

MANAGEMENT OF SEVERE SEPSIS OF ABDOMINAL ORIGIN

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ABSTRACT

Severe sepsis is a life-threatening condition that may occur as a sequela of intra-abdominal infections (IAIs) of all types. Diagnosis of IAIs is predicated upon the combination of physical examination and imaging techniques. Diffuse peritonitis usually requires urgent surgical intervention. In the absence of diffuse peritonitis, abdominal computed tomography remains the most useful test for the diagnosis of IAIs, and is essential to both guide therapeutic interventions and evaluate suspected treatment failure in the critically ill patient. Parameters most consistently associated with poor outcomes in patients with IAIs include increased illness severity, failed source control, inadequate empiric antimicrobial therapy, and healthcare-acquired, as opposed to community-acquired infection. Whereas community-acquired IAI is characterized predominantly by enteric gram-negative bacilli and anaerobes that are susceptible to narrow-spectrum agents, healthcare-acquired IAI (e.g., anastomotic dehiscence, postoperative organ-space surgical site infection) frequently involves at least one multi-drug resistant pathogen, necessitating broad-spectrum therapy guided by both culture results and local antibiograms. The cornerstone of effective treatment for abdominal sepsis is early and adequate source control, which is supplemented by antibiotic therapy, restoration of a functional gastrointestinal tract (if possible), and support of organ dysfunction. Furthermore, mitigation of deranged immune and coagulation responses via therapy with recombinant human activated protein C may improve survival significantly in severe cases complicated by septic shock and multiple organ dysfunction syndrome.

Key words: Intra-abdominal infection; sepsis; laparotomy; peritonitis; source control; critical care; activated protein; antibiotics

Intra-abdominal infections (IAIs) represent a diverse group of diseases that are encountered commonly in surgical practice. Most IAIs may be controlled effectively and with low associated morbidity through removal or repair of the infected focus, treatment with narrow-spectrum pathogen-specific antimicrobial therapy (if indicated), and restoration of anatomy

if resection is performed for definitive source control. However, in certain instances, overwhelming infection leads to excessive activation of the immune response, generalized inflammation, hemodynamic instability, multiple organ dysfunction syndrome (MODS), and eventual death. In such cases of severe sepsis or septic shock secondary to IAI, termed abdominal sepsis, mortality is approximately 25–35% (1, 2), but may exceed 70% (3, 4). Treatment of abdominal sepsis is predicated upon adequate physical drainage or resection of the infected focus, termed source control, which may range from percutaneous drainage to serial laparotomies and open abdominal wound management in severe cases (5). However, both judicious antimicrobial therapy and effective

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support of organ dysfunction also impact upon survival. This review will highlight the symbiotic disciplines of surgery, infectious diseases, and critical care in the management of abdominal sepsis.

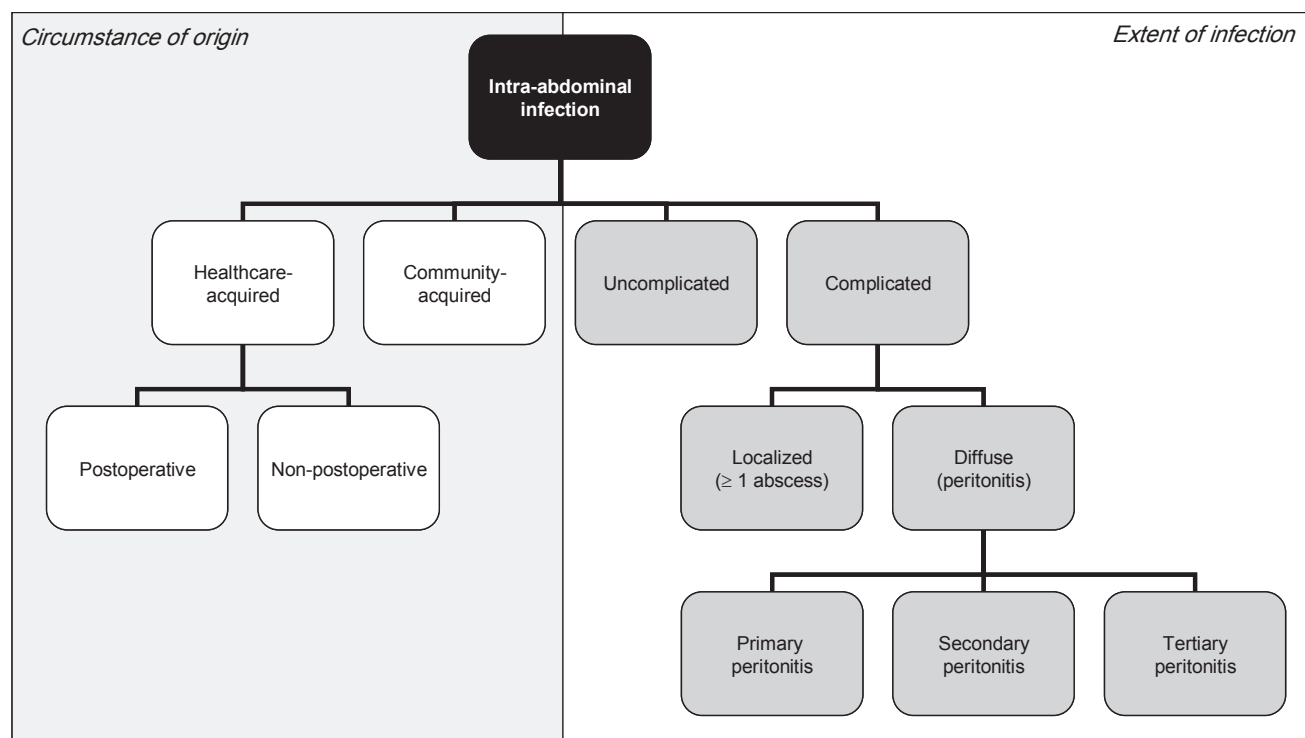
DEFINITIONS

Guidelines put forth recently by the International Sepsis Forum Consensus Conference form the basis for the current definitions of IAIs, as well as the five additional most common infections in patients with sepsis (pneumonia, blood stream infection, urosepsis, surgical site infection [SSI], and catheter-related infection) (6). In the most general sense, IAI is defined as infection of any intra-abdominal viscus, with or (rarely) without involvement of the overlying peritoneum. Infections of the gastrointestinal (GI) tract are dichotomized traditionally and for clinical research purposes into uncomplicated and complicated types (Fig. 1) (7). In the former, infection is contained within a single organ, such that there is no anatomic disruption of the GI tract. In the majority of uncomplicated IAIs, definitive management is surgical, and antibiotics are not warranted beyond prophylaxis of the incision against SSI. Uncomplicated IAIs almost never cause critical illness and are not considered further herein, although a complicating nosocomial infection could make matters worse (8).

By contrast, complicated IAIs extend beyond the source organ and into the peritoneal cavity through

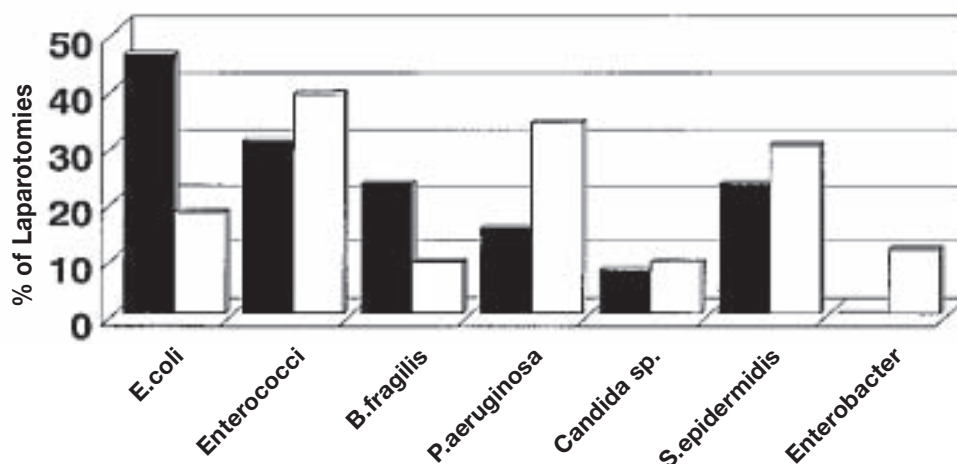
a perforated viscus, thereby stimulating the systemic inflammatory response to a greater degree. The extent of infection depends upon containment by local intra-peritoneal host defenses, although dissemination of pathogens is facilitated in general by the presence of peritoneal fluid and repetitive motion of the diaphragm. Contained infection results in the formation of an intra-abdominal abscess, with minimal or no inflammation of the overlying peritoneum. Abscess formation is facilitated by foreign bodies (to lower the inoculum size) and microbial synergy, and creates a low pH environment that impairs phagocyte function and impedes permeation of both immune cells and antibiotics. Uncontained spread of infection leads to diffuse peritonitis, a condition characterized by higher mortality, and necessitating urgent celiotomy (9).

Peritonitis is defined according to both its cause and extent. In primary peritonitis, the source of infection does not arise from the GI tract, and there is no identifiable anatomical derangement of the intra-abdominal viscera. By contrast, secondary peritonitis is due to infection of the abdominal viscera, and may arise as a consequence of perforation, ischemic necrosis, or penetrating injury. Tertiary peritonitis is defined as peritonitis that persists after more than one failed source control procedure (9). Management of tertiary peritonitis presents a particular challenge due to the increased likelihood of infection with multi-drug-resistant (MDR) organisms such as enterococci, *Pseudomonas aeruginosa*, and *Candida* spp. (Fig. 2), as



Intra-abdominal infections are classified based on both the circumstance of origin (healthcare-acquired vs. community-acquired) and the extent of infection (uncomplicated vs. complicated).

Fig. 1. Classification scheme for intra-abdominal infections.



Results from a study in which peritoneal isolates from 15 patients with secondary peritonitis (closed bars) were compared to those of 44 patients with tertiary peritonitis (open bars) (9). The most common microbial isolates from patients with secondary peritonitis were *Escherichia coli*, *Enterococcus*, and *Bacteroides fragilis*. In contrast, the predominant organisms isolated at laparotomy in those with tertiary peritonitis were *Enterococcus*, *Candida*, *Staphylococcus epidermidis*, and *Enterobacter*. Reproduced with permission.

Fig. 2. Differences in the microbiology of secondary vs. tertiary peritonitis.

well as the frequent need for re-laparotomy in hemodynamically tenuous patients. Whether tertiary peritonitis represents invasive infection or colonization in the setting of complete failure of abdominal host defenses is controversial, as is the use of open-abdomen management techniques to promote mechanical peritoneal toilet (discussed below). Fortunately, the incidence of tertiary peritonitis is decreasing (10).

One final distinction of crucial importance involves differentiation of community-acquired (CA-) from healthcare-acquired IAI (HA-IAI). The former is characterized in general by microorganisms that are sensitive to narrow-spectrum antimicrobial agents. Conversely, HA-IAIs develop in hospitalized patients, residents of long-term care facilities, or patients who have been treated recently with antibiotics. All post-operative IAIs are considered HA-IAIs. Although

HA-IAIs are far less common than CA-IAIs, they are associated with markedly increased mortality due to both underlying patient health status and increased likelihood of infection caused by MDR organisms (11).

Although most IAIs result in activation of the inflammatory cascade to some degree, strict criteria exist for the documentation of the systemic inflammatory response syndrome (SIRS). The diagnosis of SIRS involves fulfillment of two or more of the following criteria: (1) Core body temperature $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$, (2) heart rate > 90 beats per minute, (3) respiratory rate > 20 breaths per minute (not ventilated) or $\text{P}_a\text{CO}_2 < 32$ mm Hg (ventilated), (4) WBC $> 12,000$, $< 4,000$ or $> 10\%$ immature forms (bands) (12). When SIRS is due to infection, it is termed sepsis. In turn, sepsis due to IAI is termed abdominal sepsis. Sepsis with acute dysfunction of at least one organ is termed severe sepsis, whereas septic shock is severe sepsis with hemodynamic instability refractory to fluid administration, with a requirement for vasopressor support.

TABLE 1

Factors associated with mortality of secondary peritonitis

Parameter	Reference
Shock	29
Increasing age	13, 18, 19, 29, 61
Increasing APACHE II score	2, 13, 17, 19, 27, 29, 110, 111
Isolation of enterococci	19, 44
Impaired consciousness	18
Inadequate empiric antibiotics	20, 29
Poor nutritional status	13, 17, 27, 111
Cardiovascular disease	13, 17, 27, 111
Inability to obtain source control	13, 17, 18, 27, 111
Immunosuppression	18
Hypoalbuminemia	61
Thrombocytopenia	61
Diffuse vs. localized peritonitis	9, 61
Symptoms > 24 hours before definitive intervention	19, 61
Subsequent nosocomial infection	8
Protein C concentration $< 66\%$ of normal	112

APACHE, Acute Physiology and Chronic Health Evaluation

EPIDEMIOLOGY

Outcomes following IAIs are influenced by the origin of the infection, the ability of the host to contain the infection, the degree of physiologic derangement due to the infection, and both the rapidity and adequacy with which the infection is treated (Table 1). Accordingly, the overall mortality rate associated with IAIs varies markedly and ranges from $< 1\%$ to $> 70\%$, although most modern case series of secondary peritonitis with severe sepsis or septic shock have reported an average mortality of approximately 30% (2-4, 9, 11, 13-20).

The most common source of infection in CA-IAIs is the appendix, followed by the colon, and then the stomach (11, 20, 21). Among patients with HA-IAIs,

the predominant etiology is enteric anastomotic disruption. Dehiscence complicates 5–10% of intra-abdominal intestinal anastomoses, and is associated with an increased likelihood of mortality (22–24). Several risk factors for intestinal anastomotic dehiscence are recognized and fall broadly into the categories of underlying health status, operative technique, and postoperative management (Table 2). In both postoperative and non-postoperative HA-IAs, the most common source of infection is the colon, followed by the stomach, pancreas, small intestine, and appendix (21, 25). Peritonitis originating from the pancreas portends a substantially higher mortality, and from the appendix lower, as compared to other abdominal viscera (11).

Mortality from HA-IAI is greater than from CA-IAI (11, 26, 27). Healthcare-associated, non-postoperative IAs, which arise in patients hospitalized for reasons unrelated to abdominal pathology, portend a particularly poor prognosis (21, 28). In such cases, diagnosis is often delayed due to both a low index of suspicion, poor underlying health status, and altered sensorium. Healthcare-associated IAs, both postoperative and non-postoperative, are significantly more likely to involve pathogens that are resistant to narrow-spectrum agents (9, 21, 25, 29) (Fig. 3). Furthermore, patients with HA-IAs are more likely to be treated in-

TABLE 2

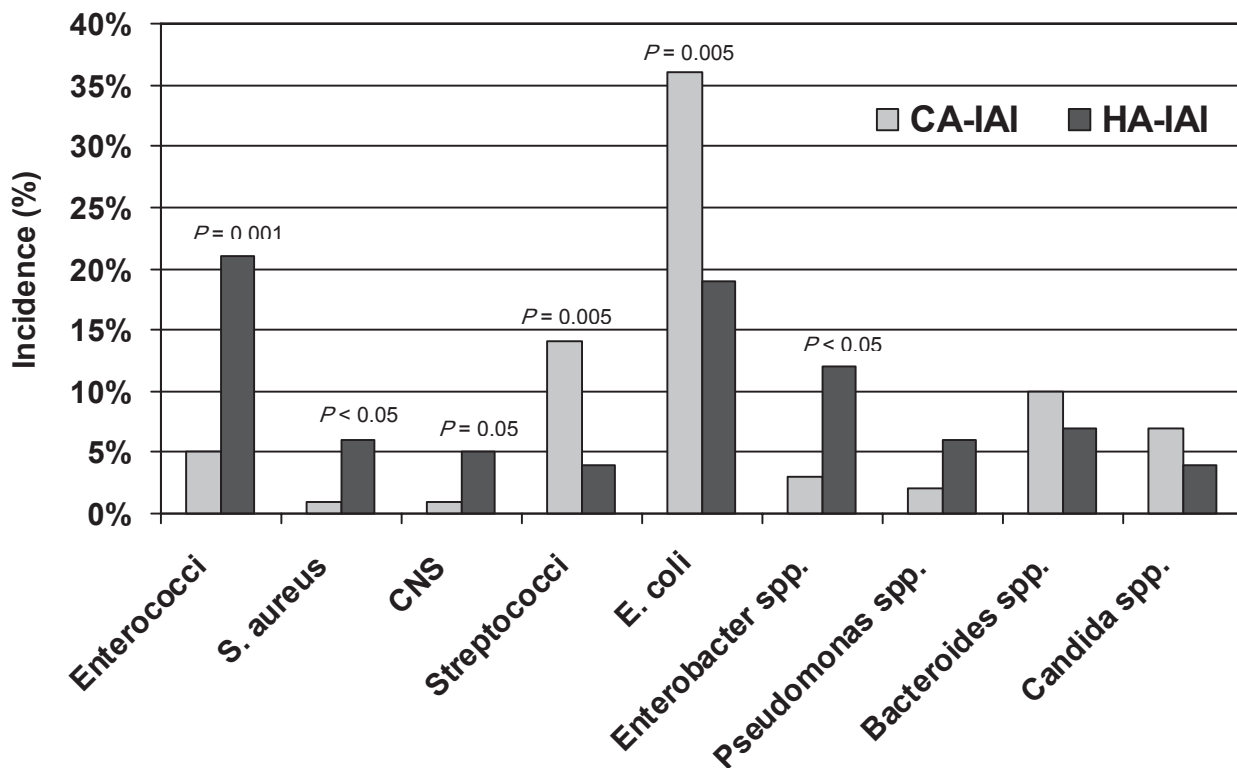
Factors associated with intra-abdominal intestinal anastomotic dehiscence.

Anastomotic tension
Hypoxia
Intra-operative or postoperative RBC transfusion
Iron deficiency
Ischemia
Malnutrition
Preoperative radiation therapy
Prolonged duration of operation
Renal failure
Shock
Steroid therapy
Tobacco use
Zinc deficiency

RBC, red blood cell.

adequately as compared to patients with CA-IAs, contributing to increased treatment failures, morbidity, and mortality (29).

As many as 40% of patients with peritonitis may progress to abdominal sepsis (30, 31). Sepsis, regardless of its source, is a leading cause of mortality worldwide. Using recent data from the United States, the rate of severe sepsis was estimated to be three



Results from a study in which peritoneal isolates from 67 patients with postoperative peritonitis were compared to those of 68 patients with community-acquired peritonitis (25). As a consequence of prior antimicrobial use, the flora of the peritoneum are altered. Whereas pathogens such as *E. coli* and streptococci are more commonly isolated in cases of community-acquired intra-abdominal infection (CA-IAI), enterococci and *S. aureus* are more prevalent in healthcare-acquired intra-abdominal infection (HA-IAI). Adapted with permission.

Fig. 3. Microbiology of community-acquired versus healthcare-acquired intra-abdominal infections.

cases per 1,000 population, for a total of 751,000 cases annually (32). Further extrapolation of this data internationally reveals a global incidence of 18 million cases annually, making sepsis a leading cause of death worldwide (33). Of these cases, approximately 20% are surgical, and one-half of surgical cases result from an abdominal source of infection. Abdominal sepsis, as compared to other sources, is associated with increased mortality (1, 34). Both abdominal sepsis, and sepsis in general, impose astronomical financial burdens upon the health care system (35).

MICROBIOLOGY

The commensal flora of the GI tract varies by location; whereas the oropharynx contains predominantly anaerobes and streptococci, both the stomach and duodenum are typically sterile. The remainder of the GI tract (*i.e.*, distal small bowel, colon, and rectum) is characterized predominantly by enteric aerobic or facultative gram-negative bacilli (GNB) (also known as *Enterobacteriaceae* or coliforms) and anaerobic GNB, which increase in percentage from the proximal jejunum to the colon, where they predominate. Pathogens isolated from cases of infected pancreatic necrosis also resemble closely the flora of the large bowel (36), as it is postulated that the pathogens may invade the retroperitoneum via bacterial translocation from the gut.

The vast majority of IAIs are polymicrobial and most commonly involve enteric GNB (Table 3) (37, 38). *In vitro* susceptibility of GNB isolated from IAIs are catalogued annually by the Study for Monitoring Antimicrobial Resistance Trends (SMART), which is an international surveillance program to monitor resistance patterns globally (39). The SMART report for 2004, the most recent year for which complete data are available, involved 81 medical centers from 28 countries for a total of 6,156 GNB from 5,731 patients. Enteric GNB comprised 86% of isolates, including *Escherichia coli* (48.4%), *Klebsiella* spp. (16%), and *En-*

terobacter spp. (9%). Although the prevalence of MDR organisms such as *P. aeruginosa* and *Acinetobacter baumannii* remained unchanged, antimicrobial resistance, particularly to fluoroquinolones and β -lactam agents, is increasing on an international scale. Furthermore, MDR GNB have now been isolated from cases of CA-IAI in parts of South America and Asia. These ominous results underscore both the discretion that must be employed when prescribing empiric antimicrobial therapy and the need for novel agents for the treatment of IAIs (40).

Anaerobic bacteria, such as *Bacteroides* spp. and *Clostridium* spp., are isolated in approximately 10% of IAIs and clearly play a role in infection (41–43). The prevalence of these bacteria is almost certainly underestimated due to both poor specimen collection technique (*e.g.*, exposure to atmospheric oxygen) and the difficulty with which they are cultured. Although anaerobic bacteria are found predominantly in the distal small bowel and colon, they may be isolated from both the stomach and proximal small bowel in cases of distal obstruction.

Finally, gram-positive bacteria, such as staphylococci and enterococci, are isolated in approximately 10–20% of IAIs, with an increased prevalence in cases of HA-IAI (25, 44) (Fig. 3). The role of enterococci in IAIs, and thus the need to provide empiric coverage against them, remains unclear (discussed below).

Although the peritoneal fluid of as many as 20% of patients with acute perforation of the GI tract may ultimately grow *Candida* spp., IAIs caused by fungi are rare in the immunocompetent host (45). However, when they do occur, they are more commonly implicated following upper GI sources of infection, as well as with infected pancreatic necrosis (19, 46). Furthermore, isolation of *Candida* spp. in patients with HA-IAIs is associated independently with mortality (21, 47, 48). In one recent series of critically ill patients with *Candida* peritonitis, mortality exceeded 50% (48).

Secondary peritonitis is accompanied by bacteremia of the same microorganism in as many as one-fourth of cases (21), and coexisting bacteremia is associated with increased mortality (21, 29). Accordingly, organisms isolated from both peritoneal fluid and blood should always be treated. Furthermore, subsequent nosocomial infections (most commonly urinary tract and surgical site infections) occur frequently in patients with IAIs and are associated with an increased likelihood of MDR infection, as well as increased morbidity and mortality (8).

DIAGNOSIS

Intra-abdominal infection in the awake patient is suspected in the presence of SIRS as well as abdominal pain and tenderness. Abdominal rigidity, guarding (either voluntary or involuntary), and rebound tenderness suggest peritonitis and the need for urgent laparotomy. Both local and diffuse inflammation may result in paralytic ileus with resultant abdominal distention, obstipation, and vomiting. Oliguria, hypo-

TABLE 3

Common pathogens isolated from complicated intra-abdominal infections (adapted from Ref. 113).

Gram-negative

Escherichia coli
Enterobacter spp.
Klebsiella spp.
Proteus spp.
Pseudomonas aeruginosa
Acinetobacter spp.

Gram-positive

Streptococci
Enterococci
Coagulase-negative staphylococci
Staphylococcus aureus

Anaerobic bacteria

Bacteroides spp.
Clostridium spp.

Fungi

Candida spp.

tension, and altered mental status may ensue in cases of septic shock.

With obtunded or comatose patients, many symptoms may be either attenuated or absent, rendering diagnosis difficult, and necessitating a high index of suspicion. Indirect evidence of infection, such as unexplained acidosis, new organ dysfunction (49), inability to tolerate enteral feeding, or unexplained fluid requirement, should prompt a diagnostic work up for IAI, especially in the setting of recent abdominal surgery.

Physical examination findings suggestive of IAI are confirmed by abdominal imaging, accomplished most commonly by computed tomography (CT) with both enteral and intravenous contrast. Due to extremely favorable performance characteristics, abdominal CT is the diagnostic test of first choice for all patients with suspected intra-abdominal pathology with few exceptions (*i.e.*, suspected acute appendicitis in a healthy young male patient) (50, 51). Abdominal CT may provide a wealth of detailed information and is useful to confirm the diagnosis of IAI, implicate the responsible pathologic process (e.g., perforated sigmoid diverticulitis with adjacent abscess), and guide the method of drainage (*i.e.*, percutaneous vs. surgical) based on the anatomic landscape.

Microbiologic diagnosis of CA-IAIs is of no value in initial treatment because culture results are not available at the time that empiric antibiotic therapy is initiated. Furthermore, because the vast majority of pathogens responsible for CA-IAIs are susceptible to narrow-spectrum agents, routine obtainment of cultures is unnecessary and has been shown to not influence outcomes (52). Conversely, microbiological analysis of HA-IAIs is mandatory due to different microbiology and the marked variability of resistance patterns observed among the isolates (53). Data from such cultures, once available, will dictate the need to modify broad-spectrum empiric therapy.

TREATMENT

Fundamental principles involved in the treatment of abdominal sepsis include source control, restoration of GI tract function, systemic antimicrobial therapy, and support of organ function. Minimization of the intervals from presentation to diagnosis and diagnosis to initiation of therapy impacts significantly upon survival (54). However, aggressive interventions such as re-laparotomy and empiric broad-spectrum antibiotic therapy must be considered with caution in light of the potential for tissue injury or substantial toxicity, respectively.

SOURCE CONTROL

Source control is defined as any and all physical means necessary to eradicate a focus or infection, as well as modify factors that maintain infection, such as leaking intestinal contents. Inadequate source control at the time of the initial operation has been associated consistently with increased mortality in patients with IAIs, despite both adequate antimicrobial

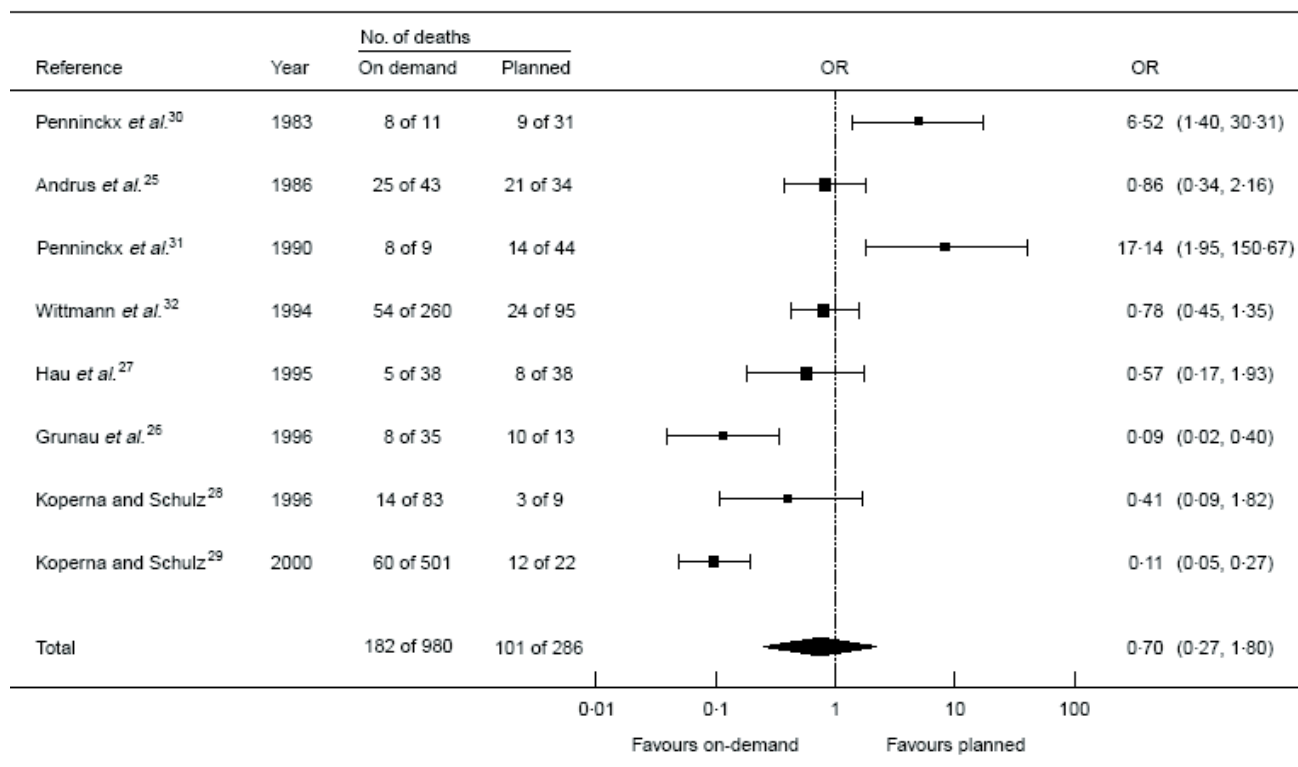
therapy and organ support (13, 55). Accordingly, barring hemodynamic instability, every effort should be made to achieve source control as soon as possible after the diagnosis of IAI has been made.

Methods of source control fall broadly into either percutaneous or operative interventions. The choice of technique is dependent upon patient acuity, anatomic site, and extent of infection. In general, the procedure that achieves source control with the least associated morbidity is preferred.

Laparotomy remains the cornerstone of care for all cases of diffuse peritonitis. One randomized trial compared celiotomy to limited surgical drainage of IAIs via an extraperitoneal approach in the absence of peritonitis (56), finding that morbidity was reduced substantially by the more limited approach, but percutaneous drainage techniques have been developed subsequently. Since then, results from several retrospective studies suggest that isolated IAIs that are anatomically amenable to percutaneous drainage may be treated with safety (57–59). The percutaneous approach is generally contraindicated when adequate drainage is not possible (*i.e.*, multiple small abscesses) or anatomically not feasible (*i.e.*, overlying bowel), and when repair of anatomic structures is necessary. Although laparoscopic drainage of IAIs has been reported, this technique has not been compared directly to either percutaneous or open drainage (60).

In cases of abdominal sepsis, a single operation may not be sufficient to achieve source control, thus necessitating re-exploration. The decision to perform an additional laparotomy is often challenging to make in the face of an unstable patient in which symptoms of reinfection are often either subtle or absent. Koperna et al. reported that increased age, hypoalbuminemia, thrombocytopenia, increased preoperative Acute Physiology and Chronic Health Evaluation (APACHE) II score, and preoperative organ failure predicted the need for re-laparotomy among a cohort of patients with secondary peritonitis (61). Mortality was increased significantly in those patients who required reoperation as compared to those who did not (51% vs. 4%, $p < 0.0001$).

Three methods of local mechanical management of abdominal sepsis following initial laparotomy for source control are currently debated: (1) Open-abdomen (also known as laparostomy), (2) planned re-laparotomy (PR), and (3) on-demand re-laparotomy (ODR). Open-abdomen management involves temporary coverage of the abdominal contents with polyglactin mesh, towels, abdominal “zipper,” or vacuum-assisted closure (4, 26, 62). In certain instances, this technique is mandated either to avoid abdominal compartment syndrome or because of physical inability to re-approximate the abdominal fascia regardless of intra-abdominal pressure. However, some experts have also advocated elective open-abdomen management for cases of abdominal sepsis in which source control is unclear or known to be inadequate (63). Purported benefits of an open abdomen include reduction in intra-abdominal pressure, more complete drainage of infection, early detection of additional anastomotic leaks or new abscesses, facilitation



Individual and pooled odds ratios (ORs) (planned versus on-demand re-laparotomy) for the eight studies included. Pooling was according to the random-effects model. Squares and bars indicate study size and confidence interval, respectively. Elongated diamond represents the confidence interval of [0.27, 1.80]. Test for heterogeneity of the eight studies: $\chi^2 = 40.7$, $df = 7$, $p < 0.001$; test for overall effect: $p = 0.50$. Reproduced with permission from (71).

Fig. 4. Results from meta-analysis of planned vs. on-demand re-laparotomy strategies for secondary peritonitis.

of reoperation (including serial laparotomies at the ICU bedside), and minimization of additional abdominal wall trauma. However, these benefits may be negated by the increased morbidity caused by fluid and protein loss, fistula formation, and ventral herniation (15, 64).

Planned re-laparotomy involves the *a priori* decision to re-explore the abdomen regardless of clinical circumstance. By contrast, ODR is performed only in the case of subsequent reinfection, usually indicated by either clinical deterioration or failure to improve despite both presumed source control and appropriate antimicrobial therapy. Planned re-laparotomy is indicated if adequate source control is clearly not obtained at the time of the initial operation. In all cases, the benefits of more effective source control must be weighed against the potential morbidity of bleeding, damage to edematous viscera or the abdominal wall (65), and stimulation of additional inflammation (66).

These three techniques (ODR, PR, open abdomen) have not been compared in a randomized fashion, and the observational literature is limited markedly by subjective management decisions made by the surgeon at the time of the initial laparotomy. This decision, in turn, is dependent on multiple clinical factors that determine patient outcome independent of man-

agement strategy, most notably the severity of illness. Methodological limitations notwithstanding, observational comparisons of the open abdomen and re-laparotomy (either PR or ODR) techniques have not demonstrated a significant advantage to either (15, 67). Furthermore, several studies, using a matched case-control design, have failed to show a benefit to the PR as compared to the ODR approach after adjusting for severity of illness (18, 61, 68–70). These findings were confirmed in a recent meta-analysis that, despite significant heterogeneity among studies, did not report a survival advantage to the PR as compared to the ODR approach [pooled odds ratio (OR) = 0.70, 95% CI [0.27, 1.80], $p = 0.50$] (Fig. 4) (71). Multi-institutional randomized controlled trials (RCTs), which theoretically eliminate confounding due to underlying clinical status or variations in patient management, are needed before any meaningful recommendations can be made.

Finally, undirected or “blind” re-laparotomy prompted by unexplained MODS in the absence of supporting clinical or radiographic data is associated with an unacceptably high rate of negative re-laparotomy (72–74). Highly specific imaging with abdominal CT has all but obviated the role for such a procedure. Rather, clinical deterioration in the absence of radiographic findings and assuming adequate antibi-

otic therapy should prompt a search for another source of infection (8).

Ample evidence suggests that source control should be obtained as early as possible after the diagnosis of IAI has been confirmed. Delayed intervention significantly decreases the ability to achieve source control, with an associated increase in mortality (18). One notable exception concerns infected pancreatic necrosis, during which delayed surgery may result in decreased mortality due to an increased opportunity for demarcation of viable tissue planes, allowing limited debridement and reduced surgical blood loss (75, 76).

RESTORATION OF FUNCTION

Following removal of infected tissue, attention should shift to the restoration of anatomy and functionality of the GI tract. Staging of procedures intended to restore intestinal continuity continues to be a matter of debate, particularly with respect to IAI caused by colonic perforations. The past two decades have witnessed a shift from the traditional three-stage procedure to the two-stage Hartmann procedure, with a decrease of associated mortality (77). Most recently, several reports have touted the safety of a one-stage procedure for colonic perforation with associated peritonitis, involving abscess drainage, resection, and primary anastomosis (78–80). However, these non-randomized trials involved patients with sepsis infrequently, and the extent of surgery should be dictated primarily by the degree of physiologic derangement, given the strong relationship between severity of illness and treatment failure. In the presence of hemodynamic instability, re-establishment of intestinal continuity of any kind may be prohibitive, necessitating re-laparotomy within the next 24–48 hours.

ANTIMICROBIAL THERAPY

Antibiotics are administered to prevent both local and hematogenous spread of infection, as well as to decrease delayed complications. Provided adequate source control has been obtained, outcomes in HAI are influenced heavily by the administration of adequate initial antimicrobial therapy, defined as at least one agent to which the offending pathogen is sensitive, in the correct dose, and in a timely manner (20, 29, 53, 81, 82). Furthermore, the increased mortality associated with inappropriate empiric antibiotic therapy cannot be reversed by subsequent modifications (20). Accordingly, knowledge of patient risk factors for infection with MDR pathogens (Table 4), as well as local resistance patterns, is essential. Stratification by risk ensures that all patients will receive therapy that is active against the offending pathogens, and minimizes superfluous use of broad-spectrum agents, which increases costs, exposes patients to potential drug toxicity, and exerts selection pressure favoring the emergence of MDR organisms (83).

Evidence-based guidelines regarding the selection of antimicrobial therapy for IAIs have been formulated by the Surgical Infection Society, the Infectious

Diseases Society of America, the American Society for Microbiology, and the Society of Infectious Disease Pharmacists (84, 85). In the case of uncomplicated IAIs, the focus of infection is treated effectively by surgical excision of the involved tissue alone, and the administration of antibiotics is unnecessary beyond preoperative prophylaxis. Additional cases in which IAI is not considered established, and thus extended antimicrobial therapy is not warranted, are summarized in Table 5.

Recommended single and multi-drug regimens for the treatment of IAIs are shown in Table 6. In general, empiric regimens should provide coverage against

TABLE 4

Risk factors for intra-abdominal infection caused by multi-drug-resistant organisms.

Hospitalization > 48 hours
Immunosuppression
Postoperative infection
Recent antibiotic therapy
Residence in skilled nursing care or long-term care facility

TABLE 5

Conditions for which prolonged (> 24 hours) of antibiotics are not warranted (adapted from Ref. 85).

Traumatic or iatrogenic bowel injury repaired within 12 hours (including intraoperative contamination)
Gastroduodenal perforation repaired within 24 hours ^a
Gangrenous appendicitis without perforation or peritonitis
Gangrenous cholecystitis without perforation or peritonitis
Transmural bowel ischemia or necrosis without perforation or peritonitis

^a In the absence of antacid therapy or malignant disease.

TABLE 6

Recommended antimicrobial regimens for the treatment of intra-abdominal infections (adapted from Ref. 85).

Single-drug regimens:

β-lactam/-lactamase inhibitor combinations
Ampicillin/sulbactam
Piperacillin/tazobactam
Ticarcillin/clavulanic acid
Carbapenems
Imipenem-cilastatin
Meropenem
Ertapenem
Cephalosporins
Cefotetan
Cefoxitin

Combination regimens:

Aminoglycoside plus metronidazole
Aztreonam plus clindamycin
Cefuroxime plus metronidazole
Fluoroquinolone plus metronidazole

TABLE 7

Conditions under which empiric coverage of enterococci may be considered for complicated intra-abdominal infections.

Healthcare-associated intra-abdominal infection
Immunocompromise
Presence of prosthetic heart valve
Prior cephalosporin or carbapenem therapy
Severe sepsis or septic shock
Tertiary peritonitis

enteric gram-negative aerobic and anaerobic bacteria, as well as β -lactam-susceptible anaerobic gram-positive cocci. In the case of CA-IAI without associated signs of sepsis, empiric therapy may be limited to narrow-spectrum agents, such as ampicillin/sulbactam or ticarcillin/clavulanic acid. However, in either HA-IAIs or IAI of any origin with associated abdominal sepsis, broad-spectrum therapy is warranted.

Generalization as to effective treatment regimens against such infections remains challenging due to substantial variability in both indigenous pathogens and resistance patterns among ICUs. Furthermore, antibiotic trials of patients with IAIs typically limit enrollment of critically ill patients or exclude them altogether (86, 87). Treatment options for HA-IAIs include extended-range β -lactam/ β -lactamase agents such as piperacillin/tazobactam, carbapenems such as imipenem-cilastatin or meropenem, or a third- or fourth-generation cephalosporin plus metronidazole. In general, fluoroquinolones should be used judiciously based on resistance emerging internationally (39). Furthermore, recent data indicate that aminoglycosides possess inferior efficacy as compared to agents with comparable activity for the treatment of IAIs, albeit with conventional (i.e., not once-daily) dosing (88). Potential ototoxicity and nephrotoxicity represent additional disincentives to selecting aminoglycosides as first-line therapy. Combination therapy directed against a specific pathogen (e.g., "double-coverage" of *Pseudomonas*) is unlikely to provide benefit in sepsis generally, and may worsen outcomes (89).

Newer agents that have demonstrated non-inferiority when compared to standard broad-spectrum regimens for the treatment of patients with IAIs include tigecycline (90), ertapenem (82), and moxifloxacin (91). Among these drugs, ertapenem is particularly appealing because of once-daily dosing and possible decreased induction of MDR GNB (92). However, whether these drugs should be used empirically for HA-IAI is unknown, particularly because the anti-pseudomonal activities of tigecycline and ertapenem, in particular, are unreliable.

The optimal duration of antimicrobial therapy is unknown. Current recommendations advise continued therapy until clinical signs of infection have resolved, including fever and abdominal pain, normalization of the WBC count, and restoration of GI function. Provided these criteria are met, the likelihood of re-infection after discontinuation of antibiotic therapy of CA-IAI is exceedingly small (93, 94). Typically, this will involve between 5–7 days of therapy, although

shorter courses have been proposed (95). In the presence of clinical improvement and a functional GI tract, antibiotics may be transitioned safely from the intravenous to the oral route (96). The optimal duration of therapy of HA-IAI is unknown and urgently in need of study (97).

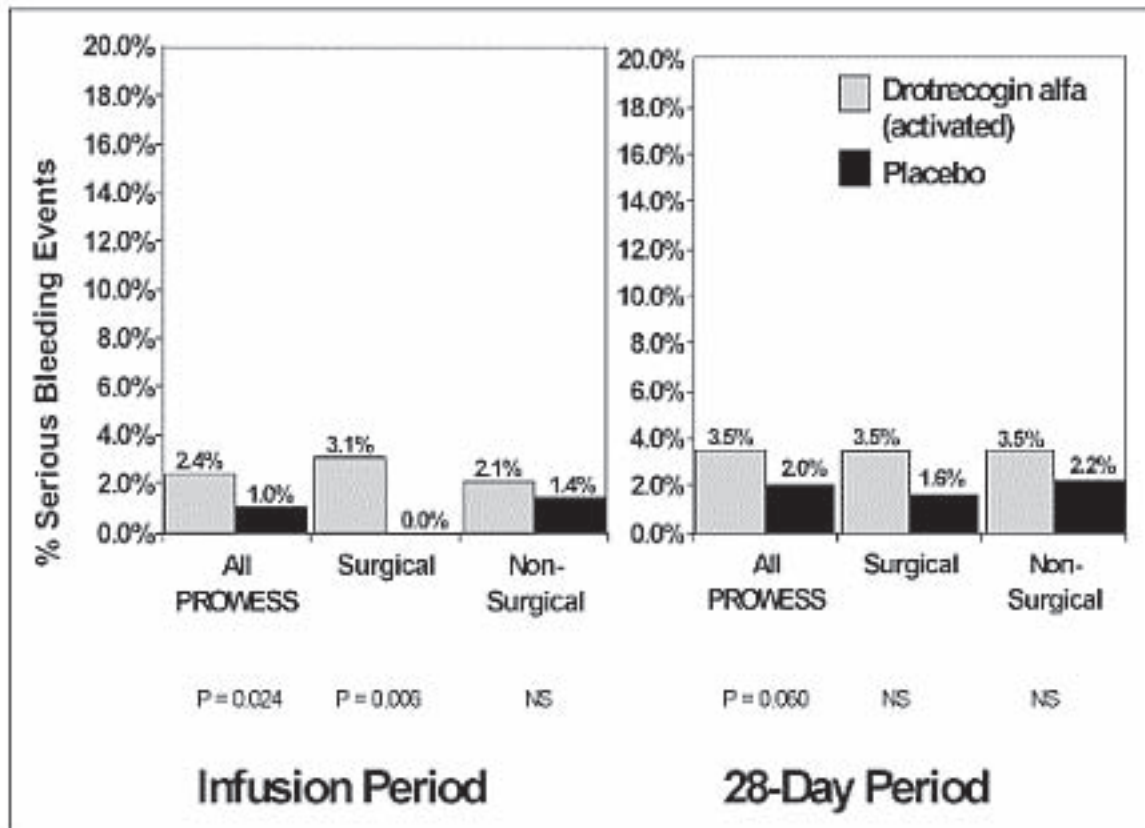
Persistent sepsis after one week of antibiotic therapy should raise the possibility of inadequate source control, tertiary peritonitis, or another nosocomial infection (e.g., ventilator-associated pneumonia). In such cases, a renewed diagnostic evaluation is preferable to either prolongation of the current antibiotic regimen or wholesale change to a more broad-spectrum empiric regimen, as persistent abdominal symptoms are usually the result of an ongoing source of infection that may be amenable to surgical treatment (98).

Although enterococci are isolated in as many as 25% of IAIs (2, 99), they are almost always found in the setting of polymicrobial infection. Isolation of enterococci from IAIs is associated with HA-IAI as opposed to CA-IAI, increasing age, more severe disease, co-isolation of MDR pathogens such as *P. aeruginosa*, and increased mortality (19, 44). However, the therapeutic implications of the association between enterococci and adverse outcomes in patients with IAIs remain unclear (100). Several RCTs have shown that treatment of such infections with antibiotic regimens that lack enterococcal activity does not result in treatment failure due to enterococcal infection (2, 25, 43, 101–107). Consequently, routine coverage of enterococci in cases of CA-IAI is not recommended (84, 85, 100). Conversely, most authorities maintain that empiric coverage of enterococci should be considered in certain clinical circumstances, including abdominal sepsis due to HA-IAI (Table 7).

Similarly, systemic antifungal therapy for treatment of *Candida* spp. isolated from IAIs is unnecessary in the absence of immunosuppression. However, isolation of fungi from two or more normally-sterile sites (e.g., peritoneal cavity and lower respiratory tract) of critically ill patients should prompt consideration of empiric antifungal therapy, typically with intravenous fluconazole. In cases of fluconazole-resistant *Candida* spp., either an echinocandin or voriconazole may be considered in lieu of amphotericin B due to the substantial systemic toxicity associated with the latter.

RECOMBINANT HUMAN ACTIVATED PROTEIN C

Drotrecogin alfa (activated) [recombinant human activated protein C (rhAPC)] gained approval worldwide for the treatment of severe sepsis associated with a high risk of death in 2001 following a pivotal RCT that demonstrated a relative risk reduction for mortality of 19% for patients treated with rhAPC as compared to placebo (108). Initial concern was raised for the use of APC specifically in surgical patients because of an attenuated absolute risk reduction for mortality compared to the overall sample (3.2% vs. 6.0%, respectively), as well as an increased risk of bleeding. In response to this criticism, a surgical evaluation committee adjudicated the results of the



P value from Pearson's chi-square test (NS = not significant). Reproduced with permission from (55).

Fig. 5. Serious bleeding events during infusion and 28-day period by treatment group [drotrecogin alfa (activated) vs. placebo].

original trial for surgical patients ($n = 474/1,690$, 28.0%), and specifically for those surgical patients with severe sepsis of abdominal origin ($n = 295/474$, 63.0%) (55). Among those patients undergoing abdominal procedures, the absolute risk reduction was 9.1%, and the relative risk of 28-day mortality was 0.70 (95% CI 0.48–1.03). In a subgroup of these patients with an APACHE II score ≥ 25 points, the absolute risk reduction was 18.2%. Furthermore, the rates of serious bleeding events among patients who received rhAPC did not differ between the surgical and non-surgical cohorts (Fig. 5). A more recent analysis of the INDEPTH database, which currently contains five clinical trials of the efficacy of rhAPC, demonstrated a significant risk reduction for mortality (adjusted OR = 0.66, 95% CI (0.45, 0.97)) for rhAPC as compared to placebo among high-risk (APACHE II score ≥ 25 points) surgical patients, over one-half of whom had had IAIs (109). Finally, a recent analysis using a matched cohort design of patients with septic shock of abdominal origin from our institution revealed a more than 5-fold increase in the likelihood of mortality in controls as compared to patients who received rhAPC (1). Therapy with rhAPC should be considered for patients with severe abdominal sepsis associated with a high risk of death, defined as an

APACHE II score ≥ 25 or dysfunction of at least two organs.

CONCLUSIONS

Although both acuity and underlying health status impact the likelihood that IAIs will progress to abdominal sepsis, a substantial body of evidence suggests that the outcomes from this disease are determined primarily by the rapidity with which source control is achieved and the extent to which the infected focus is cleared. Antibiotic therapy is secondary to adequate source control and ineffective in its absence. Furthermore, antibiotics must be administered with respect to the likelihood that HA-IAI is due to MDR pathogens. Selection of the optimal method for both source control and restoration of GI tract anatomy involves a risk-benefit analysis concerning patient stability, extent of infection, and associated morbidity. Emerging therapies (e.g., rhAPC) directed at modulation of the coagulation and immune responses have provided effective adjuncts to the treatment of abdominal sepsis. Collective implementation of these principles affords the critically ill patient with IAI the greatest chance for survival.

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