Treatment of the complex abdomen and acute intestinal failure

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ABDOMINAL SEPSIS

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ABSTRACT

**Purpose of the review** – To summarize the recent evidence on the treatment of abdominal sepsis with a specific emphasis on the surgical treatment.

**Recent findings** – A multitude of surgical approaches towards abdominal sepsis are practised. Recent evidence shows that immediate closure of the abdomen has a better outcome. A short course of antibiotics has a similar effect as a long-course of antibiotics in patients with intra-abdominal infection without severe sepsis.

**Summary** – Management of abdominal sepsis requires a multidisciplinary approach. Closing the abdomen permanently after source control and only reopening it in case of deterioration of the patient without other (percutaneous) options is the preferred strategy. There is no convincing evidence that damage control surgery is beneficial in patients with abdominal sepsis. If primary closure of the abdomen is impossible due to excessive visceral edema, delayed closure using negative pressure therapy with continuous mesh-mediated fascial traction shows the best results.
INTRODUCTION

Abdominal sepsis, or secondary peritonitis, is a challenge faced by many surgeons every day worldwide. Multiple underlying diseases causing abdominal sepsis can be identified and treatment depends on the type and severity. Immediate diagnosis and correct treatment are of utmost importance to improve patients’ outcome. This review will focus on the treatment of abdominal sepsis with a specific emphasis on surgical treatment. Especially new evidence, published in the last few years will be discussed.

Abdominal sepsis

An intra-abdominal infection (IAI) is, after a pulmonary focus, regarded as the second most common cause of sepsis\(^1\). An uncomplicated IAI rarely gives rise to critical illness with failure of other organs. Conversely, a complicated IAI (cIAI) that is caused by a disruption of the gastrointestinal tract or other hollow viscus, results in either localized or diffuse inflammation of the peritoneum and subsequent sepsis. This situation is also referred to as abdominal sepsis or secondary peritonitis. Abdominal sepsis can be caused by a spontaneous perforation, e.g. gastric ulcer perforation, complicated diverticulitis (community acquired) or as a complication of elective abdominal surgery (healthcare associated). This distinction is crucial with respect to underlying pathogens and related antibiotic treatment choice.

Due to a variety of definitions and patient characteristics mortality rates reported vary between 7.6-36\(^{\%}\).\(^2\)\(^-\)\(^4\). Recently, Sartelli et al. have conducted two large studies covering a wide geographical area and reported an overall mortality rate of abdominal sepsis of 7.6% in Europe (2) and 10.5 % worldwide\(^5\). In 2016 an international group of experts has updated the definitions for sepsis and septic shock originally developed in 1991\(^6\) and first updated in 2001\(^7\). Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction on itself can be identified as an acute change in total sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of two or more points\(^8\). A subset of sepsis, in which circulatory, cellular, and metabolic abnormalities result in suboptimal tissue oxygenation and perfusion is defined as septic shock and associated with a greater risk of mortality\(^9\). According to the surviving sepsis guidelines\(^10\) resuscitation in the first 6 hours, to maintain tissue perfusion, is of utmost importance to prevent multi organ failure and to improve outcome.

Antimicrobial and antifungal therapy

Immediate administration of broad-spectrum antibiotics as soon as cultures have been taken can be lifesaving. However, the preferred strategy might be patient and origin dependent. Targeted therapy should be based on culture results and checked at least twice a day by the
treating team. Every 30 minutes delay of the administration of antibiotics can worsen outcome\textsuperscript{11}. A Cochrane review by Wong et al.\textsuperscript{12} showed that no specific recommendations can be made for the first line antibiotic treatment in adults with abdominal sepsis, as all regimens showed equivocal efficacy. Therefore, the decision for a specific antimicrobial strategy requires other factors to consider, such as local guidelines and preferences, microbial resistance patterns, ease of administration, costs, and availability.

Worldwide, antimicrobial resistance is an increasing problem mainly caused by misuse and consequently overuse of antibiotics. The STOP-IT trial of Sawyer et al.\textsuperscript{13} has randomized 518 patients with an intra-abdominal infection to receive antibiotics until 2 days after the resolution of clinical symptoms (fever, leukocytosis, and ileus) versus a fixed short course of antibiotics (4 +/- 1 day). On average the two groups show a difference in duration of treatment; 4 days in the experimental group versus 8 days in the control group (absolute difference -4.0, 95% CI -4.7 - -3.3). No significant between-group difference is found in the composite endpoint of surgical site infection, recurrent intraabdominal infection and death (absolute difference, -0.5 percentage point, 95%CI: -7.0 to 8.0; P = 0.92). The Kaplan-Meier curve is showed in figure 1. However, some crucial remarks can be made about this trial that determine which weight should be given to its results. First, given the number of included patients versus participating centers the number of included patients per center per year is very low, pointing towards a highly selected study population. Secondly, included patients were not severely ill or septic as the median APACHE-II score was only 10.1 (SD 0.3) and mortality 1%. Median hospital stay was only 7 days and about a third of the patients were treated by drainage with surgery. Thirdly, only 77.2% of patients received the allocated treatment, while for the remaining patients no difference in treatment between the two groups was achieved. Finally, the STOP-IT trial was prematurely terminated because of 'futility concerns' against the background of slow accrual, while criteria for futility interim analysis were not described in the protocol nor was such analysis desirable from a methodological point of view. This resulted in only 39.6% (400 of the actually included 518) of the calculated sample size of 1010 patients being available that really received the targeted experimental or control treatment.

Last year, several articles based on new analyses of the STOP-IT trial data have been published. These studies have found that a short-course of antibiotics is also safe for patients with known risk factors for complications (diabetes, obesity, or increased severity of illness)\textsuperscript{14}, as well as for patients who had percutaneous drainage of an intraabdominal abscess\textsuperscript{15} or presented with sepsis\textsuperscript{16}. A recently published post hoc analysis of this study also reveals that addition of vancomycin occurred in nearly one third of the patients and often in more severely ill patients. Despite this selection bias, no substantial differences in adverse outcomes are demonstrated based on the STOP-it trial data, suggesting limited utility for adding vancomycin to abdominal sepsis treatment regimens\textsuperscript{17}.
ABDOMINAL SEPSIS

Intraabdominal sepsis with Candida species is associated with poor outcome. A recent study has isolated Candida spp. in 28.9% of the patients with secondary peritonitis. The Amarcand2 study, a prospective cohort study in France, has compared anti-fungal therapy, empiric and targeted in patients with Candida peritonitis. Among the 279 ICU patients receiving systemic antifungal therapy for Candida peritonitis, 26% were treated based on proven infection, 30% were treated for suspicion of Candida peritonitis eventually confirmed, and 43% had eventually no Candida peritonitis. The day-28 mortality was similar in both groups (24% and 28% in the confirmed and non-confirmed candida peritonitis, respectively), and was similar whether the treatment was empiric or targeted. A delayed initiation of systemic antifungal therapy did not impact the prognosis for severely ill patients (SOFA≥7), while it increased the death rate among less severely ill patients.

Aforementioned studies and outcomes indorse the importance of a careful and thorough approach to antibiotic and antifungal use. Specific recommendation on therapy selection are beyond the scope of present review but a clear overview has been published in 2016 by Sartelli et al.
Surgical strategies

The key task in the surgical management of patients with abdominal sepsis is source control. Resection of the affected organ and/or restoration of the gastro-intestinal tract are the crucial steps in eliminating abdominal sepsis. Different surgical strategies have been used over the years, depending on surgeon and setting. Generally, three different surgical approaches towards abdominal sepsis can be distinguished: a planned relaparotomy (PR), a (planned) open abdomen (OA) and a relaparotomy on demand (ROD). Definitions are presented in Table 1.

**Table 1. Definitions**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>PR</td>
<td>Planned Relaparotomy</td>
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<tr>
<td>ROD</td>
<td>Relaparotomy On Demand</td>
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<tr>
<td>OA</td>
<td>Open Abdomen</td>
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<tr>
<td>DCS</td>
<td>Damage Control Surgery</td>
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<tr>
<td>RSCL</td>
<td>Rapid Source Control Laparotomy</td>
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<tr>
<td>TAC</td>
<td>Temporary Abdominal Closure</td>
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<td>PL</td>
<td>Peritoneal Lavage</td>
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In the planned strategy the surgeon reevaluates the abdominal cavity, usually every 36-48 hours, until peritonitis is absent. In the case of an OA the fascia is intentionally not approximated or not possible to approximate. The former two strategies are in contrast with a ROD, where the abdomen is closed primary and the patient is re-operated only in case of deterioration or lack of improvement with presumably an abdominal focus.

Up to 2007 a PR was a commonly performed strategy. This changed when the RELAP trial was published. In this study 232 patients with severe peritonitis have been randomized between a PR and a ROD. The primary endpoint was death and/or peritonitis related morbidity within a 12-month follow-up period. A total of 42% of the ROD patients underwent a relaparotomy compared with 94% of the PR patients. No significant difference in composite primary endpoint was found (57% ROD versus 65% planned, p=0.25). However, a substantial reduction in relaparotomies, health care utilization, medical costs, and ICU - and hospital stay were found. In the same year, Robledo et al. published a RCT including 40 patients with severe peritonitis and randomized between OA and ROD. This study was stopped halfway because of a twofold increased risk of death in the OA group (relative risk and odds ratio for death were respectively 1.83 and 2.85 times higher).
Unfortunately, the favorable results of an on-demand strategy are not generally recognized and some surgeons still perform planned relaparotomies. One possible explanation is that the surgeon may not be confident about source control and therefore defers definitive closure of the abdomen. For this scenario the phrase “a planned relaparotomy is for the surgeon not for the patient”, is particularly applicable. In our opinion this strategy should be strongly discouraged considering the risks of unselected reopening the abdomen while two thirds subsequently demonstrate negative findings. More explicit, ROD is absolutely the preferred strategy if one weighs the low risk of (short-term) complications against the risk of long-term complications (as seen for PR). Another explanation for the persistent use of unselected relaparotomies is the damage control surgery (DCS) approach, adopted from trauma care, also in patients with abdominal sepsis. DCS refers to staged laparotomies to manage trauma patients who are physiologically decompensated. In the first laparotomy only necessary and limited procedures are performed (i.e., stapling of the damaged bowel or intraabdominal packing for bleeding) and reconstructive surgery is performed when a patient is hemodynamically stable again. Adapted from trauma surgery, DCS in abdominal sepsis is often referred to as rapid source control laparotomy (RSCL). To decide for DCS in trauma patients the lethal triad parameters (hypothermia, acidosis, and coagulopathy) are applied. A recently published retrospective study of Becher et al. evaluated whether this lethal triad is also applicable for non-trauma patients. No survival advantage was found in this study. However, in patients with elevated lactate, pH ≤ 7.25, age ≥ 70 years and male gender performing a RSCL may decrease mortality in patients with preoperative severe sepsis or septic shock. Prospective validation of these parameters is still required. A three group propensity score matched case cohort study compared DSC in intraperitoneal sepsis (RSCL) to DCS in penetrating trauma and blunt trauma. Propensity scoring was performed using demographic and presenting physiologic data. They found that in patients with RSCL the rate of primary fascial closure was lowest and time to definitive closure was increased (RR 1.8; 1.3–2.2; P < 0.03). Intra-abdominal complication and mortality rates were higher for RSCL. These results strongly support the concept that abdominal trauma and abdominal sepsis require a different approach. There is no convincing evidence that DCS or RSCL is beneficial in patients with abdominal sepsis. Therefore, we recommend, without delay, a prompt solution to close the abdomen and no ‘hit and run’ surgery. If fear for anastomotic leakage in a hemodynamically unstable patient exists, opting for a deviating enterostomy or no anastomosis can be considered.

Predicting which patients require a ROD remains challenging. A study investigating different scoring systems on the RELAP data did not find any of the widely-used scoring systems of clinical value in decision making. A new prediction model was developed and recently validated in 69 patients and 161 assessments (Atema et al., submitted). This model showed fair accuracy (AUC or ROC 0.79). In clinical practice a low score showed a good negative predictive value for ongoing sepsis.
Some surgeons fear an abdominal compartment syndrome (ACS) and therefore choose to intentionally leave the abdomen open. In our opinion, delayed instead of primary closure is not justifiable for the prevention of an ACS. With adequate resuscitation volumes (vasoactive agents, colloid resuscitation, limit crystalloids) bowel edema can be decreased and organ perfusion will be maintained. If needed, abdominal fluid collections can be removed by percutaneous catheter drainage. Applying these concepts ACS is an infrequent complication of abdominal sepsis, and therefore does not justify an intentional open abdomen. For treatment of ACS opening the abdomen is usually unavoidable.

Nonetheless, in approximately 10% of patients with abdominal sepsis, primary fascial closure is not possible due to excessive visceral edema. However, to avoid evisceration and to increase chances of delayed closure, temporary abdominal closure (TAC) is required to avoid damage to the abdominal content and retraction of the fascia. TAC techniques are numerous with significantly different results, and the risk of enterocutaneous fistula formation (ECF) is considerable in many – if not all - of these techniques. A recently published systematic review and meta-analysis of Atema et al. describes the results of different TAC techniques; negative pressure wound therapy (NPWT), NPWT with continuous mesh-mediated fascial traction, dynamic retention sutures, mesh inlay, Bogota bag, zipper, loose packing and Wittman patch. This review includes 78 series (of which only one RCT) of open abdomen in 4358 patients of whom 50% or more had peritonitis of non-trauma origin. NPWT with continuous mesh-mediated fascial traction shows the best results with a 73.1% weighted fascial closure rate, 20% weighed mortality rate and only a 5.7% weighed fistula rate. In this technique the mesh is only temporarily, and removed during the final fascial closure step, Figure 2. The results of the other abdominal closure techniques are shown in Figure 2.

If an open abdomen is inevitable (due to visceral edema) and a TAC technique is applied, it is strongly advised to stepwise close the fascia as soon as possible since early closure is associated with better outcome. A systematic review and meta-analysis by Chen et al. have shown significantly lower mortality (OR 0.53 95% CI 0.40-0.70) and postoperative complications (OR 0.68 95% CI 0.52-0.90) in favor of early fascial closure as compared to delayed fascial closure for non-trauma patients. Two more recent studies confirm this conclusion. Smith et al. have shown that patients whose definitive closure is delayed for more than eight days are more than twice at risk of death at 90 days follow-up (RR 2.15; 1.2-3.5; P < 0.002). Loftus et al. have performed a retrospective cohort study comparing trauma and intra-abdominal sepsis patients treated with OA and NPWT as TAC, showing that trauma patients have a higher fascial closure rate at discharge (90% versus 76%). Moreover, predictive factors for fascial closure are different for trauma and non-trauma patients. For patients with abdominal sepsis a relaparotomy within 48 hours is associated with successful fascial closure, possibly because
closure is then part of the reoperative plan, whereas ≥ 3 diagnostic or therapeutic laparotomies are associated with failure to achieve fascial closure.

Figure 2. Negative pressure therapy with continuous mesh-mediated fascial traction after decompression laparotomy for abdominal compartment syndrome due to intra-abdominal infection. This therapy comprises a proactive closure planning that ideally should be completed within 8 days. (a) Initial temporary abdominal closure with inlay lightweight synthetic mesh closure after decompression laparotomy. (b) Since this inlay mesh is not a good solution an AbThera device was placed 2 days later. The lightweight mesh was removed. Here preparing for placement of the visceral protective sheet of AbThera with its octopus-like shaped foam between the two layers of the sheet. On top of the AbThera sheet, a new heavy weight synthetic mesh is placed as an inlay to the medial fascial edges. The mesh is closed on traction over the visceral protective layer of AbThera. (c) A perforated foam layer and adhesive drape applied on top of the AbThera sheet and mesh, and connected to negative pressure pump. (d) Situation after 2 AbThera changes. (e) Fourth AbThera change, the synthetic mesh is reefed almost maximally. The underlying visceral protective sheet of AbThera is visible. (f) Final closure step when the AbThera and synthetic mesh are removed, and the fascia is closed completely. Here, fascial closure was done over an intra-abdominal sublay Strattice biologic mesh that can hold high lateral tension without tearing because of remnant visceral edema. The skin was closed and closed incision negative pressure wound therapy was applied.
<table>
<thead>
<tr>
<th>Technique</th>
<th>Series n</th>
<th>Patients n</th>
<th>Peritonitis etiology</th>
<th>Fascial closure</th>
<th>Fistula</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>NPWT</td>
<td>32</td>
<td>1627</td>
<td>82.8† (77.5-87.0)</td>
<td>51.5† (46.6-56.3)</td>
<td>14.6† (12.1-17.6)</td>
<td>30.0† (25.6-34.8)</td>
</tr>
<tr>
<td>NPWT with fascial traction</td>
<td>6</td>
<td>463</td>
<td>90.3†‡ (69.6-97.4)</td>
<td>73.1† (63.3-81.0)</td>
<td>5.7†‡ (2.2-14.1)</td>
<td>21.5† (15.2-29.5)</td>
</tr>
<tr>
<td>Mesh</td>
<td>8</td>
<td>583</td>
<td>84.6†‡ (72.9-91.8)</td>
<td>34.2†‡ (9.7-71.5)</td>
<td>17.2† (9.3-29.5)</td>
<td>34.4†‡ (23.0-48.0)</td>
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<tr>
<td>Bogota bag</td>
<td>6</td>
<td>363</td>
<td>88.5†‡ (74.1-95.4)</td>
<td>47.0†‡ (14.1-82.7)</td>
<td>10.4† (5.9-17.8)</td>
<td>27.1† (18.0-38.6)</td>
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<tr>
<td>Zipper</td>
<td>5</td>
<td>124</td>
<td>92.9 (85.3-96.8)</td>
<td>34.0† (16.7-56.9)</td>
<td>12.5 (7.0-21.2)</td>
<td>39.1 (30.8-48.0)</td>
</tr>
<tr>
<td>Dynamic retention sutures</td>
<td>5</td>
<td>77</td>
<td>80.1 (60.7-91.2)</td>
<td>73.6 (51.1-88.1)</td>
<td>11.6 (4.5-26.9)</td>
<td>11.1 (4.5-25.0)</td>
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<td>Loose packing</td>
<td>2</td>
<td>42</td>
<td>96.6 (84.2-99.3)</td>
<td>na</td>
<td>15.7 (7.4-30.4)</td>
<td>40.0† (26.5-56.5)</td>
</tr>
<tr>
<td>Wittmann patch*</td>
<td>1</td>
<td>128</td>
<td>85</td>
<td>119</td>
<td>3</td>
<td>24</td>
</tr>
</tbody>
</table>

† = $\chi^2 < 0.1$, ‡ = $I^2 > 75\%$, * = actual numbers given instead of percentages

TAC = temporary abdominal closure, NPWT = negative pressure wound therapy, na = not applicable (combined number of patients ≤20)
A potential new strategy in the inevitable OA is the use of a non-crosslinked biologic mesh. The biologic mesh has shown potential in contaminated (bridging) hernia repairs but studies in the acute setting are lacking. The potential advantage is the ability to bridge the fascial gap and thereby close the abdominal cavity without the need for short-term, additional closure procedures (bridging technique). With this technique the abdomen can be closed immediately, without additional surgery as is required for most TAC techniques. Last but not least, due to the characteristics of the non-crosslinked biologic mesh tremendous fascial traction is possible, increasing the chances of primary fascial closure over an intra-abdominal sublay biologic mesh (reinforcement technique). Although initial costs of the use of a biologic mesh may seem high, a successful and early fascial closure likely prevents many complications and possibly costs arising from an open abdomen or repeated sheet changes associated with negative pressure therapy.

The role of peritoneal lavage

(Laparoscopic) peritoneal lavage (PL) has been proposed as a promising alternative to provide source control instead of resection. However, most studies on the subject have been performed in patients with diverticulitis Hinchey classification stage 3-4, and controversial outcomes are reported.

A recent RCT of Angenete et al., the DiLALA trial, has evaluated short term outcomes (12 weeks) in patients with purulent peritonitis (Hinchey III) receiving either laparoscopic peritoneal lavage (LPL) or a colonic resection and stoma (Hartmann’s procedure). Morbidity and mortality after laparoscopic lavage are not significantly different compared with a Hartmann’s procedure. However, LPL resulted in shorter operating time, shorter time in the recovery unit, and shorter hospital stay. Catry et al. have shown in a prospective observational study, including 40 patients, that LPL for perforated diverticulitis is associated with a high risk of inadequate intra-abdominal sepsis control requiring a Hartmann’s procedure in up to 25% of patients. These results are in line with another recently published RCT. The Dutch LOLA/LADIES-trial compared LPL to Hartmann procedure in patients with diverticulitis Hinchey stage III/IV. Due to a higher combined major morbidity and mortality rate in the LPL group within 30 days after operation or in hospital (39% versus 8%, OR 2.74, 95% CI 1.03- 7.27, p=0.0427) the trial was terminated prematurely. Therefore, the authors concluded that LPL is not superior to sigmoidectomy for the treatment of purulent perforated diverticulitis. Also published in 2015 is the SCANDIV trial, a randomized clinical superiority trial including 199 patients for either LPL or colon resection. The primary outcome, being severe postoperative complications (Clavien-Dindo score >IIIa) within 90 days, was observed in 30.7% of the patients in the LPL group and in 26.0% of the colon resection group (difference, 4.7% [95% CI, -7.9% to 17.0%]; P = .53). There was no significant difference in mortality (13.9% vs 11.5%), difference, 2.4% [95% CI, -7.2% to...
11.9%; P = .67. However, the reoperation rate in the LPL group was significantly higher 15 of 74 patients (20.3%) than in the colon resection group (4 of 70 patients [5.7%]; difference, 14.6% [95% CI, 3.5% to 25.6%]; P = .01. Moreover, four sigmoid carcinomas were missed with LPL. These results do not support LPL for treatment of perforated diverticulitis.

Resection and primary anastomosis may be safer and more effective, but for a firmer conclusion the results of the other part of the LADIES trial, comparing resection with primary anastomosis to Hartmann procedure, need to be awaited. So far, the available evidence does not favor LPL. However, long-term outcomes of the DILALA trial and completion of the LAPLAND trial38,39 are still needed.

**Conclusion**

Management of abdominal sepsis requires a multidisciplinary approach. Closing the abdomen after source control and only reopening it in case of deterioration of the patient without other (percutaneous) options is the preferred strategy in abdominal sepsis. There is no convincing evidence that damage control surgery is beneficial in patients with abdominal sepsis, but this approach interferes with the principle of closing the abdomen whenever possible. If closing the abdomen is not possible due to excessive visceral edema or reopening the abdomen is needed in case of an actual ACS, negative pressure therapy with continuous mesh-mediated fascial traction shows the best results.
REFERENCES

