

CLINICAL AND SCIENTIFIC IMPORTANCE OF SOURCE CONTROL IN ABDOMINAL INFECTIONS: SUMMARY OF A SYMPOSIUM

John M.A. Bohnen, MD;* John C. Marshall, MD;* Donald E. Fry, MD;† Steven B. Johnson, MD;‡ Joseph S. Solomkin, MD§

In May 1997, a panel of surgeon-investigators met to discuss the clinical importance and research implications of controlling the source of abdominal infections. It was concluded that source control is critical to therapeutic success and that antimicrobial therapy and other adjunctive interventions will fail if the source of infection is not controlled by resection, exteriorization or other means. The panelists presented different definitions of source control, depending on the scientific purpose of the definition. All participants agreed that failure to consider the adequacy of source control of infection has limited the value of most clinical trials of therapeutic anti-infective agents. Besides recognizing source control as an essential goal of patient care, the panelists emphasized the need for further investigative work to define, record and stratify the adequacy of source control in clinical trials of therapeutic agents for abdominal infections.

En mai 1997, un groupe de chirurgiens chercheurs s'est réuni pour discuter de l'importance clinique du contrôle à la source des infections abdominales et de ses répercussions sur la recherche. Le panel a conclu qu'il est crucial de contrôler la source d'infection pour que le traitement réussisse, et qu'une thérapie aux antimicrobiens et d'autres interventions d'appoint échoueront si l'on ne contrôle pas la source d'infection par résection, extériorisation ou autrement. Les panélistes ont présenté des définitions différentes du contrôle de la source selon l'objet scientifique de la définition. Tous les participants ont reconnu qu'en ne tenant pas compte de la suffisance du contrôle de la source d'infection, on a limité la valeur de la plupart des études cliniques portant sur des agents anti-infectieux thérapeutiques. Les membres du panel ont reconnu que le contrôle de la source d'infection constitue un but essentiel du soin des patients et ils ont aussi souligné que d'autres études s'imposent pour définir, consigner et stratifier la suffisance des moyens de contrôle de la source dans le cadre d'études cliniques portant sur des agents thérapeutiques contre des infections abdominales.

On May 3, 1997, the Surgical Infection Society (SIS) sponsored a panel discussion on control of the source of microbial contamination in abdominal infections. Dr. John Marshall from the University of Toronto chaired and in-

troduced the panel, charging them with defining source control, assessing its impact on clinical trials of therapeutic agents and considering how guidelines could be developed to incorporate source control and related issues in the design of clinical trials.

"Source control" refers to management of the source of leakage of microbial pathogens from the gut, such as by resection or drainage. Although the panelists concentrated on scientific issues, they voiced repeatedly the clinical implications of source control.

*From the *Department of Surgery, University of Toronto, Toronto, Ont., the †Department of Surgery, University of New Mexico, Albuquerque, NM, the ‡Department of Surgery, University of Arizona, Tucson, Ariz., and the §Department of Surgery, University of Cincinnati, Cincinnati, Ohio*

Presented as a panel discussion at the 17th annual meeting of the Surgical Infection Society in Pittsburgh, Penn., May 3, 1997

Accepted for publication June 4, 1998

Correspondence to: Dr. J.M.A. Bohnen, Room 204, Jones Building, St. Michael's Hospital, Wellesley Central Site, 160 Wellesley St. E, Toronto ON M4Y 1J3; fax 416 926-4916

© 1999 Canadian Medical Association (text and abstract/résumé)

DEFINITION

The clinical and scientific importance of source control was discussed by Dr. Donald Fry and became a recurring theme of the session. Dr. Fry stated that continuous leakage of infected material from a gastrointestinal source would guarantee the failure of treatment with any therapeutic regimen. Examples of ill-advised surgical strategies, such as repairing rather than exteriorizing a dehiscence intestinal anastomosis and performing a major gastric resection in a physiologically compromised patient, were cited.

The speakers could not agree on a definition of source control (Table I). Dr. Fry defined source control as a mechanical process that contains, restricts and eradicates from the peritoneal cavity microbial pathogens, inflammatory exudates and necrotic tissue that drive the systemic septic response. Dr. Bohnen expressed a narrower definition of source control: mechanical procedures that stop further leakage of microbial contaminants from the gut or other source, using a single method or a combination of methods such as patch, closure, resection, drainage, diversion or exteriorization. Dr. Bohnen stated that source control should be separated definitionally from methods used to reduce the amount of material resulting in an inflammatory response (i.e., peritoneal toilet), as these 2 therapeutic actions differ in technique and

purpose. For example, without control of a gastrointestinal leak, a patient with generalized peritonitis will usually die or suffer some other adverse outcome regardless of the appropriateness of anti-infective agents; however, once a gut leak has been controlled successfully, incomplete peritoneal toilet may be compensated for by antimicrobial agents. How well anti-infective agents fulfil that purpose is an important outcome measured in clinical trials. Without control of the gut leak (“source control” by narrow definition), the efficacy of antimicrobial agents is difficult to measure.

Dr. Steven Johnson proposed that sepsis trials evaluating the efficacy of mediator-directed therapies should use a broader definition of source control. Under this concept, source control is predicated on manoeuvres to eradicate the source of infection. These manoeuvres may be surgical, such as operative or percutaneous drainage procedures, or they may encompass anti-infective agents directed at killing the offending pathogens. This definition provides an appreciation that studies on mediator-directed therapies attempt to modulate the host response or eliminate an offending toxin stimulating the host response and are not directed at removing the inciting pathogens. This definition encompasses 2 mechanisms of source control, surgical and non-surgical, and therefore can be used to define 2 patient populations: surgi-

cally amenable and not surgically amenable. This is a logical approach to studies of therapeutic agents that are not designed to eliminate the source of infection but rather to modulate the host response.

The consensus agreement of the panel was that definitions of source control are essential for research purposes, that different definitions may be necessary depending on the agent being investigated and that further work on definitions is needed.

IMPACT ON CLINICAL TRIALS

The impact of source control on therapeutic trials was discussed. The panelists agreed that failure to deal with the issue of source control in clinical trials has impeded our ability to answer important questions about the efficacy of therapeutic agents. Dr. Bohnen presented evidence that failure to consider source control has limited the value of clinical trials of antimicrobial therapy in abdominal infections. Antibiotic therapy is only a minor determinant of outcomes that depend on numerous patient and treatment-related factors (Table II). To measure accurately the effects of antimicrobial therapy in treatment groups in a clinical trial, potentially confounding determinants of outcome must be similarly apportioned between groups. Although it is difficult to manipulate patient-related factors, they can be stratified: recent

Table I

Definitions of Source Control

Definition	Description
Narrow	Prevention of leakage of microbial contaminants into the peritoneal cavity from the gut or other source
Broad	Prevention of leakage of microbial contaminants and removal of microbes already present in the peritoneal cavity (peritoneal toilet)
Broadest	Prevention of leakage of microbial contaminants, peritoneal toilet and antimicrobial therapy

Table II

Determinants of Outcomes of Abdominal Infections

Patient factors	Treatment factors
Severity of abdominal infection	Resuscitation
Delay in presentation	Source control
Underlying and intercurrent illness	Peritoneal toilet
Acute physiologic deficit	Wound management
	Antibiotics

studies in abdominal infection have promoted equivalence between treatment groups by controlling or stratifying the degree of illness by using the APACHE II scoring system.¹ Control or stratification of treatment modalities has been more elusive. Recent "state of the art," large, prospective, randomized controlled trials have not provided explicit analysis of source control, peritoneal toilet or wound management. These clinical trials were intended to measure the effects of antimicrobial therapy, but the results may have been confounded by the effects of variations in source control and the other determinants of outcome listed in Table II. Clinical trials have left us with the dubious result that when broad clinical criteria are used to measure outcome, no antimicrobial regimen appears to be superior to any other, as long as *Escherichia coli* and *Bacteroides* sp. are covered. Whether this reflects a biologic truth or whether clinical trials have not been sensitive enough to detect small differences among therapeutic regimens will be impossible to determine until source control is removed as a confounding factor. Other questions about antibiotic therapy, such as optimal duration and dosage of therapeutic agents will be similarly difficult to evaluate until the "background noise" of other treatment factors has been eliminated.

Dr. Johnson pointed to a similar problem existing in trials that evaluated mediator-directed therapies. Enthusiasm for mediator-directed therapies has waned because of a failure to show efficacy in multiple trials. Is this because mediator-directed therapies are not efficacious or because the designs of these trials have not been sensitive enough to detect differences in outcome because of overshadowing by confounding variables? Is it possible that an efficacious agent may not

have enough effect to influence outcome when applied as a single agent for a markedly heterogeneous, critically ill patient population? Until clinical trials remove the impact of multiple confounding variables, the answers to these questions will elude us.

Important differences exist between study designs for anti-infective and mediator-directed therapies. Although both types of study are designed to detect efficacy in septic patients, there are differences in therapeutic targets and definitions of efficacy end points. The target for anti-infective studies is the source of infection, whereas for mediator-directed studies, the host response is the therapeutic target. In antibiotic studies, efficacy is typically defined as eradication of the infectious source whereas in mediator-directed studies the end point is typically the all-cause 28-day death rate. Mediator-directed studies have more heterogeneous patient populations than disease-specific antibiotic studies and simpler placebo-controlled study designs. Because of these differences, conclusions or inferences derived from antibiotic studies may not be applicable to studies of mediator-directed therapies.

The presence of a surgically amenable source of infection can be defined and, as noted in a study that was presented at last year's Surgical Infection Society meeting by Dr. Johnson, is a significant prognostic indicator.² That study analysed patients who received placebo in a multicentre sepsis trial evaluating an anti-enterobacteriaceae common antigen monoclonal antibody. A surgically amenable source of infection was present in 49%. The abdomen was the most common site of infection among these patients. The death rate was 29% for patients with surgically amenable sources of infection versus 39% for patients with non-surgically amenable sources of infection ($p = 0.033$). This difference

remained when the results were adjusted for illness severity by APACHE II score at study entry. The impact on the death rate of the presence of a surgically amenable infection source was greater than the impact of adequacy of antibiotic therapy. Further, the death rate and the length of stay in the intensive care unit were less for patients receiving adequate surgical source control than for those whose surgical source control was inadequate. This study demonstrated the importance of surgical source control on the death rate and that the evaluation of source control must be incorporated into the design of studies of mediator-directed therapies. This evaluation must be done accurately by surgeons experienced in clinical trials.

Other outcome determinants that may confound the results of mediator-directed therapies for sepsis trials include the following:

- the type of pathogen, since modulation of host defences may be detrimental to the treatment of certain intracellular infections such as *Listeria* and *Legionella*, and certain fungal infections^{3,4}
- the quantity and quality of the cytokine response to the infection, since different cytokine levels may have beneficial or detrimental effects^{5,6}
- differences in the site of infection, which may result in different effects of mediator-directed therapies, since anti-tumour necrosis factor (TNF) agents appear to be more beneficial in experimental intravascular infections than in peritonitis.⁷
- genetic determinants, since septic patients homozygous for the TNF- β 2 allele have a higher death rate than those heterozygous for TNF- β 1/ β 2 or homozygous for TNF- β 1.⁸ It is apparent from these studies that cytokines play a critical role in the outcome of sepsis, and their role appears to be greatest at the local level. Atten-

tion to the adequacy of eradication or control of the local infection is therefore critical.

Dr. Solomkin discussed approaches to the assessment of patients in clinical trials of therapy for abdominal infections. From the start, we are interested in studying patients who have a significant chance of dying or having recurrent abdominal infection after initial treatment. This probability can be quantitated for populations of patients by using the APACHE II physiologic scoring system.¹ Such patients are not encountered as often as patients with less serious problems like appendicitis, so multicentre trials are needed. Patients suitable for inclusion in clinical trials should have conditions associated with significant pathogenic micro-organisms (which should exclude recently perforated ulcers) that are amenable to surgical drainage and are then isolated from further peritoneal contamination. The latter point separates superinfection from treatment failure and would exclude conditions in which the pathogens cannot be isolated from external or ongoing contamination, such as evolving fistula, scheduled repeat laparotomies and inability to confirm that all intestinal perforations have been closed.

Dr. Solomkin pointed out that, ideally, the end points of treatment must be clearly related to the activity of the agent under study; therefore, mortality may not be a good outcome measure of antibiotic efficacy, since underlying medical conditions are important causes of death. Study end points should be measured and documented objectively; this is not true for the commonly used designation of treatment failure in abdominal infection trials, "need for further antibiotics." The study end points should contain information about the mechanism of treatment failure. These requirements for study end points are

best met by the use of recurrent abdominal or other surgical site infection as the primary end point.

Dr. Marshall presented 2 cases, taken from actual randomized trials, to illustrate some of the clinical and methodologic issues that had been discussed. The first was that of a 64-year-old man, admitted with lower gastrointestinal bleeding, who underwent a right hemicolectomy. Five days later he had a laparotomy and drainage of multiple intraperitoneal collections secondary to an anastomotic leak. This was managed by reanastomosis, and at that point he was entered into the clinical trial. Was source control adequate in this case? The panelists and audience did not believe that the patient had appropriate treatment (i.e., the reanastomosis) unless there was an obviously correctable cause of anastomotic failure, but could not agree on whether source control could be considered "adequate" for the purpose of the clinical trial. Would the same standard of adequacy of source control apply for a sepsis trial as for a trial of antibiotics in abdominal infection?

The second case was that of a 71-year-old man in whom a perforated duodenal ulcer developed 9 days after elective aortic valve replacement. The perforation was patched, and 6 days later he had an upper gastrointestinal hemorrhage that was successfully controlled endoscopically. The next day, he underwent vagotomy and antrectomy because of the risk of bleeding. Two days later, bile was noted draining through the surgical wound. The next day, critically ill, he underwent laparotomy in the intensive care unit to place drains adjacent to the leak. He was enrolled in a clinical trial when the bile leak was noted. Dr. Marshall asked if adequacy of therapy would be measured against what is possible under the circumstances or against what

is ideal. If a process that requires surgical intervention cannot be optimally managed, should these patients be excluded from clinical trials? It was agreed generally that such patients should be excluded from clinical trials but exactly how this could be done without losing too many seriously ill patients was debated. One suggestion was to exclude any patient whose gut had leaked a second time, after the initial attempt to achieve source control surgically.

DEVELOPMENT OF GUIDELINES

A number of recommendations came out of the discussions. Dr. Fry gave a sensible clinical approach to the indications for achieving control of the source of abdominal infection. For *de novo* secondary peritonitis and presumed postoperative abscess within the first 7 days after laparotomy, the indication for achieving source control is clinical. For abscesses that develop more than 7 days after operation, the indications for and techniques of source control should depend on the results of diagnostic imaging such as computed tomography. For so-called "tertiary peritonitis," that is, abdominal infection after courses of surgical and antibiotic therapy, treatment must be individualized according to the clinical scenario and surgeon preference. There is a point beyond which source control will not affect outcome; diagnostic delay is therefore an important cause of treatment failure.

Changes in study design that would enhance the value of clinical trials were enunciated. Inclusion criteria should promote the study of clinically homogeneous groups of sick patients in whom control of the source of infection is achievable. The technique and adequacy of source control and other potentially confounding deter-

minants of outcome, extraneous to the therapeutic agent being studied, should be defined, recorded, assigned equally among treatment groups where possible and standardized where appropriate by stereotyped management protocols. The definition of the adequacy of source control may require a scoring system, based on the degree of certainty of source control or the temporal relationship between the presumed acquisition of source control and the therapeutic intervention. "Inadequate" source control does not necessarily imply that the procedure was inappropriate, since patient factors may have supervened. Case records from clinical trials should be reviewed by experts in surgical therapy before treatment blinding is broken to facilitate unbiased allocation of designations of confounding outcome determinants and the outcomes of therapy. Therapeutic end points should be closely related to the intervention being studied and reflect the purpose of the therapeutic agent: recurrent and persistent infections in antibiotic trials and mortality and recovery from organ dysfunction in sepsis trials of mediator-directed therapy.

CONCLUSIONS

Control of the source of abdominal infection is important clinically and an essential variable for consideration in research studies of therapeutic agents. Unlike patient factors such as age, diagnosis and physiologic response, source control is in the hands of clinicians. Failure to control the source of abdominal infection is a potentially avoidable and often fatal cause of treatment failure. Lack of assessment of the adequacy of source control in individual patients has limited the value of clinical trials of therapeutic modalities.

RECOMMENDATIONS

At operation for abdominal infection, the surgeon must attempt to control the source of infection by means of closure, resection, exteriorization or drainage. By the third day after operative intervention for abdominal infection, persistent signs of infection or failure to improve clinically should prompt a search for extra-abdominal and intra-abdominal infection. Unless infection is found outside the peritoneal cavity, a surgically correctable intra-abdominal disorder should be sought and controlled by diagnostic imaging, percutaneous drainage, laparoscopy or laparotomy. Simply changing antibiotics in patients not appearing to improve after surgical intervention for abdominal infection is likely to fail unless the underlying anatomic cause of clinical failure is treated.

In clinical trials of therapeutic modalities for abdominal infections, study protocols should include mechanisms that record and evaluate the operative procedure and adequacy of source control for each patient. Such evaluations should be performed initially by the local study investigator, then reviewed and revised if appropriate according to previously determined criteria, by a panel of experts. Cases judged to have incurred failure of source control should be analysed separately from other cases. Scientific organizations should develop standards to determine the adequacy of source control in studies of therapeutic modalities in surgical infections. Scientific journals should require that such standards be met before accepting reports of clinical trials for publication.

References

1. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818-29.
2. Johnson SB, Albertson TE, MacArthur R, Panacek EA, Black G, Cowens JW. Impact of surgical source control on outcome from gram negative sepsis. Paper presented at the 16th annual meeting of the Surgical Infection Society, Milwaukee, Wisc., Apr. 27, 1996.
3. Nakane A, Minagawa T, Kato K. Endogenous tumor necrosis factor is essential to host resistance against *Listeria monocytogenes* infection. *Infect Immun* 1988;56:2563-9.
4. Allendoerfer R, Magee DM, Smith JG, Bonewall L, Graybill JR. Induction of tumor necrosis factor-alpha in murine *Candida albicans* infection. *J Infect Dis* 1993;167:1168-72.
5. Alexander HR, Sheppard BC, Jensen JC, Langstein HN, Buresh CM, Venmson D, et al. Treatment of recombinant human tumor necrosis factor-alpha protects rats against the lethality hypotension and hypothermia of gram-negative sepsis. *J Clin Invest* 1991;8:34-9.
6. Mancilla J, Garcia P, Dinarello CA. The interleukin-1 receptor antagonist can either reduce or enhance the lethality of *Klebsiella pneumoniae* sepsis in newborn rats. *Infect Immun* 1993;61:926-32.
7. Bagby GJ, Plessaka KJ, Wilson LA, Thompson JJ, Nelson S. Divergent efficacy of antibody to tumor necrosis factor-alpha in intravascular and peritonitis models of sepsis. *J Infect Dis* 1991;163:83-8.
8. Stuber F, Petersen M, Bokelmann F, Schade U. A genomic polymorphism with the tumor necrosis factor locus influences plasma tumor necrosis factor-alpha concentrations and outcome of patients with severe sepsis. *Crit Care Med* 1996;24:381-4.