19 Update in Intensive Care and Emergency Medicine

Edited by J.-L.Vincent

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Clinical Trials for the Treatment of Sepsis

With 61 Figures and 74 Tables

Springer-Verlag
Berlin Heidelberg New York
London Paris Tokyo
Hong Kong Barcelona
Budapest

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ISBN-13:978-3-642-79226-7 e-ISBN-13:978-3-642-79224-3
DOI: 10.1007/978-3-642-79224-3

Softcover reprint of the hardcover 1st edition 1995

SPIN: 10478360 19/3130-5 4 3 2 1 0 – Printed on acid-free paper

Preface

Sepsis and Innovative Treatment: The Odyssey

R. C. Bone

The Odyssey by Homer, dates back to the 8th century, B.C. [1]. It is a great epic adventure of Odysseus's dramatic journey from Troy back home to Ithaca. Odysseus survives the ordeals of this journey and returns with new powers and insights. The study of the pathogenesis and treatment of sepsis has also been an odyssey. I feel we will return from this odyssey with new insights and treatments. However, as with Odysseus, this will occur only after considerable struggle.

In the 1980s we had a rather simplistic view of sepsis. It was a highly lethal complication caused by infection and often characterized by shock and multi-organ failure. Our knowledge of the inflammatory responses associated with sepsis was embryonic compared to today. The inflammatory response was often treatment with mega-dose corticosteroids along with fluid resuscitation, vasopressors and antibiotics. Because of the paucity of multi-center controlled trials documenting the risk/benefit ratio of the treatment of sepsis with corticosteroids, two large multi-center controlled trials were organized to evaluate the role of corticosteroids in sepsis [2, 3]. Because animal models showed benefits of corticosteroids only with pre-treatment or early treatment, a definition of sepsis was used that did not require positive culture documentation or septic shock to be included in the studied population. The sepsis syndrome was used as a definition and is as follows:

> Sepsis syndrome consists of sepsis which is clinical evidence of infection, tachypnea, tachycardia and hyperthermia or hypothermia plus evidence of altered organ perfusion including one or more of the following:
>
> 1) acute changes in mental status;
> 2) $PaO_2/FiO_2 \leq 280$ without other pulmonary or cardiovascular diseases as the cause;
> 3) increased lactate, and
> 4) oliguria [4].

The sepsis syndrome had a predictable mortality rate, incidence of shock, incidence of bacteremia, and subsequent development of multi-organ failure. This definition or a modification of it has been used for all subsequent large sepsis trials.

Our hope of finding a "magic bullet" to treat sepsis has been frustrating. Part of this frustration emanates from our incomplete understanding of sepsis and the conduct of clinical trials. However, like Odysseus, we now recognize that we are now on an incredible journey with a destination yet to be determined. What are the bright spots?

1) Our knowledge of the pathogenesis of sepsis has made incredible advances in the past two decades;
2) Our knowledge of the epidemiology of sepsis has advanced;
3) Our appreciation of the complexity of the inflammatory response and its beneficial and detrimental aspects are now appreciated more completely; and
4) Our design and conduct of clinical trials have achieved greater scrutiny.

These advances have been achieved because of dedicated investigators that have carefully documented the results of their trials, a pharmaceutical industry that has fostered the support and leadership possible to conduct such trials, and the Federal Drug Administration (FDA) which has worked diligently with investigators and the pharmaceutical industry to learn from our past clinical trials.

I believe we are now on an analytic review of our sepsis trials that may allow us to enter a new stage in the understanding of sepsis. This Round Table Conference on Clinical Trials for the Treatment of Sepsis is such a much-needed scrutiny. I regret that I was unable to attend the Conference in Brussels on March 12–14, 1994, because of a hypernephroma that hopefully was cured by a nephrectomy. Indeed, I was encountering my own odyssey. I appreciate the invitation from Drs Vincent and Sibbald to write a preface to this Round Table Conference. I feel we are on the brink of a new understanding and possible new treatments for sepsis. Our odyssey with sepsis has just begun!

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Common Abbreviations

ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
ATP	Adenosine triphosphate
AIDS	Acquired immuno-deficiency syndrome
COP	Colloid osmotic pressure
CPAP	Continuous positive airway pressure
DIC	Disseminated intravascular coagulation
DNA	Desoxyribonucleic acid
DO_2	Oxygen delivery
G-CSF	Granulocyte-colony stimulating factor
GI	Gastrointestinal
GSH	Glutathione
ICU	Intensive care unit
IL	Interleukin
IV	Intravenous
IVIG	Intravenous immunoglobulin G
IL-1ra	Interleukin-1 receptor antagonist
LPS	Lipopolysaccharide
MODS	Multiple organ dysfunction syndrome
MOF	Multiple organ failure
NADPH	Nicotinamide adenine dinucleotide phosphate
NAC	N-acetylcysteine
NMR	Nuclear magnetic resonance
PAF	Platelet activating factor
PCr	Phosphocreatine
PDH	Pyruvate dehydrogenase
PEEP	Positive end-expiratory pressure
pHi	Gastric intramucosal pH
REE	Resting energy expenditure

ROC	Receiver-operator-characteristics
ROS	Reactive oxygen species
SIRS	Systemic inflammatory response syndrome
SOD	Superoxide dismutase
TNF	Tumor necrosis factor
TPN	Total parenteral nutrition
VO_2	Oxygen consumption/uptake

Clinical Trials in the Treatment of Sepsis: An Evidence-Based Approach

D.J. Cook

Using the Literature to Solve Patient Problems

The purpose of this Round Table Conference on Clinical Trials for the Treatment of Sepsis is to summarize the current, most valid literature in the field.

The biomedical literature is expanding at a compound rate of 6–7% per year; it doubles every 10 to 15 years [1]. Keeping abreast of the latest medical developments in sepsis is a daunting prospect for clinicians. Today, more than ever, practitioners require the ability to efficiently assess the validity and applicability of published evidence, and the ability to incorporate this assessment into patient care [2, 3]. When any promising therapeutic option is available to clinicians, they are burdened with the dilemma of deciding who, if anyone, should receive this therapy. To make these difficult treatment decisions involves proficiently selecting, critiquing, synthesizing and applying relevant information from the critical care literature. It also involves identifying all available options and possible outcomes, weighing the benefits against the risks and costs, and factoring in logistic, economic, legal and possibly social considerations [4]. If every intensivist attempted to do this for every diagnostic or therapeutic decision, the result would be exhaustion!

Clearly, shortcuts are needed. Physicians are now beginning to use the medical literature more effectively to guide clinical therapy. A profusion of articles instructing clinicians on how to access [5], evaluate [6], and interpret [7] the medical literature exist. Another solution to the complexity of day to day decision making in the ICU is replacing preference-based practice with practice based on current, comprehensive summaries and evidence-based clinical recommendations [8].

We hope that the proceedings of this conference, in which we critically appraise and summarize the relevant literature on the management of sepsis, will help to serve this goal, and direct future research in this field.

Organization of the Conference

The conference was divided into five sessions. Session I is "The Epidemiology of Sepsis", in which an overview of the distribution and determinants of

sepsis has been provided. Session II focused on "Monitoring the Treatment of Sepsis". Endotoxins and inflammatory mediators, measures of total body and organ-specific oxygen availability, multiple organ dysfunction and illness severity scores will be discussed in light of their descriptive and prognostic utility in the septic state. In Session III, entitled "The Clinical Management of Sepsis", widely used therapeutic interventions were critically examined, with reference to the quality of evidence supporting their use in daily practice. In these chapters, we will refer readers to the level of evidence provided by the current literature on the use of antibiotics, intravenous fluids, transfusion therapy, vasoactive drugs and nutrition. Session IV is on the "Investigational Therapy of Sepsis". In this session, newer experimental modalities have been highlighted, including anti-endotoxin therapy, non-steroidal anti-inflammatory drugs and steroids, anti-TNF, interleukin antibodies, platelet activating factor antagonists, granulocyte-colony stimulating factors, pentoxifylline, prostaglandins, N-acetylcysteine and bradykinin antagonists. Because many of these agents have not been evaluated in randomized clinical trials in humans, the strenght of inference that can be drawn from these studies will be tempered by the fact that the evidence may be biologic but not clinical. Though they may yield important information about modifying the pathophysiology of sepsis, many of these studies are hypothesis-generating, and must still be rigorously evaluated in clinical trials before they are adopted into daily practice. Session V in this conference is entitled, "Designing the Ideal Clinical Trial for the Treatment of Sepsis". In these addresses, the principles of clinical epidemiology and biostatistics were used to highlight crucial issues in the design and conduct of trials in sepsis. Strategies which were addressed included choosing the design, specifying the population, intervention and outcomes, avoiding bias and minimizing random error, and considering statistical and economic issues. Practical problems about trial monitoring and the ethics of experimentation in animals and humans were also addressed.

Clinical Judgement and Evidence in Therapeutic Decision-Making

What rules of evidence ought to apply when expert committees meet to generate recommendations for the clinical management of patients with sepsis? Should only the thoroughly validated results of randomized clinical trials be admissible to avoid or minimize the application of useless or harmful therapy? Or, to maximize the potential benefits to patients, should a synthesis of the experience of seasoned clinicians form the basis for such recommendations?

Ample precedent exists for the latter approach even when attempts are made to replace it [9]. However, for the following reasons, the non-experimental evidence that represents the recalled experiences of clinicians will tend to overestimate efficacy:

1. Even in critically ill patients with marked physiologic derangements, some symptoms (e.g. transient ischemic attacks) or signs (e.g. increased intracranial pressure) and extreme laboratory test results, when they are reassessed a short time later, tend to return toward the more usual, normal result [10]. Because of this universal tendency for regression toward the mean, which may be part of the natural history of a condition, any treatment (regardless of it efficacy) that is initiated in the interim will appear efficacious, even when it might not be.
2. Routine clinical practice is never "blind"; clinicians always know when active treatment is under way. As a result, the desire of clinicians for success can cause an overestimate of the efficacy of an intervention (recall bias). The overestimate may in part be a consequence of bias in interpretation of diagnostic tests which indicate whether patients have developed an adverse outcome (such as the radiographic diagnosis of ARDS). In rare situations when critically ill patients are conscious and aware of their treatment in a clinical trial, their desire for a successful outcome, and the well-known placebo effect [11] may also tend to overestimate the benefit of treatment.
3. Favorable treatment responses are more likely to be recognized and remembered by clinicians when their patients comply with treatments. There are already 6 documented instances in which compliant patients in the placebo groups of randomized trials exhibited far more favorable outcomes (including survival) than their non-compliant companions [12–17]. Because high compliance is therefore a marker for better outcomes, even when treatment is useless, our uncontrolled clinical experiences often will cause us to conclude that compliant patients (i. e. most ICU patients) must have been receiving efficacious therapy.

For the preceding reasons, treatment based upon uncontrolled clinical experience risks precipitating the widespread application of treatments that are useless or even harmful. These same treatments are much less likely to be judged efficacious in double-blind, randomized trials than in uncontrolled case series of unblinded, "open" comparisons with contemporaneous or historical series of patients; hence the maxim: "Therapeutic reports with controls tend to have no enthusiasm, and reports with enthusiasm tend to have no controls."

The foregoing discussion should not be misinterpreted as constituting a mandate for discarding the large body of uncontrolled observations by clinicians who have managed patients with sepsis. For some treatments of sepsis, randomized control trials have not yet been carried out (nor because of overwhelming evidence of efficacy from cohort studies, are they likely to be conducted), and the only information base for generating some of the recommendations comes from systematic clinical observations.

However, it is clear that it is important, whenever possible, to base firm recommendations (and especially those involving risk to patients) on the results of rigorously controlled investigations and scientific overviews, and to

be much more circumspect when recommendations rest only on the results of data from subexperimental studies, non-human studies and uncontrolled clinical observations. This philosophy and approach to practice is often referred to as evidence-based medicine [13].

Levels of Evidence and Grades of Recommendations

In this conference, we use a set of guidelines called, "Levels of Evidence and Grades of Recommendations". These guidelines for interpreting the literature were fruitfully adopted by the participants of the First [14] and Second [15] American College of Chest Physicians Antithrombotic Consensus Conferences. The result was a series of evidence-based clinical recommendations supported by summaries of the best available evidence for all treatments of thrombotic disorders. The definition of levels of evidence and grades of recommendations were also adopted by the Canadian Cardiovascular Society Task Force on the Use of Thrombolytic Therapy; the Canadian Cardiovascular Society Consensus Conference on the Management of the Postmyocardial Infarction Patient [16]; The Ontario Oncology Group, and is now being used to formulate recommendations of the US Preventive Health Services Task Force (David Sackett, personal communication, Washington 1992).

These guidelines are simple, and useful in evaluating the validity of primary clinical trials. The guidelines we are using in this conference are also relevant in evaluating the validity of scientific review articles. If a comprehensive and unbiased overview of methodologically rigorous studies is available, it follows that this should be used in developing treatment policies. An overview that incorporates a quantitative summary of the data is called a meta-analysis, and, in resolving issues of therapeutic effectiveness, represents the highest form of evidence for deciding on the strength of inference supporting a treatment recommendation [17]. Scientific overviews, when optimally conducted, include all the relevant trials of high quality (Level I or II evidence), chosen in an explicit, unbiased fashion.

The participants in this conference, when summarizing what was known about the causes, clinical course, and management of sepsis, began by specifying the level of evidence that was used in each case, according a classification described below. This framework can be applied to primary research (individual studies) and synthetic research (scientific overviews or meta-analyses).

Primary Research: Individual Studies

Level I: Randomized Trials with Low False-Positive (α) and Low False-Negative (β) Errors (High Power)

By "low false-positive (α) error" is meant a "positive" trial that demonstrated a statistically significant benefit from experimental treatment. For ex-

ample, there have now been several randomized trials in which oral anticoagulants produced very large, statistically significant reductions in the risk of stroke and death among patients with non-valvular atrial fibrillation. By "low false-negative (β) error (high power)" is meant a "negative" trial that demonstrated no effect of therapy, yet was large enough to exclude the possiblity of a clinically important benefit (i.e. had very narrow 95% confidence intervals, the upper end of which was less than the minimum clinically important benefit, thereby excluding any improvement due to the test treatment). For example, the ISIS-III randomized trial has ruled out any clinically significant difference in the efficacy of streptokinase, tPA, and APSAK in acute myocardial infarction. The elements of a valid and useful randomized trial are summarized in Table 1.

The advent of meta-analysis permits us to sharpen this classification further by generating a "pooled" estimate of the treatment's efficacy across all the high quality, relevant trials. Meta-analyses also reveal any inconsistencies in the estimates of efficacy between trials ("heterogeneity"), highlighting those that require further scrutiny before an overall treatment policy can be generated.

Level II: Randomized Trials with High False-Positive (α) and/or High False-Negative (β) Errors (Low Power)

By "high false-positive (α) error" is meant a trial with an interesting positive trend that is not statistically significant. For example, the HA-1A study by Ziegler and colleagues [9] generated a positive but not statistically significant trend favoring HA-1A in sepsis (placebo: 43% mortality; HA-1A: 39%, $p=0.24$). By "high false-negative (β) error (low power)" is meant a "negative" trial which concluded that therapy was not efficacious, yet was compatible with the real possibility of a clinically important benefit (i.e. had very wide 95% confidence intervals on the effect of experimental therapy). For example, several trials of anticoagulants in completed thrombotic stroke con-

Table 1. Elements of a valid and useful randomized trial

1. Are the results valid?
   a) Was the assignment of patients to treatments really randomized?
   b) Were all patients who entered the study accounted for at its conclusion?
   c) Were the clinical outcomes measured blindly?
2. Is the therapeutic effect important?
   a) Were both statistical and clinical significance considered?
   b) Were all clinically relevant outcomes reported?
3. Are the results relevant to my patient?
   a) Were the study patients recognizably similar to my own?
   b) Is the therapeutic maneuvre feasible in my practice?

cluded that such treatment was ineffective when, in fact, the confidence intervals on the treatment effect they observed ranged from virtually eliminating subsequent deterioration and death to doubling the risk of these outcomes. In this situation, the 95% confidence interval includes the minimal clinically important difference, and clearly the strength of inference is lower than would be the case for Level I studies.

The advent of meta-analysis has a major impact here, for it can show that two or more high-quality, homogeneous but small (and therefore Level II) trials really provide Level I evidence of treatment efficacy. Stated another way, when Level II studies are pooled, the lower limit of the confidence interval around the pooled estimate may then become greater than the minimal clinically important difference, rendering the aggregate of several Level II studies now Level I evidence.

Level III: Non-Randomized Concurrent Cohort Comparisons between Contemporaneous Patients who did and did not Receive Antisepsis Therapy

In this case, the outcomes of patients who receive (and complied with) antisepsis therapy would be compared with those of contemporaneous patients who did not (through contraindication, oversight, local practice, refusal, etc.) receive these same interventions. The biases described earlier are usually in play here. Although Level III–V data can be subjected to meta-analysis, such overviews are difficult to interpret, and we therefore do not recommend this approach.

Level IV: Non-Randomized Historical Cohort Comparisons between Current Patients who did Receive Antithrombotic Agents and Former Patients (from the Same Institution or form the Literature) who did not

In this case, the outcomes of patients who received antisepsis therapy (as a result of a local treatment policy) would be compared with those of patients treated in earlier era or at another institution (when and where different treatment policies prevailed). To the biases already presented, must be added those that result from inappropriate comparisons over time and space.

Level V: Case Series without Controls

In this situation, the reader is simply informed about the fate of a group of patients with sepsis. Such series may contain useful information about clinical course and prognosis but can only hint at efficacy.