Proposed Definitions for Diagnosis, Severity Scoring, Stratification, and Outcome for Trials on Intraabdominal Infection

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Analysis of the experience with scientific studies on patients with secondary intraabdominal infection has revealed that problems of interpretation and comparability between studies exist as they relate to variable diagnostic criteria, unmeasured severity of disease, and unclear outcome measures. A consistent system of definitions has been developed to address these deficiencies. Intraabdominal infection is defined as clinical peritonitis requiring both operative and microbiological confirmation for proof of infection. The APACHE II system is proposed for grading the severity of the infection and for stratification of patient risk of mortality. Mortality and time until death, on one hand, and recovery and time until recovery, on the other, are proposed as the main outcome measures, both being independently and positively defined. It is anticipated that this system of minimum rules will produce studies that can be compared, hence, accelerating knowledge and understanding about intraabdominal infection and its best treatment.

Clinical trials are the best means of assessing the usefulness of new treatments and are defined as prospective studies comparing the effect and value of an intervention or an intervention strategy against a control in patients [1]. A good trial requires inter alia adequate numbers of patients which, in turn, depends on the clinically relevant difference between the study interventions. Each patient’s disease must be unambiguously diagnosed and the response variable(s) must be clear and evaluable in each patient.

In general, our current therapy of intraabdominal infection has not developed through the process of clinical trials but by accumulation of experience with new treatments and a gradual change in attitudes. Examples of progress were the transition from late to early surgery, recognition of the importance of adequate fluid resuscitation, appropriate antibiotic use, and the development of intensive care units.

The combination of surgery and antimicrobial chemotherapy is fundamental for successful treatment of intraabdominal infection. The goal is eradication of the septic focus and elimination of the pathogenic bacteria. The excision of a gangrenous appendix under antibiotic cover exemplifies the treatment principle. Complete recovery after one operation and a course of antibiotics is the expectation; however, some 20-40% of the patients with severe infection will require a second operation and many patients will have their initial antibiotic altered for a variety of reasons [2–4]. This situation has invited investigators to improve the operation by radical debridement [5, 6], and the open abdomen or planned reoperations [7–13]. Investigators have also tried to improve the efficacy of antimicrobial therapy through intraoperative or postoperative irrigations [14–24].

The many studies on treatment of intraabdominal infection are largely unintelligible because random control design was not used and because the patient groups of related studies are not comparable. To remedy this situation, Meakins and associates [25] proposed a stratification system which combined anatomy with 3 functional risk classes as determined with the Acute Physiology Score [26]. Assessing the system in patients showed that the mortality was mainly related to the severity of the systemic response while anatomy or etiology of the infection only contributed slightly [4]. Others found identical results [27]. At the same time, guidelines for conducting trials, especially antibiotic trials, in patients with intraabdominal infection have been formulated [28–31]. Following the recent development of severity scoring and risk factor analysis, this article will redefine the classification of intraabdominal infections and propose new and more precise definitions for treatment results.

Definition of Intraabdominal Infection

There can be no comprehensive definition of intraabdominal infection prior to its confirmation at surgery. Secondary perito-
Table 1. Definition of intraabdominal infection.

<table>
<thead>
<tr>
<th>Preoperative information</th>
<th>Clinical signs of peritonitis likely to be caused by a disease process originating from the gastrointestinal tract, or an intraabdominal infective disease process as demonstrated with imaging techniques</th>
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</thead>
<tbody>
<tr>
<td>Operative findings</td>
<td>Confirming a peritoneal infection</td>
</tr>
<tr>
<td>a. Localized</td>
<td></td>
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<tr>
<td>b. Diffuse, or percutaneous puncture with recovery of pus</td>
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<tr>
<td>Postoperative information</td>
<td>Positive bacteriological culture</td>
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</table>

nitis, which is the most common cause, is usually defined as an acute, suppurative inflammation of the peritoneal cavity, arising as a consequence of primary disease of the abdominal viscera, of blunt or penetrating trauma, or operations within the peritoneal spaces [32]. Obvious bacterial contamination of the peritoneal cavity is considered important by some [33] while others widen the definition to include aseptic to polymicrobial inflammation [34].

The weakness of the above definitions is shown by the inability to reflect the clinician's opinion and judgment about the diagnosis before surgery and the importance of identifying the microbes in proof of the infection. Developing these ideas had led to the definition shown in Table 1, in which affirmative information from 3 consecutive sources is required—preoperative, intraoperative, and postoperative information. Preoperatively, signs of peritonitis must be present, or an infectious process can be suspected with imaging techniques. The following preoperative signs are suggestive of infection: (a) fever, (b) abdominal tenderness (local and rebound), (c) abdominal rigidity, (d) abdominal distension, and (e) absence of bowel action. The intraoperative information must confirm the existence of a disease process that is likely to be infectious, or, if not operated, percutaneous puncture must yield pus. At operation, the following findings are signs of infection: (a) acute inflammation of the peritoneum, (b) purulent or feculent exudate, (c) fibrinous deposits, (d) tissue necrosis, (e) localized abscesses, and (f) frank viscus perforation. Postoperative information verifies and identifies the pathogen.

Persistent Peritonitis with Organ Systems Failure

Some patients display, usually after primary treatment, a course of organ malfunction which may proceed to frank multiple systems organ failure [35–40]. This syndrome is associated with a high mortality that is roughly proportional to the number of failed organs (1 = 10%, 2 = 40%, 3 = 90% mortality) and further increases as the failure persists. Persisting or recurrent infection has usually been implicated as the cause of organ failure leading to attempts to diagnose abscesses [2, 41, 42]. It is, however, common clinical experience that diagnostic measures—principally, computed tomography scan—often fail to demonstrate a clear-cut abscess in these patients. Reoperation may not demonstrate, with certainty, an infectious process although some kind of diseased tissue and some fluid is often found, and surgery does not immediately improve the patient’s condition [43]. Cultures from the operative site or blood stream often grow organisms of unclear significance which is paralleled by the experience that changing the antibiotic regimen is insignificant unless directed against organism-proven septicemia. Bacteriological studies have shown that mortality in these patients was significantly related to findings of enterococci [44–46], Staphylococcus epidermidis [47–49], or Candida [50–52]. Systematic analysis of the bacteriology of patients with intraabdominal infection and multiple systems organ failure has clearly demonstrated that the important flora is different from that of secondary peritonitis [53, 54]. It has been suggested that the reservoir of this new flora is in the intestines, especially the stomach, which harbor these organisms in large quantities [54]. Multiple systems organ failure can be viewed as a common systemic response to severe trauma and infection [55–57] with a special microflora. Some of these patients will be considered for inclusion in a trial at this late stage of their illness, e.g., after referral from another hospital. Their severity score and the duration of the illness will then both be important information and must be recorded.

Categorization by Diagnosis and by the Disease Process

Only those patients with a clinical diagnosis and operative and microbiological confirmation will be classified as patients with intraabdominal infection (Table 1). Occasionally, patients who entered into a trial will not have their diagnosis confirmed by the intraoperative or the bacteriological findings. These patients should be reported as patients with operatively negative peritonitis regardless of culture, or patients with bacteriologically negative peritonitis regardless of the operative findings. Every patient could then be assigned one of the above diagnostic categories. It is important that all randomized patients be reported.

A further subdivision which can be based on the intraoperative information should record the location or anatomical structure from which the infection originated, the etiology of the disease process of that organ, and the type of the resulting infection as specified in Table 2. The patients should be grouped by only one item from each category as best describes the infection in the opinion of the operating surgeon.

Selection of Patients for the Trial

The significance of clear entry criteria and an ascertained diagnosis relates to the interpretation of the study; however, the diagnosis will have to await operative and bacteriological confirmation. Eligible patients, therefore, must be selected according to an operational definition of likely intraabdominal infection. This was specified as the preoperative information (Table 1). Every eligible patient will then undergo surgery or percutaneous puncture at the time of inclusion in the study.

Stratification by Severity of Disease

A comprehensive description of both an acute disease and the patient's response to that disease carries an estimate of the prognosis of the patient. If the information is systematically arranged and weighted by importance, a scale of severity is achieved. The severity scale can be used to stratify patients with a common disease. The reliability of the scale relates to its capacity to predict some specific outcome event, and if suc-