the daunting task of establishing basic definitions as well as suggesting an agenda for future scientific investigation. Regardless of whether the consensus definitions and recommendations of the Committee have a major impact of health care and research in the area of ALI, it is clear that open and meaningful discussions of these issues between scientists in North America and Europe have begun. There is certainly much that remains to be done and follow-up conferences have been scheduled during which discussion will center around issues in clinical management. These points will include ventilation, pharmacology, and other forms of supportive therapy. It is sincerely hoped that these conferences will spur the development of an integrated international strategy for defining, quantifying, and studying acute lung injury and the acute respiratory distress syndrome.

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