Intra-Abdominal Hypertension and Abdominal Compartment Syndrome:

Epidemiology and markers for adverse outcome

Steven Gertjan Strang

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Chapter 1

General introduction and outline of thesis

GENERAL INTRODUCTION

Intra-abdominal hypertension (IAH) is the condition of increased intra-abdominal pressure (IAP) observed in severely ill or injured patients. Abdominal compartment syndrome (ACS) is new organ failure resulting from high IAP levels. ACS was first described in 1890 by Heinricius, but came more apparent in the 1990s (1, 2). Pediatric surgeons first recognized the syndrome after closing the abdominal wall in surgery for omphaloceles (3, 4). Later, following the introduction of damage control surgery and surgery for abdominal aortic ruptures, ACS was seen more often and therefore more commonly known (5-8). Due to increase of peri-operative survival in successful damage control surgery (DCS), patients who previously exsanguinated on the operating table now progressed to the intensive care units alive. Then they developed acute cardiac, respiratory, and renal failure resulting from increased abdominal pressure and still died as a consequence (1). The first attempts to treat this acute ACS aimed at abdominal decompression with removal of fluid, blood, or packs from the abdomen, and subsequent open abdominal treatment. Despite the direct decrease in IAP and initial recovery of organ function, early reports still noted high mortality (up to 75%) due to reperfusion injury (9). Morbidity numbers were also very high, for example 25% of patients treated with open abdomen develop wound complications (10). As the outcome of patients with ACS remained poor, the next step focused on prevention of ACS. Modifiable risk factors were systematically identified and addressed. Reduction of crystalloid resuscitation volumes, liberal and early using of the open abdomen for a prolonged period, goal directed correction of coagulopathy, timely hemorrhage control, and use of hemostatic resuscitation with tranexamic acid seemed to decrease ACS occurrence and mortality considerably (11-16). Whether these new approaches may have led to the decrease of IAH and ACS prevalence is still subject of debate in current literature.

Definitions

The Abdominal Compartment Society (WSACS) was established in 2004 and aimed to set up and improve research and management of ACS. Their evidence-based consensus definitions, guidelines on management, and research strategies were recommended and published, stating intra-bladder measurement of IAP as a standard (17). Intra-abdominal pressure (IAP) was defined as the steady state pressure concealed within the abdominal

cavity. Most critically ill patients in the intensive care unit (ICU) have an IAP of 5-7 mmHg (18). For organs concealed within the abdominal cavity, the perfusion pressure was defined as the mean arterial pressure (MAP) minus the IAP (Abdominal Perfusion Pressure: APP = MAP – IAP). This indicates that as IAP increases, hemodynamic perfusion pressure decreases which results in organ function deterioration depending on the compliance of the abdominal wall (19). Intra-abdominal hypertension (IAH) was defined as a sustained intra-abdominal pressure of over 12 mmHg. This value was established arbitrarily, primarily aiming at research purposes for indicating which patients 'intra-abdominal pressure is increased inappropriately'. Intra-abdominal hypertension pressure was graded as follows: Grade I = IAP 12 to 15 mmHg; Grade II = IAP 16 to 20 mmHg; Grade III = IAP 21 to 25 mmHg; and Grade IV = IAP above 25 mmHg. ACS was defined for research purposes as IAP at more than 20 mm Hg with new organ dysfunction or failure. For clinical purposes, ACS is better defined as IAH-induced new organ dysfunction without a strict intra-abdominal pressure threshold, since no intra-abdominal pressure level can predict ACS in all patients. *Primary* IAH or ACS was defined as a condition associated with injury or disease in the abdominopelvic region that frequently requires early surgical or interventional radiological intervention. *Secondary* IAH or ACS refers to conditions that do not originate from the abdominopelvic region (17). Recurrent ACS refers to the condition in which ACS redevelops following previous surgical or medical treatment of ACS. Little is known about this rare condition of recurrent ACS and especially in which patient high grade IAH (i.e. IAP above 20mmHg) or ACS still develops after surgical abdominal decompression.

Epidemiology

Most epidemiologic studies regarding ACS have been performed in trauma populations, and reported a considerably varying prevalence. Initial reports of ACS in major trauma populations showed a mortality rate of more than 60% and a prevalence higher than 30% (9, 20-22). The largest study until now (n=706; 10 years after the first publications) showed a prevalence of ACS of 1% among all admission on a trauma ICU (23). Another study demonstrated a prevalence of 14% among 188 patients with torso injury (24). Presumably, the different prevalences were likely related to the different patient populations studied. This literature suggested that the prevalence of ACS is highest among the most critically ill or injured patients, which likely resulted from the amount of blood

loss or the resuscitation volumes given to these patients and subsequent inflammatory reactions. The prevalence of intra-abdominal hypertension (IAH) was less well characterized, mainly due to the different definitions used in literature, and the not fully understood clinical relevance of the condition. Since management of these severely injured or ill patients has developed tremendously, current prevalence and mortality numbers presumably decreased significantly from those stated above. The introduction of goal directed resuscitation and transfusion, and permissive hypotension in these patients directly aimed at prevention of inflammation, over-resuscitation and edema. However, the effects on prevalence and outcome of ACS and IAH remain unknown.

Etiology and risk factors

ACS generally occurs in critically ill patients due to variety of medical and surgical conditions (25). These conditions can be grouped as conditions that diminish abdominal wall compliance (torso trauma, major burns, BMI, abdominal surgery, and abdominal hernia repair), conditions that increase intra-luminal contents (ileus, gastroparesis, and volvulus), conditions that increase intra-abdominal content (hemorrhage, ascites, abscess, and intra-abdominal tumors), conditions that decrease intra-abdominal volume (mechanical ventilation with high pressure, retroperitoneal tumors and acute pancreatitis), conditions associated with capillary leakage or fluid resuscitation (acidosis, hypothermia, positive fluid balance, massive resuscitation and poly transfusion), and miscellaneous conditions (coagulopathy, increased head of bed angle, peritonitis, and sepsis) (24, 26-32). Most patients in the ICU are subject to at least one of these factors, but patients with severe trauma, burn injuries, pancreatitis, or (abdominal) sepsis have multiple of these risk factors. Specifically those groups are prone for IAH, ACS, and associated morbidity and mortality. An overview of all risk factors for IAH and ACS are included in the 2013 WSACS consensus (17). Most of these risk factors are not modifiable, but specifically over-resuscitation and uncontrolled transfusion strategies play a central (and iatrogenic) role in ACS development. Introduction of plasma resuscitation for severe burn patients and restrictive fluid resuscitation in patients with acute pancreatitis proved to half the prevalence of IAH and ACS, respectively (33, 34). Of all listed risk factors, it remains unknown which are the most important ones and how these risk factors are interrelated.

Physiology

Intra-abdominal hypertension leads to swelling, hypoxia, and dysfunction at a cellular level, extensive fluid resuscitation leads to edematous and fluid-filled bowels (35). Decrease of venous return and deterioration of cardiac output due to effects of increasing IAP, triggers more fluid infusion. As a result of blood loss and dilution by (crystalloid) infusion, the oncotic pressure decreases. Subsequently, fluid flows into the interstitium or third space, an effect termed 'third spacing'. Fluids that accumulate intra-abdominally increase IAP further and causes the patients' condition to deteriorate. When this downwards spiral of more fluid resuscitation is not interrupted, the abdominal perfusion pressure will no longer be sufficient for adequate organ function and ACS emerges.

Intra-abdominal hypertension has an effect on almost every organ system (36). Physiologic effects mainly involve the intra-abdominal organs, but pathologic effects extend outside the abdomen. The most common signs are increased ventilation pressures and decreased urinary output. However, as IAP raises high enough, multiple organ systems will fail and eventually death will follow. Most clinically important consequences of IAH are discussed in more detail below.

Respiratory system

Due to a raised diaphragm, the thoracic volume and compliance decreases. To overcome this, ventilation pressures become higher (resulting in barotrauma), the functional residual capacity decreases and ventilation–perfusion mismatch increases, resulting impaired oxygenation (37, 38). Also, patients with ACS are at high risk for acute respiratory distress syndrome (ARDS). Causality is not known, but similar diseases or injuries increase both IAP and the risk of ARDS. A decreased thoracoabdominal compliance is associated with increased IAP and the risk of ARDS (39).

Cardiovascular system

Intra-abdominal hypertension reduces cardiac return through compression of the inferior vena cava and pooling of blood below the groin (40). Stroke volume is decreased by a raised diaphragm; contractibility is reduced through increased loading on the right ventricle against increased pulmonary pressures. Reduced cardiac output results in compensatory increases of systemic vascular resistance, which is worsened by direct compression of the abdominal aorta and systemic vasculature.

Renal system

Renal vein compression increases venous resistance, which impairs venous outflow (41). Renal artery vasoconstriction is induced by the sympathetic activity and renin-angiotensin systems, resulting from decreased cardiac output (42). These factors result in progressive reduction of urine output.

Gastro-intestinal system

Intra-abdominal pressure induced splanchnic perfusion, reduced cardiac output and increased splanchnic vascular resistance, results in gut ischemia and infarction (19, 43, 44). As a consequence, toxins, bacteria, and undigested food particles may pass the enterocyte layer, enter the underlying vasculature, and trigger systemic inflammatory reactions that may progress to multiple organ dysfunction syndrome and even death. These interstitial effects are thought to be the first to occur (24). A possible central role of the intestines in the development and outcome of IAH and ACS is studied in this thesis.

Clinical presentation

Typically, a patient with primary ACS suffers from a severe traumatic abdominal bleeding undergoes massive transfusion and laparotomy. After surgical hemostasis the abdominal wall is closed, patients are subsequently admitted to the ICU for stabilization and resuscitation (45, 46). Deterioration can lead to acidosis, coagulopathy and hypothermia. These three physiological disturbances aggravate each other independently, leading to a 'vicious circle of death'. This will lead to shock, intestinal edema, and increased IAP, especially if tight abdominal packs are left (47). When not taken back to theatre for decompression, ACS emerges and most of these patients die. Secondary ACS is seen in patients who did not have abdominal injury or surgery. In those patients, ACS emerges as

a result of massive bleeding outside the abdomen and a subsequent need for large volume resuscitation and transfusion, e.g. after a major pelvic injury (48). The resulting increase in IAP in these patients will lead again to the same vicious circle of death. This presentation of secondary ACS is also seen in patients with severe pancreatitis and burns, emphasizing the crucial role of fluid resuscitation in its development (49-51).

Diagnostics

The diagnosis of IAH/ACS requires measurement of IAP. Measurements should be performed routinely and repeatedly among high-risk patients in the ICU (17). Pressure can be measured directly by an intra-abdominally positioned catheter or indirectly by measurement of abdominal wall resistance and by using intra-gastric, intracolonic, intra-vesical (bladder), or inferior vena cava catheters (52-54). Measurement of bladder (*i.e.*, intra-vesical) pressure is the standard method to screen for IAH/ACS. It is simple and cheap because a standard urinary catheter can be used, it is accurate, but care must be taken to ensure consistent head and body positioning from one measurement to another. Intra-abdominal pressure is measured via the patient's Foley (bladder) catheter after instilling up to 25mL of sterile saline. The catheter is attached to a pressure transducer and the pressure is measured at end-expiration in the supine position after ensuring that abdominal muscle contractions are absent. The transducer should be zeroed at the level of the midaxillary line. Commercially available systems have also been developed to simplify measurement. The correlation between bladder pressure and directly measured IAP is strong (55). As accurate measurement of IAP requires free movement of the bladder wall, the bladder pressure is not reliable in the presence of intraperitoneal adhesions, pelvic fractures, bladder oppressive hematomas, abdominal packs, or a neurogenic bladder (52).

For diagnosis of ACS, new organ failure has to be confirmed. No strict criteria for new organ failure are used. In a clinical setting, a deterioration of a patients' condition at the time of peak IAP (above 20 mmHg) is enough to suspect ACS. However, it is challenging to distinguish whether or not new organ failure results from the increased pressure or as a result of the underlying condition (e.g. pancreatitis related SIRS). Abdominal decompression would not improve organ failure in the latter situation.

For research purposes, scoring of new organ failure is mostly done based on the standardized organ failure assessment (SOFA) score (56). This scoring system is developed and validated for tracking a patients' condition during ICU admission (57). The scoring system consists of six sub-domains for the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological system. Every sub-domain can be scored from 0 to 4 depending on defined clinical, laboratory, or treatment related variables. The SOFA score can be calculated once a day. A significant increase in one sub-score at the time of peak IAP (above 20 mmHg), would confirm ACS. But as individual patients have different capacities in overcoming the effects of IAH, no specific criterion of organ failure or cut-off level of IAP is sufficient for a definitive diagnose of ACS.

Although not generally accepted, radiologic findings can be helpful for diagnosing of guiding therapy for ACS (58). A round belly sign on Computed Tomography (CT) is suggestive for ACS, and narrowing of upper intra-hepatic IVC (defined as IVC diameter < 3mm on two or three consecutive CT images), and renal displacement are seen among patients with ACS (59). CT and ultrasound can also be helpful for the localization of fluid collections; guided drainage can be therapeutic as well. Plain radiographs or magnetic resonance imaging have no value in diagnosing or evaluating ACS.

All these available diagnostics have their own value in the work up for IAH and ACS, but unfortunately none is indicative for short term or long term adverse outcomes. The level of IAP, duration of IAH, or the number of failing organs have no absolute predictive value for the outcome of treated or untreated IAH or ACS. Therefore, they do not provide definitive answers whether or not to open the abdomen. New diagnostic tools for that aim would be very helpful for clinicians in the ICU.

Management

Evidence based treatment algorithms for IAH/ACS are available at the website of WSACS. These algorithms summarize the updated WSACS guidelines of 2013 (17). The most important features are discussed below.

The first steps in management can start as soon as IAH/ACS is recognized. Determination of increased IAP is easy; identification that the patient has an IAP-related problem is very challenging. Early recognition of a problem however can improve the patients' outcome significantly. The WSACS algorithm starts with non-invasive and low risk therapies. Whether these measures are effective depends on the patient. As IAH can rapidly develop into devastating ACS, a repeated evaluation of the effect of a given treatment is of key importance. Sequential measurement of IAP every four to six hours is advocated.

If a patient has developed IAH without signs of organ failure, non-invasive or minimally invasive measures are feasible. Conservative treatment of IAH focuses on five points. Evacuation of intra-luminal content, evacuation of intra-abdominal space occupying lesions (for example radiologic drainage of fluid collections), improvement of abdominal wall compliance (sedation and relaxation), optimizing of fluid balance and optimizing systemic or regional perfusion (for example goal-directed resuscitation). Some of the newer treatments such as tissue plasminogen activator assisted evacuation of retroperitoneal hematoma, theophylline infusions to reduce circulating adenosine concentrations, octreotide for limitation of reperfusion injury, and continuous negative extra-abdominal pressure (CNAP) to reduce IAP, are all promising treatment options for specific patient populations. Future studies are warranted to confirm some of these findings (60).

When prevention of ACS is not possible, surgical decompression of the abdomen is warranted, leaving the abdomen open afterwards. Although generally accepted and advocated by WSACS as treatment of choice, it is still associated with high morbidity, closure problems and high costs (61). On the other hand, the long term outcome of abdominal decompression is not as debilitating and life altering as might be expected (62).

Outcome

Intra-abdominal hypertension (IAH) causes tissue hypoperfusion, which may lead to multi-organ failure, and death. The effect of decompressive laparotomy on outcomes in patients with abdominal compartment syndrome is not well studied. Although IAH is not a predictor of multi organ failure per se, mortality for patients who have progressed to ACS is high, ranging from 40 to 100 percent (26, 63). A prospective cohort study included 33 adult patients who underwent decompressive laparotomy, showed an overall 28-day mortality of 36%, and 55% at one year (64). Thus, outcome for patients with ACS is very bad. Whether or not modern treatment options have resulted in lower prevalence and mortality remains unknown and is one of the study questions of this thesis.

Prediction of IAH, ACS, and related outcome

A large prospective cohort of patients with severe trauma identified hemoglobin concentration, central venous-to-arterial carbon dioxide difference (CO_2 GAP), temperature, base deficit, administered crystalloid volume and urinary output as early predictors for both primary and secondary ACS (24). Clinically, primary and secondary ACS both have the same presentations (IAH and organ dysfunction). However, injury patterns, resuscitation, and causes can differ. Analogous to this, predictors of primary ACS also include factors indicative of damage control management, and secondary ACS has features of high resuscitation volumes. Although gastric mucosal acidosis (measured by tonometry) is a sensitive and independent predictor of ACS, this method is not used in clinical practice. Accurate prediction of IAH-related adverse outcomes and ACS, would be a final step in prevention of these complications. Nevertheless, a valid predictive tool is not yet available.

Aim of this thesis

The aim of this thesis is to (1) determine the current understanding and management strategies of IAH/ACS among surgeons, (2) determine risk factors for primary, secondary and recurrent ACS, (3) determine current prevalence and outcome in recent literature, following implementation of up to date management guidelines, and (4) identify a prediction model for IAH and ACS and their associated adverse outcomes.

Outline of this thesis

The first part is this thesis outlines the problem of IAH and ACS, and gives an overview of current clinical practice. **Chapter 1** is the introduction of this thesis in which clinically relevant literature regarding recognition, management and outcome with IAH/ACS is summarized. Whether or not up to date practices for patients with these conditions were known or implemented is demonstrated in **Chapter 2.** This chapter describes the outcomes of a questionnaire survey among surgeons in Dutch hospitals.

Part two of this thesis contains four manuscripts describing epidemiologic data of IAH/ACS of specified patient groups. **Chapter 3** describes a retrospective study of patients who have undergone trauma laparotomy in a level 1 trauma center in Australia. The aim of this study was to identify risk factors for high-grade IAH (an IAP >20 mmHg). A comparison was made between characteristics of patients who developed high-grade IAH following trauma laparotomy versus those patients who did not. In **Chapter 4,** the authors determined the prevalence and mortality rate of ACS among severely injured patients. A systematic review and data pooling of all available literature was performed for this. Data of studies performed before and after introduction of the WSACS guidelines were compared. **Chapter 5** describes a systematic review and meta-analysis which determined the prevalence and outcome of IAH and ACS among severe burn patients. This systematic review also provides an overview of management options for these patients as found in literature. In **Chapter 6**, data of a prospective observational study of 58 patients with severe burn injuries admitted to two burn centers in the Netherlands (BURNIAH study) are presented. The aim of this study was to determine the prevalence and outcome of IAH among patient's adult patients with burn injuries ≥15% of total body surface area (TBSA). Also, urinary Intestinal Fatty Acid Binding Protein (I-FABP biomarker) was tested as potential predictor for IAH and ACS and early marker for related adverse outcomes.

The third part of this thesis contains three studies that investigate the usefulness of potential biomarkers as predictors for IAH, ACS and related adverse outcomes. The first two chapters of this part describe the I-Fabulous study. This is the largest prospective multi-center cohort study up to date of 198 patients with two or more risk factors for IAH/ACS admitted to the ICU. The aim of this study was to determine the usefulness of urinary and serum I-FABP as a predictor for IAH and ACS and early marker for related

adverse outcomes. **Chapter 7** is the published protocol of this study. In **Chapter 8,** the outcomes of the study are presented. The outcomes of an experimental model of IAH in rats were describes in **Chapter 9**. This study aimed to determine the relation between IAP and respiratory parameters, hemodynamic parameters, and the development of early intestinal ischemia in rats. Also, serum albumin-cobalt binding ACB capacity was tested as early marker for IAH related intestinal ischemia.

Part four of this thesis serves as a discussion of the chapters and summarizes most relevant outcomes. **Chapter 10** is the general discussion with future perspectives. Summaries of the thesis are provided in English (**Chapter 11**) and in Dutch (**Chapter 12**).

References

1. Schein M. Abdominal Compartment Syndrome. Abdominal Compartment Syndrome Edited by: IvaturyR, Cheatham M, Malbrain M, Sugrue M Georgetown, Texas: LandesBiosciences. 2006;2006:1-7.
2. Van Hee R. Historical highlights in concept and treatment of abdominal compartment syndrome. Acta Clin Belg. 2007;62 Suppl 1:9-15.
3. Hershenson MB, Brouillette RT, Klemka L, Raffensperger JD, Poznanski AK, Hunt CE. Respiratory insufficiency in newborns with abdominal wall defects. J Pediatr Surg. 1985;20(4):348-53.
4. Wesley JR, Drongowski R, Coran AG. Intragastric pressure measurement: a guide for reduction and closure of the silastic chimney in omphalocele and gastroschisis. J Pediatr Surg. 1981;16(3):264-70.
5. Burch JM, Ortiz VB, Richardson RJ, Martin RR, Mattox KL, Jordan GL, Jr. Abbreviated laparotomy and planned reoperation for critically injured patients. Ann Surg. 1992;215(5):476-83; discussion 83-4.
6. Fietsam R, Jr., Villalba M, Glover JL, Clark K. Intra-abdominal compartment syndrome as a complication of ruptured abdominal aortic aneurysm repair. Am Surg. 1989;55(6):396-402.
7. Kron IL, Harman PK, Nolan SP. The measurement of intra-abdominal pressure as a criterion for abdominal re-exploration. Ann Surg. 1984;199(1):28-30.
8. Stone HH, Strom PR, Mullins RJ. Management of the major coagulopathy with onset during laparotomy. Ann Surg. 1983;197(5):532-5.
9. Morris JA, Jr., Eddy VA, Blinman TA, Rutherford EJ, Sharp KW. The staged celiotomy for trauma. Issues in unpacking and reconstruction. Ann Surg. 1993;217(5):576-84; discussion 84-6.
10. Miller RS, Morris JA, Jr., Diaz JJ, Jr., Herring MB, May AK. Complications after 344 damage-control open celiotomies. J Trauma. 2005;59(6):1365-71; discussion 71-4.
11. Cotton BA, Gunter OL, Isbell J, Au BK, Robertson AM, Morris JA, Jr., et al. Damage control hematology: the impact of a trauma exsanguination protocol on survival and blood product utilization. J Trauma. 2008;64(5):1177-82; discussion 82-3.

12. Duchesne JC, Kimonis K, Marr AB, Rennie KV, Wahl G, Wells JE, et al. Damage control resuscitation in combination with damage control laparotomy: a survival advantage. J Trauma. 2010;69(1):46-52.
13. Gunter OL, Jr., Au BK, Isbell JM, Mowery NT, Young PP, Cotton BA. Optimizing outcomes in damage control resuscitation: identifying blood product ratios associated with improved survival. J Trauma. 2008;65(3):527-34.
14. Hess JR, Holcomb JB, Hoyt DB. Damage control resuscitation: the need for specific blood products to treat the coagulopathy of trauma. Transfusion. 2006;46(5):685-6.
15. Schochl H, Forster L, Woidke R, Solomon C, Voelckel W. Use of rotation thromboelastometry (ROTEM) to achieve successful treatment of polytrauma with fibrinogen concentrate and prothrombin complex concentrate. Anaesthesia. 2010;65(2):199-203.
16. Williams-Johnson JA, McDonald AH, Strachan GG, Williams EW. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2) A randomised, placebo-controlled trial. West Indian Med J. 2010;59(6):612-24.
17. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med. 2013;39(7):1190-206.
18. Sanchez NC, Tenofsky PL, Dort JM, Shen LY, Helmer SD, Smith RS. What is normal intra-abdominal pressure? Am Surg. 2001;67(3):243-8.
19. Diebel LN, Dulchavsky SA, Wilson RF. Effect of increased intra-abdominal pressure on mesenteric arterial and intestinal mucosal blood flow. J Trauma. 1992;33(1):45-8; discussion 8-9.
20. Ivatury RR, Porter JM, Simon RJ, Islam S, John R, Stahl WM. Intra-abdominal hypertension after life-threatening penetrating abdominal trauma: prophylaxis, incidence, and clinical relevance to gastric mucosal pH and abdominal compartment syndrome. J Trauma. 1998;44(6):1016-21; discussion 21-3.

21. Offner PJ, de Souza AL, Moore EE, Biffl WL, Franciose RJ, Johnson JL, et al. Avoidance of abdominal compartment syndrome in damage-control laparotomy after trauma. Arch Surg. 2001;136(6):676-81.
22. Raeburn CD, Moore EE, Biffl WL, Johnson JL, Meldrum DR, Offner PJ, et al. The abdominal compartment syndrome is a morbid complication of postinjury damage control surgery. Am J Surg. 2001;182(6):542-6.
23. Hong JJ, Cohn SM, Perez JM, Dolich MO, Brown M, McKenney MG. Prospective study of the incidence and outcome of intra-abdominal hypertension and the abdominal compartment syndrome. Br J Surg. 2002;89(5):591-6.
24. Balogh Z, McKinley BA, Holcomb JB, Miller CC, Cocanour CS, Kozar RA, et al. Both primary and secondary abdominal compartment syndrome can be predicted early and are harbingers of multiple organ failure. J Trauma. 2003;54(5):848-59; discussion 59-61.
25. Malbrain ML, Chiumello D, Pelosi P, Bihari D, Innes R, Ranieri VM, et al. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. Crit Care Med. 2005;33(2):315-22.
26. Balogh ZJ, Martin A, van Wessem KP, King KL, Mackay P, Havill K. Mission to eliminate postinjury abdominal compartment syndrome. Arch Surg. 2011;146(8):938-43.
27. Reintam Blaser A, Parm P, Kitus R, Starkopf J. Risk factors for intra-abdominal hypertension in mechanically ventilated patients. Acta Anaesthesiol Scand. 2011;55(5):607-14.
28. Dalfino L, Tullo L, Donadio I, Malcangi V, Brienza N. Intra-abdominal hypertension and acute renal failure in critically ill patients. Intensive Care Med. 2008;34(4):707-13.
29. Madigan MC, Kemp CD, Johnson JC, Cotton BA. Secondary abdominal compartment syndrome after severe extremity injury: are early, aggressive fluid resuscitation strategies to blame? J Trauma. 2008;64(2):280-5.
30. Cheatham ML, De Waele JJ, De Laet I, De Keulenaer B, Widder S, Kirkpatrick AW, et al. The impact of body position on intra-abdominal pressure measurement: a multicenter analysis. Crit Care Med. 2009;37(7):2187-90.

31. Ouellet JF, Leppaniemi A, Ball CG, Cheatham ML, D'Amours S, Kirkpatrick AW. Alternatives to formal abdominal decompression. Am Surg. 2011;77 Suppl 1:S51-7.
32. De Keulenaer BL, De Waele JJ, Malbrain ML. Nonoperative management of intra-abdominal hypertension and abdominal compartment syndrome: evolving concepts. Am Surg. 2011;77 Suppl 1:S34-41.
33. Mao EQ, Tang YQ, Fei J, Qin S, Wu J, Li L, et al. Fluid therapy for severe acute pancreatitis in acute response stage. Chin Med J (Engl). 2009;122(2):169-73.
34. O'Mara MS, Slater H, Goldfarb IW, Caushaj PF. A prospective, randomized evaluation of intra-abdominal pressures with crystalloid and colloid resuscitation in burn patients. J Trauma. 2005;58(5):1011-8.
35. Balogh Z, McKinley BA, Cox CS, Jr., Allen SJ, Cocanour CS, Kozar RA, et al. Abdominal compartment syndrome: the cause or effect of postinjury multiple organ failure. Shock. 2003;20(6):483-92.
36. Malbrain ML, Marik PE, Witters I, Cordemans C, Kirkpatrick AW, Roberts DJ, et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. Anaesthesiol Intensive Ther. 2014;46(5):361-80.
37. Ridings PC, Bloomfield GL, Blocher CR, Sugerman HJ. Cardiopulmonary effects of raised intra-abdominal pressure before and after intravascular volume expansion. J Trauma. 1995;39(6):1071-5.
38. Cullen DJ, Coyle JP, Teplick R, Long MC. Cardiovascular, pulmonary, and renal effects of massively increased intra-abdominal pressure in critically ill patients. Crit Care Med. 1989;17(2):118-21.
39. Gattinoni L, Pelosi P, Suter PM, Pedoto A, Vercesi P, Lissoni A. Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes? Am J Respir Crit Care Med. 1998;158(1):3-11.
40. Cheatham M, Malbrain ML. Cardiovascular implications of elevated intra-abdominal pressure. Ivatury R, Cheatham M, Malbrain ML, Sugrue M, (eds) Abdominal compartment syndrome Georgetown, TX: Landes Bioscience. 2006;2006:89–104.
41. Doty JM, Saggi BH, Blocher CR, Fakhry I, Gehr T, Sica D, et al. Effects of increased renal parenchymal pressure on renal function. J Trauma. 2000;48(5):874-7.

42. Shenasky JH, 2nd. The renal hemodynamic and functional effects of external counterpressure. Surg Gynecol Obstet. 1972;134(2):253-8.
43. Rasmussen IB, Berggren U, Arvidsson D, Ljungdahl M, Haglund U. Effects of pneumoperitoneum on splanchnic hemodynamics: an experimental study in pigs. Eur J Surg. 1995;161(11):819-26.
44. Sugrue M, Jones F, Lee A, Buist MD, Deane S, Bauman A, et al. Intraabdominal pressure and gastric intramucosal pH: is there an association? World J Surg. 1996;20(8):988-91.
45. Burrows R, Edington J, Robbs JV. A wolf in wolf's clothing--the abdominal compartment syndrome. S Afr Med J. 1995;85(1):46-8.
46. Rotondo MF, Schwab CW, McGonigal MD, Phillips GR, 3rd, Fruchterman TM, Kauder DR, et al. 'Damage control': an approach for improved survival in exsanguinating penetrating abdominal injury. J Trauma. 1993;35(3):375-82; discussion 82-3.
47. Balogh Z, McKinley BA, Cocanour CS, Kozar RA, Valdivia A, Sailors RM, et al. Supranormal trauma resuscitation causes more cases of abdominal compartment syndrome. Arch Surg. 2003;138(6):637-42; discussion 42-3.
48. Maxwell RA, Fabian TC, Croce MA, Davis KA. Secondary abdominal compartment syndrome: an underappreciated manifestation of severe hemorrhagic shock. J Trauma. 1999;47(6):995-9.
49. Leppaniemi A. Open Abdomen after Severe Acute Pancreatitis. Eur J Trauma Emerg Surg. 2008;34(1):17-23.
50. Oda J, Ueyama M, Yamashita K, Inoue T, Noborio M, Ode Y, et al. Hypertonic lactated saline resuscitation reduces the risk of abdominal compartment syndrome in severely burned patients. J Trauma. 2006;60(1):64-71.
51. Oda J, Yamashita K, Inoue T, Hosotsubo H, Aoki Y, Ode Y, et al. Acute lung injury and multiple organ dysfunction syndrome secondary to intra-abdominal hypertension and abdominal decompression in extensively burned patients. J Trauma. 2007;62(6):1365-9.
52. Malbrain ML. Different techniques to measure intra-abdominal pressure (IAP): time for a critical re-appraisal. Intensive Care Med. 2004;30(3):357-71.

53. van Waes OJF, Jaquet JB, Hop WC, Morak MJ, IJzermans JM, Koning J. A Single-Lumen Central Venous Catheter for Continuous and Direct Intra-abdominal Pressure Measurement. Eur J Trauma Emerg Surg. 2009;35(6):532-7.
54. van Ramshorst GH, Salih M, Hop WC, van Waes OJF, Kleinrensink GJ, Goossens RH, et al. Noninvasive assessment of intra-abdominal pressure by measurement of abdominal wall tension. J Surg Res. 2011;171(1):240-4.
55. Fusco MA, Martin RS, Chang MC. Estimation of intra-abdominal pressure by bladder pressure measurement: validity and methodology. J Trauma. 2001;50(2):297-302.
56. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10.
57. Moreno R, Vincent JL, Matos R, Mendonca A, Cantraine F, Thijs L, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Working Group on Sepsis related Problems of the ESICM. Intensive Care Med. 1999;25(7):686-96.
58. Sugrue G, Malbrain M, Pereira B, Wise R, Sugrue M. Modern imaging techniques in intra-abdominal hypertension and abdominal compartment syndrome: a bench to bedside overview. Anaesthesiol Intensive Ther. 2018;50(3):234-42.
59. Pickhardt PJ, Shimony JS, Heiken JP, Buchman TG, Fisher AJ. The abdominal compartment syndrome: CT findings. AJR Am J Roentgenol. 1999;173(3):575-9.
60. De Keulenaer B, Regli A, De Laet I, Roberts D, Malbrain ML. What's new in medical management strategies for raised intra-abdominal pressure: evacuating intra-abdominal contents, improving abdominal wall compliance, pharmacotherapy, and continuous negative extra-abdominal pressure. Anaesthesiol Intensive Ther. 2015;47(1):54-62.
61. De Waele J, Desender L, De Laet I, Ceelen W, Pattyn P, Hoste E. Abdominal decompression for abdominal compartment syndrome in critically ill patients: a retrospective study. Acta Clin Belg. 2010;65(6):399-403.
62. Cheatham ML, Safcsak K. Longterm impact of abdominal decompression: a prospective comparative analysis. J Am Coll Surg. 2008;207(4):573-9.
63. An G, West MA. Abdominal compartment syndrome: a concise clinical review. Crit Care Med. 2008;36(4):1304-10.

64. De Waele JJ, Kimball E, Malbrain M, Nesbitt I, Cohen J, Kaloiani V, et al. Decompressive laparotomy for abdominal compartment syndrome. Br J Surg. 2016;103(6):709-15.

Chapter 2

Recognition and management of intra-abdominal hypertension and abdominal compartment syndrome; a questionnaire survey among Dutch surgeons

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ABSTRACT

Purpose: Intra-abdominal hypertension (IAH) and Abdominal compartment syndrome (ACS) are relatively rare, but severe complications. Although many advances were made in recent years, the recognition and management remains subject of debate. The aim of this study was to determine the current state of awareness, knowledge and use of evidence-based medicine regarding IAH and ACS among Dutch surgeons.

Methods: A literature-based and expert consensus survey was developed. One surgeon in every hospital in The Netherlands was asked to complete the online questionnaire.

Results: Sixty of 87 (69 %) invited surgeons completed the questionnaire. Intra-abdominal pressure (IAP) was measured using intra-vesical methods by 55 (98 %) respondents. Diuretics (N = 38; 63 %) and laparotomy (N = 33; 55 %) were considered useful treatments for IAH or prevention of ACS by a majority. Only 16 (27 %) respondents used evidenced based (WSACS – Abdominal Compartment Society) guidelines in daily practice and 37 (62 %) respondents are willing to do so. Although 35 (58 %) surgeons agreed that IAH is only a symptom, not requiring treatment. Forty-one percent of experienced respondents suggested that prevalence of ACS remained unchanged. Nearly all respondents (N = 59; 98 %) believed that open abdomen management improves patient outcomes, many (N = 46; 77 %) confirm the high complications rate of this treatment.

Conclusion: The definitions of IAH and ACS and the related diagnostic and therapeutic challenges are relatively well known by Dutch surgeons. Despite limited use of the evidence-based guidelines, the willingness to do so is high. Most respondents favor open abdomen treatment for patients with imminent ACS, despite the high complication rates associated with this treatment.

INTRODUCTION

Abdominal compartment syndrome (ACS) is a severe, but relatively rare complication. IAH is more common and can proceed into ACS in some of cases. Over recent years many advances regarding the recognition and management of ACS have been made. Nonetheless, randomized controlled trials on the subject are still scarce. Current management of ACS is based upon the up-to-date, evidence-based recommendations provided by the World Society of the Abdominal Compartment Syndrome (WSACS) (1). The strength of these recommendations is of varying quality. As a result, the management of ACS is still subject of debate and differs across hospitals.

Multiple studies have been conducted to identify the then current state of awareness, knowledge and use of evidence-based medicine regarding IAH and ACS. One of the most noticeable findings of these studies was that the awareness of IAP measurements and treatment options of IAH and ACS was generally low (2-9). In addition, cut-off points for treatment of ACS are poorly known or understood (3, 10-13). There is little agreement on the indications for open abdomen treatment and what type of temporary abdominal closure devices should be used (14-18). Most recent studies conclude that awareness among health care providers improved over recent years, but guidelines are still not uniformly applied or knowledge was inadequate (19-21).

The most recent survey was performed in 2010. Since then, new developments, such as the introduction of updated WSACS guidelines in 2013, may have improved outcome. Quality of previous questionnaires was variable. The response rates of these questionnaires ranged from 26 to 90 %. Other limitations were duration of more than 2 years and most studies were carried out by a wide variety of health care workers. Only six specifically focused on surgeons, yet surgeons ultimately decide whether or not to apply an open abdomen decompression (2-4, 8, 14, 15). No comparable surveys have been performed in The Netherlands.

The primary aim of this study was to identify the current state of awareness, knowledge and use of evidence-based medicine regarding IAH and ACS among Dutch surgeons. Secondary aims were to identify the current annual number of ACS cases per hospital and, to assess outcome of ACS patients.

METHODS

This questionnaire study was conducted and reported in accordance with the guidelines for survey research of Bennett, *et al.*(22).

Ethical statement

The current study used data that were obtained from surgeons using a survey. The questionnaire was anonymous. An independent officer of data and privacy protection in our hospital reviewed the survey procedure and confirmed that participants' anonymity was protected. Since patients were not involved in the study, the institutional Medical Research Ethics Committee did not have to review the protocol.

Questionnaire

The questionnaire was based upon a previously published questionnaire by the WSACS study group (21). Key questions were adopted and response options were added to make them more up-to-date. The questionnaire was drafted in Dutch and pretested by a panel of five experts and critically appraised on relevance, completeness, and style (OJFVW, MHJV, RSB, DHB, and KAK). The final version of the structured questionnaire consisted of five parts with a total of 29 questions; one part for participant's information and four parts for questions related to (1) IAP measurement, (2) IAH, (3) ACS, (4) open abdomen treatment and abdominal closure techniques. The full questionnaire is available in English (Appendix 1).

Selection of respondents

Surgical department of all Dutch hospitals with ICU facilities (N = 87) was asked to provide the name of the surgeon with the most ICU affinity. If a hospital had multiple locations with ICU facilities, only one surgeon was selected. All named surgeons were approached by telephone and informed about the purpose and method of the survey. Since one surgeon in every hospital throughout the country was selected, the targeted group of surgeons was presumed a representative cross-section of the care which patients in The Netherlands receive. Dutch surgical departments are relatively well informed and the rate of evidence-based guideline implementation is high. The results of this survey are

therefore applicable for to Western European standards. For this survey, a sample size calculation was considered unnecessary.

Distribution of survey

The questionnaire was distributed online using LimeSurvey software [Version 2.05+, LimeSurvey Project Team, Carsten Schmitz (2015), LimeSurvey Project Hamburg, Germany]. After obtaining verbal informed consent, a link to the questionnaire with unique and secure access codes was sent by email. This first invitation was sent on January 29, 2015. Reminders were sent every 2 weeks until the survey was closed on April 13, 2015. An opt-out link was clearly marked, the questionnaire could also be sent by mail or email if requested.

Data

Data were stored online by a secured function of the software used. Following survey closure, data were downloaded to an SPSS file. Questionnaires that were completed on paper were entered manually into the SPSS database. Only complete data sets were included in the analysis.

Analysis

All data were of categorical nature and are shown as numbers with corresponding percentages. Descriptive analysis was performed in SPSS version 21.0 (SPSS Statistics for Windows, Released 2012, Armonk, New York, IBM Corporation). No comparisons were made with previously performed surveys since differences between questionnaires and populations were considered too large.

RESULTS

Respondents

Sixty surgeons completed the questionnaire (response rate: 69 %). Ten partial responses were excluded. Most respondents had a primary focus on trauma surgery (N = 29; 48 %) or oncological surgery (N = 20; 33 %) (Figure 1). The majority (N = 38; 63 %) had over 10 years of surgical experience and more than half of respondents worked in a general teaching hospital (N = 34; 57 %).

Intra-abdominal pressure measurements

Intra-abdominal pressure measurements were performed in 58 (96%) of the hospitals of respondents. Forty-seven (78%) respondents claimed to know the difference between IAH and ACS, and 57 (95%) respondents had seen at least one patient with ACS in their hospital.

Fifty-five (98%) respondents use intra-vesical methods for IAP measurement. The largest group of respondents (N=14; 25%) measures intra-abdominal pressure three times daily on average (Figure 2).

Forty-nine (88%) respondents waits with measuring of IAP until there is a clear suspicion for ACS and 22 (39%) respondents start measurements as soon as risk factor(s) for ACS are identified (Figure 3).

Intra-abdominal hypertension

Forty-two (70%) respondents claimed to use the definition of IAH as set by the WSACS (Table 1). Of the seven treatment options listed, only diuretics (N=38; 63%) and laparotomy (N=33; 55%) were considered very useful or fairly useful by the majority of respondents (Figure 4). Thirty-five (58%) respondents agreed to the statement that IAH is only a symptom and as such needs no treatment.

Abdominal compartment syndrome

For ACS, the majority of respondents (N=31, 52%) used the definition as proposed by the WSACS (Figure 5). It was noteworthy that 17 (28%) respondents used a higher threshold for ACS.

Most respondents (n=33; 55%) were not familiar with the WSACS guidelines for the treatment of ACS. Whereas 27 (45%) respondents were familiar with the guidelines, only 16 (27%) actually implemented them in daily practice. Another 37 (62%) respondents plan to do so in the future (Table 2). A minority (n=6; 10%) disputes that the guidelines improve outcome of patients with ACS. Eighteen (30%) respondents answered that patients with ACS should be treated with surgical decompression in 76% to 100% of cases in their hospital (Figure 6). Another 18 (30%) indicated that this was done in 51-75% of cases. The vast majority of respondents considered these factors useful or had no clear opinion on the usefulness (Figure 7). A large group (N=26; 43%) stated that a superior indicator for surgical decompression would be a useful addition in to clinical practice (Table 3).

The mortality rate of patients with ACS who are not treated with surgical decompression was estimated between 26% and 50% by 18 (30%) respondents and between 51% and 75% by 22 (37%) respondents (Figure 8). If patients with ACS were treated with surgical decompression, the largest group of respondents (N=28; 47%) estimated a mortality rate of 10 to 25%.

Open abdomen treatment and abdominal closure techniques

Fifty-three (88%) respondents considered surgical abdominal decompression useful in the prevention of ACS (Table 4). However, the majority felt that ACS may not always be prevented.

The respondents were asked which factors would affect their decision whether or not to close the abdomen after surgical decompression. Most respondents answered that an increase in ventilation pressures is either useful (N=36; 60%) or very useful (N=12; 20%) in this decision (Figure 9). In addition, tension on the abdominal wall while closing the abdomen, planned reoperation, application of abdominal packings, hemodynamic instability at closure and visceral edema were considered by the majority of respondents. If primary closure is not possible, several devices are available for temporary closure. Among the respondents, application of a Vicryl® mesh was the most popular method for temporary closure, chosen by 38 (63%) respondents (Table 5). Many respondents selected multiple methods of temporary closure, 22 (37%) respondents selected two methods and 18 (30%) even selected three.

The largest group (n=27; 45%) of respondents prefers definitive abdominal closure in multiple stages (Table 6). An almost equally large group (n=26; 43%) prefers the component separation technique.

Almost all respondents (n=59; 98%) believed that open abdomen management improves patient outcomes, although many (n=46; 77%) acknowledged a high complication rate associated with open abdomen management (Table 7). Only one respondent stated that the possible positive effects of open abdomen management do not outweigh the complications that might arise because of this treatment.

DISCUSSION

This study is the first survey detailing awareness, knowledge, and use of evidence-based medicine and outcome regarding intra-abdominal hypertension and abdominal compartment syndrome among Dutch surgeons. The definitions of the WSACS are well known now, but the clinical practice guidelines of this society are still waiting to be implemented in hospitals. Much disagreement exists today with respect to treatment and outcome of intra-abdominal hypertension and abdominal compartment syndrome among Dutch surgeons.

Ninety-five percent of respondents had previously treated a patient with ACS in their hospital. This was in line with the 97 % reported by Tiwari, *et al*. (12). IAP measurements were regularly performed in 96 % of the participating hospitals, which was markedly higher than the 31–47 % reported in other surveys (4, 5). The frequency of IAP measurements, however, varied greatly among hospitals. In 13 (23 %) hospitals, IAP was measured less than once per 24 h. This frequency is rather low since IAP related morbidity can potentially develop or progress within a few hours (23).
There is still no consensus on the management of IAH and ACS. Although many respondents believed that IAH is only a symptom which does not necessarily needs to be treated, several different treatment options for IAH to prevent ACS were considered useful. For example, the use of diuretics and laparotomy are considered valuable. The majority of respondents were indifferent about other treatment options or regarded them as useless. This indifference about IAH treatment has previously been noted by Kimball, *et al.* (2).
Most respondents (88 %) think that surgical decompression could prevent ACS and improve patient outcomes. This is markedly higher than the 60 % of respondents who would recommend decompression laparotomy as reported by Zhou, *et al.*(9). Despite several indicators for surgical abdominal decompression were believed to be useful, 43 % of our respondents felt the need for a superior indicator.

There is disagreement between respondents and literature regarding temporary abdominal closure (TAC) devices. Respondents reported to prefer mesh assisted TAC. Although evidence is not conclusive, literature slightly favors vacuum assisted techniques

(24). Definitive closure techniques ideally bring the edges of the abdominal fascia together primarily (primary closure). If this is not feasible, simple coverage or functional closure can be provided. These latter techniques are generally regarded as inferior with respect to patient outcome. Respondents seem to be aware of this, since they mostly preferred staged abdominal closure, followed by the component separation closure technique. The vast majority of respondents were convinced of the necessity of open abdomen treatment for patients with imminent ACS, even though they were aware of the high complication rate associated with this treatment. Apparently they estimate that benefits of open abdomen treatment outweigh the chance of complications. This statement is confirmed by the presumed mortality reduction as result of open abdomen decompression as demonstrated in Figure 8. The current study confirms there is a large support for this treatment, even though there is disagreement recent literature regarding the benefits of open abdominal decompression in pancreatitis patients with ACS (25, 26).

The strength of the current study is its robust methodology. The survey was based on previous questionnaires, was developed by an expert group, and was repeatedly pretested. Surgeons were kindly, but persistently urged to participate. The online software enables swift responding and easy data collection. The nationwide coverage of this survey is also considered a strength.

Taken into account the 10 incomplete responses, the response rate of 69 % was fairly high. This number is at the upper end of response rates of the previously performed surveys on IAH and ACS (range 26–90 %) (2-21).

The skewed distribution of the primary focus of respondents can be regarded a limitation of this study, but is representative of the clinical practice in The Netherlands. The overrepresentation of trauma surgeons and oncological surgeons may be the result of the connection between these sub-specializations and intensive care medicine. It was, however, not the intention to approximate a cross-section of all Dutch surgeons, but rather of the care patients actually receive. Assuming that patients will usually be treated by a physician with the most relevant knowledge and experience, we are convinced that the results of this study really demonstrate the awareness and knowledge of the surgeon

with the largest relevant experience and knowledge. Another shortcoming is that the estimation of change in ACS occurrence over the last 10 years could be subject to recall bias. Although this was an important question, its outcomes were likely to be inaccurate. For example, six respondents indicated that a decrease in ACS incidence did not occur, while they ticked a lower number of cases category for last year compare than for 10 years ago (Table 2). However, this question does give insights in the perception of the experienced surgeon.

The overall knowledge and implementation of WSACS recommendations were lower than expected. This may be due to the fact that the vast majority of the respondents received their surgical training before the WSACS guidelines were developed. ACS treatment is currently implemented in these training programs. The results of the current study and the implementation in surgical training programs should result in increased awareness in the future.

In conclusion, the definitions of IAH and ACS and related diagnostic and therapeutic challenges are relatively well known among Dutch surgeons. Although use of the WSACS guidelines is currently limited, the willingness to do so is large. The vast majority of respondents are convinced of the necessity of open abdomen treatment for patients with imminent ACS, even though this treatment is associated with high complication rates. To decrease the complication rate, many respondents support the need for a superior indicator for surgical abdominal decompression.

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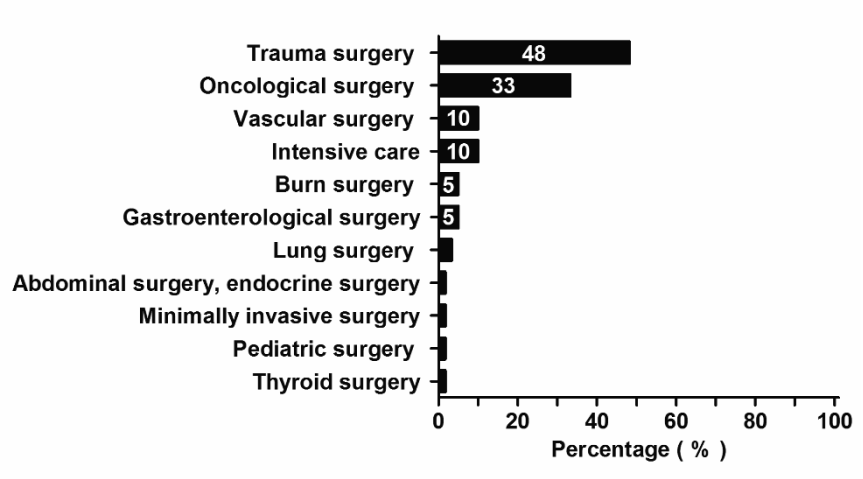
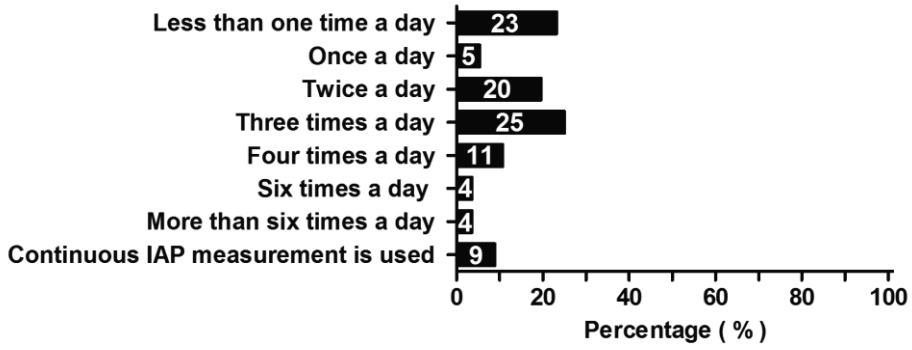
Figure 1. Primary focus of respondents



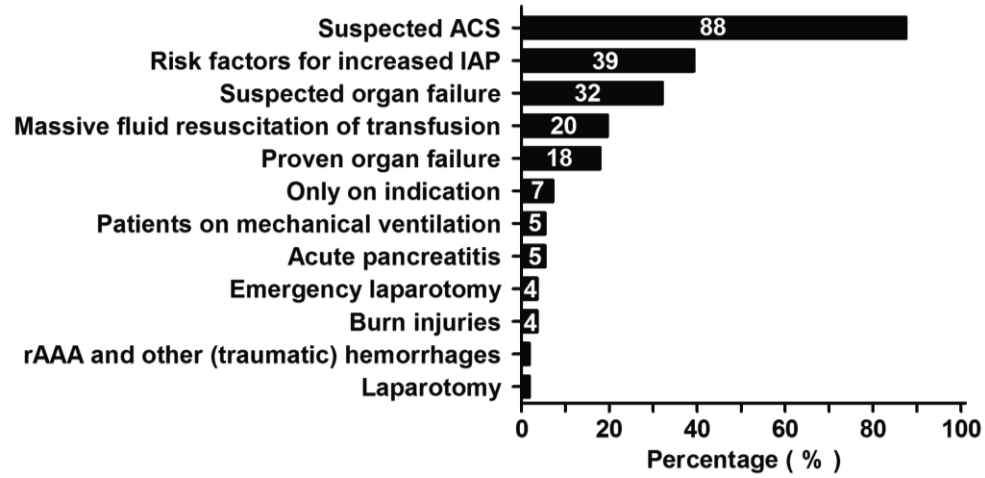
Primary focus of respondents is arranged on the y-axis from highest to lowest frequency. Percentages of all respondents are shown in the bars.

Figure 2. Number of IAP measurements performed daily in the individual patient



Percentages of all respondents are shown in the bars.

Figure 3. Percentage of patients in which IAP measurements are performed more or less routinely (patients with or after a/an:)

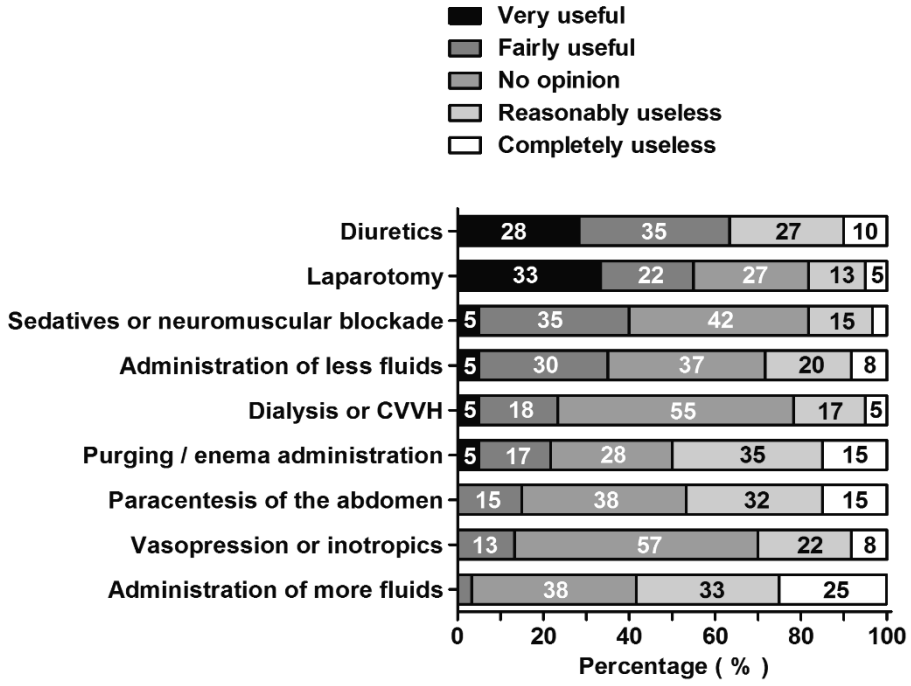


Percentages of all respondents are shown in the bars.

Table 1. Used definition for IAH (not ACS)

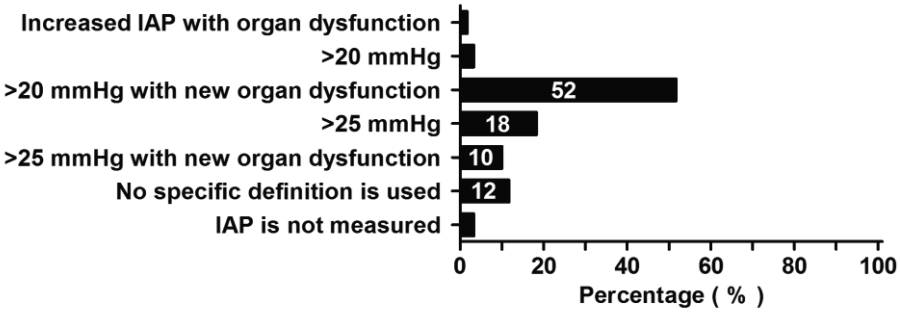
	N	%
An IAP of ≥ 12 mmHg, as stated by the WSACS	42	70
An IAP of > 18 mmHg	1	2
An IAP of > 20 mmHg	1	2
Ongoing or increasing IAP at multiple measurements	1	2
No definition	15	25

Figure 4. Usefulness of treatments for IAH in order to prevent ACS



Therapy options are arranged from highest to lowest summed percentage of very useful and fairly useful. Percentages of all respondents are shown in the bars.

Figure 5. Definition used for ACS (not IAH, an IAP of:)

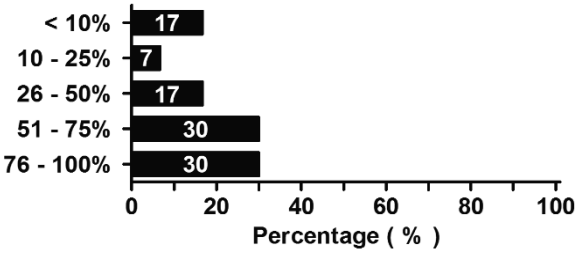


Percentages of all respondents are shown in the bars.

Table 2. Implementation of WSACS guidelines and recommendations for treatment of Abdominal Compartment Syndrome

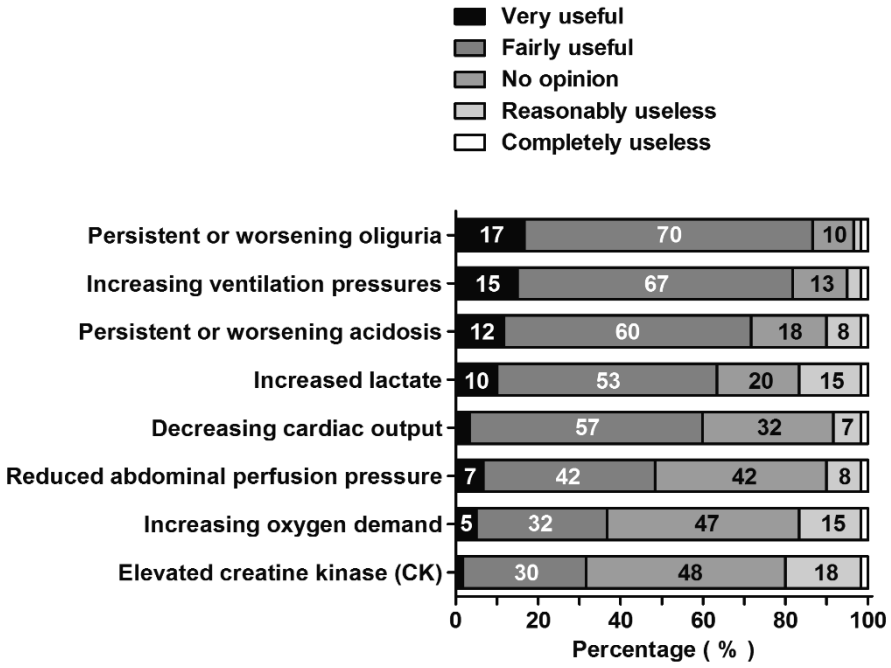
	N	%
This guideline is used	16	27
This guideline is not used but implementation is favored in the near future	37	62
This guideline is not used because it presumably does not improve the outcome of patients	6	10
There is no need for such a guideline	1	2

Figure 6. Number of ACS patients per hospital, treated with a surgical abdominal decompression



Percentages of all respondents are shown in the bars.

Figure 7. Usefulness of factors in deciding for surgical abdominal decompression (in addition to intra-abdominal pressure)

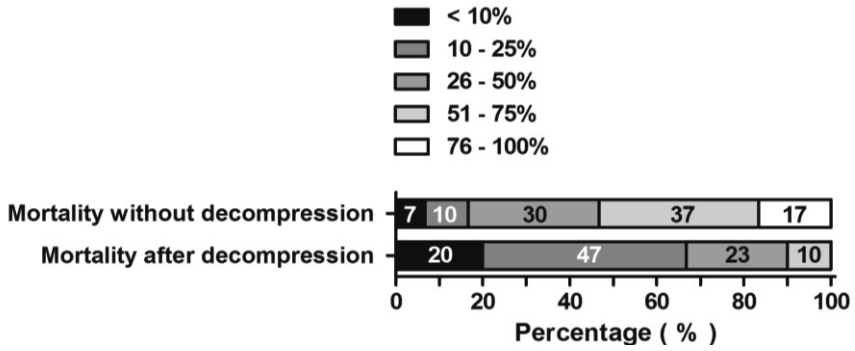


Factors are arranged from highest to lowest summed percentage of very useful and fairly useful. Percentages of all respondents are shown in the bars.

Table 3. Need for superior indicators of abdominal decompression (for example a serum marker of hypo-perfusion of abdominal organs)

	N	%
Yes, there is a need for superior indicators	26	43
I do not know / no opinion	26	43
No, there is no need for superior indicators	8	13

Figure 8. Estimated mortality rate among patients with ACS

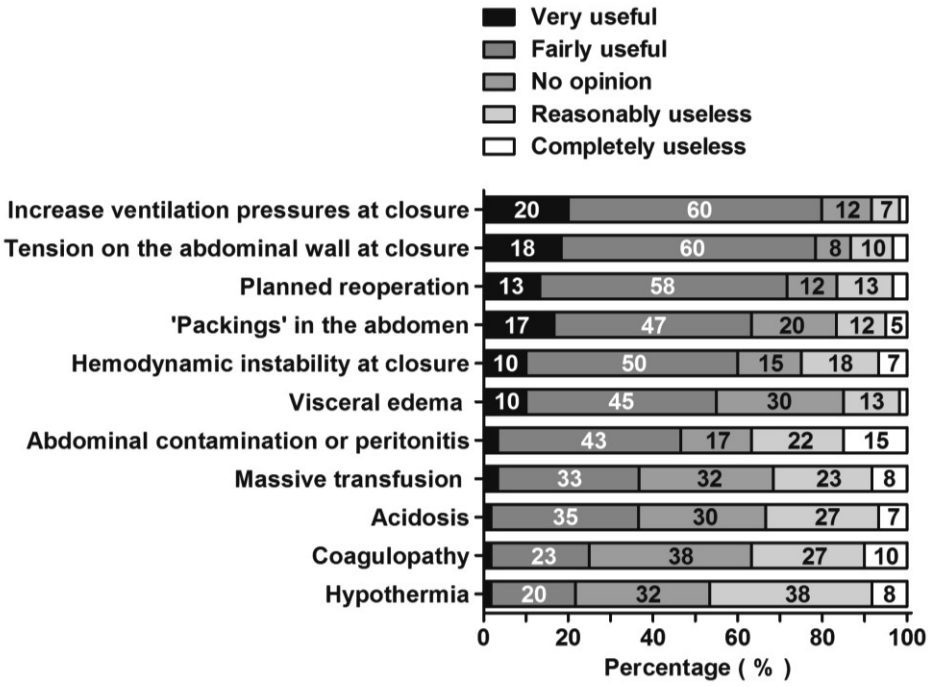


Percentages of all respondents are shown in the bars.

Table 4. Open abdominal treatment prevents ACS

	N	%
Yes, always	16	27
Yes, but not always	37	62
I am not sure	6	10
No, never	1	2

Figure 9. Usefulness of factors in deciding not to close the abdomen after surgical decompression



Factors are arranged from highest to lowest summed percentage of very useful and fairly useful. Percentages of all respondents are shown in the bars.

Table 5. Used <u>temporary</u> abdominal closure method or devices

	N	%
Mesh placement (Vicryl®)	38	63
Bogota / silo bag	28	47
Abdominal VAC	14	23
Vacuum pack	14	23
Only closure of the fascia	3	5
Closure of the skin (with surgical clamps)	3	5
Closing of the skin with thick suture	1	2
Regular gauze cover	1	2

Prcentages add up to more than 100% because respondents could tick more than 1 answer.

Table 6. Used definitive abdominal closure method

	N	%
Staged closure of the abdomen	27	45
Component separation technique	26	43
Absorbable mesh	22	37
Complete closure of fascia and skin	21	35
Only closure of the fascia	20	33
Non-absorbable mesh	17	28
ABRA system	12	20
Only closure of the skin	5	8
Delayed hernia	1	2
Dual mesh	1	2
Try to prevent non-resorbable materials	1	2

Percentages add up to more than 100% because respondents could tick more than one answer.

Table 7. Reply to statement: "Open abdomen treatment improves the outcome of patients with ACS"

	N	%
Agree	13	22
Agree, but open abdomen treatment is associated with many complications	46	77
Disagree, the complications outweigh the benefits of open abdomen treatment	1	2

REFERENCES

1. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med. 2013;39(7):1190-206.
2. Kimball EJ, Rollins MD, Mone MC, Hansen HJ, Baraghoshi GK, Johnston C, et al. Survey of intensive care physicians on the recognition and management of intra-abdominal hypertension and abdominal compartment syndrome. Critical care medicine. 2006;34(9):2340-8.
3. Kirkpatrick AW, Laupland KB, Karmali S, Bergeron E, Stewart TC, Findlay C, et al. Spill your guts! Perceptions of Trauma Association of Canada member surgeons regarding the open abdomen and the abdominal compartment syndrome. J Trauma. 2006;60(2):279-86.
4. De Laet IE, Hoste EA, De Waele JJ. Survey on the perception and management of the abdominal compartment syndrome among Belgian surgeons. Acta Chir Belg. 2007;107(6):648-52.
5. Burke BA, Latenser BA. Defining intra-abdominal hypertension and abdominal compartment syndrome in acute thermal injury: a multicenter survey. J Burn Care Res. 2008;29(4):580-4.
6. Otto J, Kaemmer D, Hoer J, Jansen M, Schumpelick V, Strik M, et al. [Importance of abdominal compartment syndrome in Germany: a questionnaire] Bedeutung des abdominellen Kompartmentsyndroms in Deutschland: Eine Umfrage. Anaesthesist. 2009;58(6):607-10.
7. Ejike JC, Newcombe J, Baerg J, Bahjri K, Mathur M. Understanding of Abdominal Compartment Syndrome among Pediatric Healthcare Providers. Crit Care Res Pract. 2010;2010:876013.
8. Costa S, Gomes A, Graca S, Ferreira A, Fernandes G, Esteves J, et al. [Abdominal compartment syndrome: survey on the awareness of Portuguese general surgeons] Sindrome de compartimento abdominal: questionario sobre a sensibilidade dos cirurgioes gerais Portugueses. Acta Med Port. 2011;24 Suppl 2:131-6.

9. Zhou JC, Zhao HC, Pan KH, Xu QP. Current recognition and management of intra-abdominal hypertension and abdominal compartment syndrome among tertiary Chinese intensive care physicians. J Zhejiang Univ Sci B. 2011;12(2):156-62.
10. Nagappan R, Ernest D, Whitfield A. Recognition and management of intra-abdominal hypertension and abdominal compartment syndrome. Crit Care Resusc. 2005;7(4):298-302.
11. Ravishankar N, Hunter J. Measurement of intra-abdominal pressure in intensive care units in the United Kingdom: a national postal questionnaire study. Br J Anaesth. 2005;94(6):763-6.
12. Tiwari A, Myint F, Hamilton G. Recognition and management of abdominal compartment syndrome in the United Kingdom. Intensive Care Med. 2006;32(6):906-9.
13. Biancofiore G, Bindi ML. Measurement and knowledge of intra-abdominal pressure in Italian Intensive Care Units. Minerva Anestesiol. 2008;74(1-2):5-8; quiz 9.
14. Mayberry JC, Goldman RK, Mullins RJ, Brand DM, Crass RA, Trunkey DD. Surveyed opinion of American trauma surgeons on the prevention of the abdominal compartment syndrome. J Trauma. 1999;47(3):509-13; discussion 13-4.
15. Karmali S, Evans D, Laupland KB, Findlay C, Ball CG, Bergeron E, et al. To close or not to close, that is one of the questions? Perceptions of Trauma Association of Canada surgical members on the management of the open abdomen. J Trauma. 2006;60(2):287-93.
16. Choi JY, Burton P, Walker S, Ghane-Asle S. Abdominal compartment syndrome after ruptured abdominal aortic aneurysm. ANZ J Surg. 2008;78(8):648-53.
17. MacLean AA, O'Keeffe T, Augenstein J. Management strategies for the open abdomen: survey of the American Association for the Surgery of Trauma membership. Acta Chir Belg. 2008;108(2):212-8.
18. Herrle F, Hasenberg T, Fini B, Jonescheit J, Shang E, Kienle P, et al. [Open abdomen 2009. A national survey of open abdomen treatment in Germany] Offenes Abdomen 2009. Umfrage zu Behandlungsstrategien des offenen Abdomens in Deutschland. Chirurg. 2011;82(8):684-90.

19. Kaussen T, Steinau G, Srinivasan PK, Otto J, Sasse M, Staudt F, et al. Recognition and management of abdominal compartment syndrome among German pediatric intensivists: results of a national survey. Ann Intensive Care. 2012;2 Suppl 1:S8.
20. Newcombe J, Mathur M, Bahjri K, Ejike JC. Pediatric critical care nurses' experience with abdominal compartment syndrome. Ann Intensive Care. 2012;2 Suppl 1:S6.
21. Wise R, Roberts DJ, Vandervelden S, Debergh D, De Waele JJ, De Laet I, et al. Awareness and knowledge of intra-abdominal hypertension and abdominal compartment syndrome: results of an international survey. Anaesthesiology intensive therapy. 2014.
22. Bennett C, Khangura S, Brehaut JC, Graham ID, Moher D, Potter BK, et al. Reporting guidelines for survey research: an analysis of published guidance and reporting practices. PLoS medicine. 2010;8(8):e1001069.
23. Rodas EB, Malhotra AK, Chhitwal R, Aboutanos MB, Duane TM, Ivatury RR. Hyperacute abdominal compartment syndrome: an unrecognized complication of massive intraoperative resuscitation for extra-abdominal injuries. The American surgeon. 2005;71(11):977-81.
24. Boele van Hensbroek P, Wind J, Dijkgraaf MG, Busch OR, Goslings JC. Temporary closure of the open abdomen: a systematic review on delayed primary fascial closure in patients with an open abdomen. World journal of surgery. 2009;33(2):199-207.
25. Ke L, Ni HB, Tong ZH, Li WQ, Li N, Li JS. The importance of timing of decompression in severe acute pancreatitis combined with abdominal compartment syndrome. The journal of trauma and acute care surgery. 2013;74(4):1060-6.
26. Mentula P, Leppaniemi A. Position paper: timely interventions in severe acute pancreatitis are crucial for survival. World journal of emergency surgery : WJES. 2014;9(1):15.

PART II - EPIDEMIOLOGY

Chapter 3

Identifying patients at risk for high-grade intra-abdominal hypertension following trauma laparotomy

Chapter 4

Prevalence and outcome of abdominal compartment syndrome in trauma patients; a systematic review

Chapter 5

A systematic review on intra-abdominal pressure in severely burned patients

Chapter 6

Prevalence of intra-abdominal hypertension and markers for associated complications in severe burn patients; a multicenter prospective cohort study (BURNIAH study)

Chapter 3

Identifying patients at risk for high-grade intraabdominal hypertension following trauma laparotomy

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ABSTRACT

Background: Abdominal Compartment Syndrome (ACS) is an uncommon but deleterious complication after trauma laparotomy. Early recognition of patients at risk of developing ACS is crucial for their outcome. The aim of this study was to compare the characteristics of patients who developed high-grade intra-abdominal hypertension (IAH) (*i.e.*, grade III or IV; intra-abdominal pressure, IAP >20 mmHg) following an injury-related laparotomy versus those who did not (*i.e.*, IAP ≤20 mmHg).

Methods: A retrospective analysis of consecutive trauma patients admitted to a level 1 trauma center in Australia between January 1, 1995 and January 31, 2010 was performed. A comparison was made between characteristics of patients who developed high-grade IAH following trauma laparotomy versus those who did not.

Results: A total of 567 patients (median age 31 years) were included in this study. Of these patients 10.2% (58/567) developed high-grade IAH of which 51.7% (30/58) developed ACS. Patients with high-grade IAH were older ($p<0.001$), had a higher Injury Severity Score ($p<0.001$), larger base deficit ($p<0.001$) and lower temperature at admission ($p=0.011$). In the first 24 hours of admission, patients with high-grade IAH received larger volumes of crystalloids ($p<0.001$), larger volumes of colloids ($p<0.001$) and more units of packed red blood cells ($p<0.001$). Following surgery prolonged prothrombin ($p<0.001$) and partial thromboplastin times ($p<0.001$) were seen. The patients with high-grade IAH suffered higher mortality rates (25.9% (15/58) vs. 12.2% (62/509); $p=0.012$).

Conclusion: Of all patients who underwent a trauma laparotomy, 10.2% developed high-grade IAH, which increases the risk of mortality. Patients with acidosis, coagulopathy, and hypothermia were especially at risk. In these patients, the abdomen should be left open until adequate resuscitation has been achieved, allowing for definitive surgery.

INTRODUCTION

Trauma is the leading cause of death in people aged 1 to 44 years and exsanguination is a common cause of death (1). Such active bleeding focus is frequently located intra-abdominally (2). In patients presenting to hospital following severe injury, hemodynamic instability or acute abdominal findings can mandate laparotomy. Laparotomy in this setting may be lifesaving.

Despite improved survival following laparotomy, patients are still at risk of developing abdominal compartment syndrome (ACS) (3, 4). ACS is a syndrome of intra-abdominal hypertension (IAH) with new onset or worsening organ failure. The World Society of the Abdominal Compartment Syndrome (WSACS) defines ACS as an intra-abdominal pressure (IAP) >20 mmHg with clinical signs of new organ failure, such as renal failure or increasing ventilation difficulties (5, 6). ACS is termed primary when it originates from intra-abdominal pathology, secondary when originating from an extra-abdominal source and tertiary or recurrent when ACS occurs in an already decompressed abdomen (7). WSACS defines IAH as an IAP ≥12 mmHg and introduced an IAH grading system for increasing severity with grades from I to IV (8). Grade I (IAP 12-15 mmHg) and II (IAP 16-20 mmHg) are referred to as low-grade IAH and Grade III (IAP 21-25 mmHg) and IV (IAP> 25 mmHg) are referred to as high-grade IAH. IAH and ACS result from decreased abdominal wall compliance and/or increased intra-abdominal volumes (fluid, edema).

ACS in isolation is generally treated through medical means or by decompressing the abdomen. The resulting laparostomy can be kept open for several days to a week using a temporary abdominal closure technique (TAC) (9). Surgeons can consider using TAC following trauma laparotomy when a patient is likely to develop IAH or ACS. However, a prolonged open abdomen is associated with higher morbidity including intra-abdominal infections, sepsis, anastomotic leakage, intestinal fistulae and sepsis (10-13). Knowledge of specific risk factors for IAH or ACS following trauma laparotomy may help the surgeon to mitigate these risks and improve outcomes. The aim of this study was to compare characteristics of patients who developed high-grade IAH following trauma laparotomy versus those patients who did not.

METHODS

A retrospective analysis was performed on trauma patients who underwent trauma laparotomy in a level I trauma center in Australia. This trauma center serves over 1 million inhabitants and admits more than 350 trauma patients annually with an injury severity score (ISS) greater than 15 (14). Data of admitted trauma patients were prospectively collected by trained trauma nurse coordinators (15). This registry has been recording more than 154 different variables for seriously injured patients, and has done so since 1994. Consecutive trauma patients who underwent trauma laparotomy within 24 hours of admission between January 1, 1995 and January 31, 2010 were included. Trauma registry data were collected as was information from clinical notes. This study was approved by the hospital's Human Research Ethics Committee.

Data collection included patient demographics, IAP's, information on organ function and diagnosis of ACS, abdominal decompression, ISS, shock, mechanism of injury, temperature on admission, lactate, base deficit, pH, hemoglobin level, resuscitation fluid(s), resuscitation volume, survival, and ICU/hospital lengths of stay. IAH and ACS were defined in accordance with the WSACS guidelines (6). Data were complete, unless specified differently in the Table footnotes.

Data were analyzed using SPSS version 16 (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.). Youden index was analysed using MedCalc version 14.10.2 (MedCalc Software, Ostend, Belgium). Inspecting frequency histograms and Q-Q plots revealed that the majority of continuous variables deviated from a standard normal distribution. Therefore, all continuous variables were regarded as non-normal and are shown as median values with first and third quartiles. Differences between patients with versus without high-grade IAH were tested using a Mann-Whitney U-test (continuous variable), a Fisher's exact test or Chi-squared test (categorical variables). Binary logistic regression analysis was performed in order to determine the strength of the association between covariates (independent variables) and the IAH grade (dependent variable; high-grade versus no high-grade IAH). Odds Ratios are presented with 95% confidence intervals. The Hosmer-Lemeshow test statistic (Chi-squared value) with corresponding p-value is given as measure of model calibration, and the area under the Receiver Operating Characteristic (ROC) curve is provided as measure of discriminatory power. The Youden Index (J = max (sensitivity + specificity - 1)), representing the maximum vertical distance

between the ROC curve and the diagonal line, was calculated in order to determine at which value of the evaluated variable the sum of sensitivity and specificity had the highest value. The Youden index was shown with its 95% confidence interval following bootstrapping (1,000 replicates and 900 random-number seeds). For continuous variables the optimal threshold value is also shown. P-values <0.05 were considered statistically significant.

RESULTS

Over a 16-year period 583 trauma patients presented to the emergency department and underwent trauma laparotomy. Of these patients, 16 underwent trauma laparotomy more than 24 hours following admission or were pregnant and therefore were not included in the study.

Baseline characteristics of the 567 included patients are shown in Table 1. Patients had a median age of 31 years, the majority of these patients were male, two-thirds sustained blunt injury and less than half had circulatory shock (defined by SBP < 90 mmHg) at the time of presentation to the emergency department. Of the included patients 10.2% (58/567) developed an IAP >20 mmHg, of which 51.7% (30/58) developed ACS. In order to compare characteristics and potential risk factors for ACS following trauma laparotomy, patients were divided into two separate groups; patients with an IAP ≤20mmHg (no high-grade IAH, N=509) and patients with an IAP >20 mmHg (high-grade IAH, N=58). The patients with high-grade IAH following trauma laparotomy were older ($p<0.001$), had a higher injury severity score (ISS; ($p<0.001$) and were more frequently in circulatory shock at presentation ($p<0.001$). Blunt abdominal trauma mechanisms were relatively more frequently seen in the high-grade IAH group than penetrating trauma mechanisms ($p=0.012$). Of the baseline characteristics investigated, higher age, higher ISS, being presented in circulatory shock, or having sustained blunt trauma increased the odds of developing a high-grade IAH (Odds Ratio, OR, 1.05, 1.03, 4.51, and 2.38, respectively).

Of the 567 laparotomies performed, immediate abdominal closure was undertaken in 479 (84.5%) patients; the abdomen was not immediately closed in 80 patients. The remaining 8 patients died during surgery or the data set could not be completed (Figure 1). Following immediate abdominal closure, 7.1% (34/479) developed high-grade IAH, of which 41.2% (14/34) developed ACS. In the group where the abdomen was not closed immediately, 30.0% (24/80) developed high-grade IAH, of this group 62.5% (15/24) still developed ACS either before or after delayed abdominal closure. In 20.8% (5/24) of patients who did not have immediate abdominal closure and developed high-grade IAH, delayed primary closure of the abdomen was not possible. Four of these five patients died (80.0%; 95%

Confidence Interval, CI 38-96%), which was substantially more than the 31.6% of patients (6/19; 95% CI 15-54%) in whom early delayed primary closure was possible (p=0.150).

A total of 57 re-laparotomies were performed in the 479 patients in whom the abdomen was directly closed; 38 in the group without high-grade IAH (8.5%; 38/445) and 19 in the high-grade IAH group (55.9%; 19/34). No significant association was found with mortality; mortality rates were 12.3 % (7/57) in patients who had a re-laparotomy versus 7.3% (31/422) in patients who did not (p=0.300).

Physiologic and fluid resuscitation parameters were identified as possible risk factors for high-grade IAH by determining values of these parameters at admission and approximately 6 hours after surgery (Table 2). Patients who developed high-grade IAH following trauma laparotomy more frequently presented with hypothermia (p=0.011) and acidosis as demonstrated by a lower pH (p<0.001), higher levels of lactate (p=0.013), and a larger base deficit (p<0.001) than those in whom IAP remained ≤20mmHg. Following laparotomy, these differences remained, except for hypothermia. On the other hand coagulopathy, expressed as a prolonged Prothrombin Time (PT) (p<0.001) or Partial Thromboplastin Time (PTT) (p<0.001), was seen following trauma laparotomy in patients with high-grade IAH. Logistic regression analysis showed that hypothermia at admission (OR 0.74) and presence of acidosis and coagulopathy (PTT) at six hours after trauma laparotomy (OR 0.05 and 1.01, respectively) significantly increased the odds of developing high-grade IAH.

Patients with high-grade IAH following laparotomy received larger volumes of resuscitation fluid in the emergency department (p=0.001) and during the first 24 hours following admission (p<0.001) compared to patients without high-grade IAH (Table 3). Even though this was mainly due to crystalloid volumes administered in the first 24 hours of admission (6.0L vs. 4.2L; p<0.001), patients also received larger volumes of colloid resuscitation in the first 24 hours of admission (2.5 vs. 1.5L, p<0.001). Patients with high-grade IAH also received more blood transfusions (17 vs. 2 units of packed red cells, p<0.001). The total resuscitation volume as well as the volume of crystalloids and colloids given in the first 24 hours all increased the odds of developing high-grade IAH (OR 1.17-1.21).

Patients with high-grade IAH following trauma laparotomy had worse outcomes than patients without high-grade IAH with a higher mortality rate (25.9% (15/58) vs. 12.2% (62/509); p=0.012), a longer median ICU length of stay (15 days vs. 1 day; p<0.001), and a longer median hospital length of stay (44 days vs. 9 days; p<0.001) (Table 4).

DISCUSSION

This analysis demonstrates associations between the development of high-grade IAH following trauma laparotomy and presence of acidosis, coagulopathy, and hypothermia. Coagulopathy is often associated with acidosis and hypothermia and these factors combined are associated with injury severity (ISS) (16). More severely injured patients often require larger volumes of resuscitation fluids which is a known risk factor for IAH (17). Moreover, a direct relation between acidosis (univariate analysis), hypothermia (multivariable analysis) and IAH has been confirmed (18, 19).

Acidosis, coagulopathy, and hypothermia could not be confirmed as independent risk factors for high-grade IAH by multivariable analysis. Nevertheless, it does suggest that the typical patient, who gets a damage control laparotomy, is also at risk for high-grade IAH. Leaving the abdomen open after a damage control laparotomy and delaying abdominal closure until coagulopathy, acidosis and hypothermia are corrected seems to be a good strategy.

Patients arriving to the emergency department in circulatory shock were twice as likely to develop high-grade IAH following trauma laparotomy. Crystalloid fluid resuscitation is a common first choice in emergency departments, but excessive use of it is a known risk factor for ACS (20). In this study, crystalloid resuscitation volumes were significantly higher in patients with high-grade IAH following trauma laparotomy. This is in concordance with the view that excessive crystalloid use is a risk factor for ACS following trauma laparotomy too. Over the studied period, no trend was observed in used volumes of crystalloid resuscitation fluid. High-grade IAH patients also received significantly larger colloid resuscitation volumes, total resuscitation volumes and more units of packed red blood cells over the first 24 hours following admission. More recently, a benefit for colloid resuscitation (including hydroxyethyl starches; HES) over crystalloid resuscitation with respect to days free from mechanical ventilation, vasopressor therapy and 90-day mortality has been suggested (21). Two other studies have advocated against the use of HES-based resuscitation, as HES-based resuscitation was associated with higher 90-day mortality rates in sepsis patients and an increased need for renal-replacement therapy in an ICU population (22, 23). Our analysis could not confirm a benefit for colloid resuscitation with respect to the development of high-grade IAH.

In the data presented, there are increased mortality rates associated with IAH grade and the use of open abdomen treatment. Mortality was highest in patients in whom delayed primary abdominal closure was not possible (80%; 4 out of 5). Inability to close the abdomen is known to be related to high morbidity and mortality (24). The presented data show significantly higher mortality following inability to close the abdomen than in patients in whom delayed abdominal closure was possible. Although the populations were too small in this analysis to attain statistical significance, it may suggest that open abdomen is an unfavourable condition. Moreover, open abdomen does not necessarily prevent ACS from occurring. In the 24 patients that developed high-grade IAH after open abdomen treatment, 15 patients still developed ACS. ACS developed during open abdomen treatment in seven of these 15 patients (46.7%) and after abdominal closure it developed in six patients (6/15; 40.0%). For the remaining two patients, it is unknown at what moment exactly the ACS was diagnosed.

The results of the current study indicated a lower mortality in patients with an open abdomen without high-grade IAH (14.7%; 5/34) than in patients with a closed abdomen and high-grade IAH (37.5%; 21/56; p=0.034). This is likely attributable to a more severe injury in the former group. Although the patients with an open abdomen without high-grade IAH were significantly younger (median age 33 vs. 52 years; p=0.001), they were more frequently in circulatory shock at presentation (83.9% (47/56) versus 58.8% (20/34); p=0.018) and had a higher median ISS (38 versus 29; p=0.048) than patient with a closed abdomen and high-grade IAH. Resuscitation (volume and composition), acidosis, coagulopathy, and hypothermia were not statistically significantly different between these two groups (data not shown).

Severely injured patients and patients in circulatory shock in whom trauma laparotomy is performed for blunt abdominal injury and who subsequently develop coagulopathy, hypothermia, or acidosis are at risk for ACS. These patients may benefit from open abdomen treatment, even though this treatment is associated with high morbidity and mortality (25, 26). Recently developed (vacuum assisted) temporary abdominal closure devices seem to improve patient outcome (27). Nevertheless, open abdomen treatment should be avoided when the development of high-grade IAH is unlikely. When open abdomen treatment is applied, abdominal closure should be aimed at as soon as possible after internal stabilization (preferably within a week).

Our study possesses several limitations. Given that ACS is a relative rare finding, patients who only developed high-grade IAH were interpreted as patients with a high risk for developing ACS. As mentioned, the number of patients who actually developed ACS was low. Even though ACS is relatively rare, its impact on patient outcome is very large, therefore early recognition of patients at risk is of developing ACS is important. Another limitation is the retrospective design of this study. Even though a retrospective design is unfavourable, it made inclusion of large patient numbers possible. The large population of patients that underwent trauma laparotomy is the main novelty of this study, it concerns the largest series published until now. Lastly, none of the identified characteristics of patients at risk for ACS could be confirmed with multivariable analysis. The multivariable analysis was hampered by the extent of redundancy and co-linearity between the covariates. This makes interpreting the findings more difficult. For example, the high mortality in patients in whom delayed abdominal closure was not possible, may also be a result of selection bias and injury severity. Larger (prospective) studies are needed to quantify the relative contribution of the demonstrated characteristics to the overall risk of high-grade IAH in patients following trauma laparotomy.

In conclusion, patients in need of a damage control laparotomy who develop acidosis, coagulopathy, and hypothermia, are at risk of IAH and ACS. At the time of trauma laparotomy in patients with these ACS risk factors, temporary abdominal closure with primary closure as early as possible, seems a good strategy.

Table 1: Patient demographics for the overall population as well as separated for the groups with an IAP ≤20 mmHg and >20 mmHg

Variable	Overall (N=567)	IAP ≤ 20 (N=509)	IAP > 20 (N=58)	P-value	OR (95% CI)	H-L Test (Chi-square)	AUC	Youden Index (95% CI; threshold)
Age (year)	31 (23-44)	30 (22-42)	50 (34-65)	<0.001	**1.05 (1.04-1.07)**	7.83 (0.450)	0.75	0.39 (0.26 - 0.47; > 35)
Males	452 (79.7%)	404 (79.4%)	48 (82.8%)	0.680[B]	1.25 (0.61-2.55)[D]	N.A.	(0.52)[G]	0.03 (0.00-0.10; N.A.)
ISS	21 (13-34)	20 (11-34)	34 (22-44)	<0.001	**1.03 (1.01-1.04)**	**24.82 (0.002)**	0.70	0.35 (0.25-0.46; >25)
Circulatory shock[A]	220 (38.8%)	179 (35.2%)	41 (70.7%)	<0.001[C]	**4.51 (2.46-8.27)[E]**	N.A.	(0.68)	0.36 (0.23-0.47; N.A.)
Blunt Injury	374 (66.0%)	327 (64.2%)	47 (81.0%)	0.012[B]	**2.38 (1.20-4.70)[F]**	N.A.	(0.58)	0.17 (0.04-0.26; N.A.)
Penetrating Injury	193 (34.0%)	182 (35.8%)	11 (19.0%)					

ACS, Abdominal Compartment Syndrome; AUC, Area under the receiver operating characteristic (ROC) curve. H-L, Hosmer-Lemeshow goodness of fit test; IAP, Intra-Abdominal Pressure (mmHg); ISS, Injury Severity Score; N.A., Not Applicable; OR, Odds Ratio.

Descriptive data are shown as median with the P_{25} - P_{75} between brackets or as number with the percentage between brackets.

[A]Data were missing for 16 patients (15 in the ≤20mmHg group and 1 in the >20mmHg group).

P-values are calculated using Mann-Whitney U-test, [B]Fisher's exact test, or [C]Chi-squared test. Odds Ratios are determined using a binary logistic regression and are expressed for the comparison of [D]males versus females as reference category; [E]Unstable versus stable; [F]Blunt versus penetrating trauma. Odds Ratios are given with the 95% confidence interval (CI) between brackets. The H-L statistic is given with the p-value between brackets. Statistically significant OR's and H-L values are shown in boldface. [G]The AUC values for these binary variables are based on only a single value of sensitivity and specificity. The Youden Index is shown with the 95% CI and (for continuous variables) the threshold value between brackets. For categorical variables, the threshold value is not applicable (N.A).

Table 2: Physiologic variables separated for the groups with an IAP ≤20 mmHg and >20 mmHg

	Overall (N=567)	IAP ≤ 20 (N=509)	IAP > 20 (N=58)	P-value	OR (95% CI)	H-L Test (Chi-square)	AUC	Youden Index (95% CI; threshold)
At admission								
Temperature (°C)[A]	36.2 (35.4 - 36.8)	36.2 (35.5 - 36.8)	35.8 (34.9 - 36.7)	0.011	**0.74 (0.57-.96)**	6.44 (0.598)	0.62	0.19 (0.09-0.27; ≤35.9)
Lactate (mmol/L)[B]	2.6 (1.7 - 5.4)	2.1 (1.7 - 4.1)	7.4 (3.0 - 12.3)	0.013	**1.33 (1.08-1.64)**	10.86 (0.210)	0.75	0.53 (0.25-0.75; >4.8)
Base deficit (mmol/L)[C]	5.0 (2.0 - 10.0)	5.0 (1.8 - 8.0)	10.0 (6.0 - 18.0)	<0.001	**1.11 (1.06-1.16)**	11.30 (0.185)	0.73	0.40 (0.23-0.49); ≥6.0)
pH[D]	7.29 (7.19 - 7.34)	7.30 (7.22 - 7.35)	7.17 (7.03 - 7.27)	<0.001	0.02 (0.003.-0.12)	12.68 (0.080)	0.73	0.43 (0.28-0.56; ≤7.19)
Hb (mmol/L)[E]	7.5 (6.1 - 8.6)	7.6 (6.2 - 8.8)	7.1 (5.3 - 8.0)	0.050	0.87 (0.73-1.04)	4.53 (0.807)	0.60	0.19 (0.08-0.27; ≤7.6)
At 6 hours after surgery								
Temperature (°C)[A]	37.1 (36.6 - 37.5)	37.1 (36.6 - 37.5)	37.0 (36.4 - 37.4)	0.176	1.04 (0.97-1.12)	10.18 (0.252)	0.56	0.12 (0.06-0.17; ≤35.8)
Lactate (mmol/L)[B]	3.7 (2.1 - 5.6)	2.9 (1.9 - 4.5)	6.2 (3.4 - 8.3)	0.005	**1.54 (1.16-2.04)**	14.30 (0.074)	0.74	0.44 (0.24-0.58; >6.1)
Base Deficit (mmol/L)[C]	5.0 (3.0 - 9.0)	5.0 (2.2 - 8.9)	8.0 (5.0 - 12.7)	<0.001	**1.08 (1.03-1.13)**	10.02 (0.264)	0.66	0.26 (0.08-0.33; ≥4.1)
pH[D]	7.30 (7.21 - 7.35)	7.30 (7.23 – 7.36)	7.23 (7.12 - 7.31)	<0.001	**0.05 (0.01-0.34)**	13.68 (0.091)	0.66	0.28 (0.14-0.41; ≤7.23)
PT (seconds)[F]	13.9 (12.7 - 16.1)	13.7 (12.6 - 15.7)	15.6 (13.9 - 20.1)	<0.001	N.D.	**N.D.**	N.D.	0.34 (0.20-0.44; >14.7)
PTT (seconds)[G]	33 (29 - 43)	32 (28 - 40)	41 (34 - 95)	<0.001	**1.01 (1.01-1.02)**	**25.30 (0.001)**	0.68	0.35 (0.21-0.44; >33)
Hb (mmol/L)[E]	6.7 (5.7 - 7.8)	6.8 (5.9 - 7.9)	6.2 (5.3 - 6.9)	0.004	**0.79 (0.65-0.95)**	4.11 (0.847)	0.63	0.23 (0.09-0.33; ≤6.4)

AUC, Area under the receiver operating characteristic (ROC) curve. Hb, Hemoglobin; H-L, Hosmer-Lemeshow goodness of fit test; IAP, Intra-Abdominal Pressure (mmHg); OR, Odds Ratio; PT, Prothrombin Time; PTT, Partial Thromboplastin Time. Descriptive data are shown as median with the P_{25} - P_{75} between brackets or as number with the percentage between brackets.

P-values are calculated using a Mann-Whitney U-test.

[A]Data were missing for 120 patients at the ED recording (106 in the ≤20mmHg group and 14 in the >20mmHg group) and for 78 patients at the 6 hours recording (76 versus 2); [B]Data were missing for 509 patients at the ED recording (461 versus 48) and for 507 patients at the 6 hours recording (464 versus 43); [C]Data were missing for 267 patients at the ED recording (252 versus 15) and for 204 patients at the 6 hours recording (203 versus 1); [D]Data were missing for 262 patients at the ED recording (247 versus 15) and for 201 patients at the 6 hours recording (199 versus 2); [E]Data were missing for 285 patients at the ED recording (266 versus 19) and for 265 patients at the 6 hours recording (257 versus 8); [F]Data were missing for 214 patients at the 6 hours recording (213 versus 1); [G]Data were missing for 212 patients at the 6 hours recording (211 versus 1).

Odds Ratios are determined using a binary logistic regression and are given with the 95% confidence interval (CI) between brackets. The H-L statistic is given with the p-value between brackets. Statistically significant OR's and H-L values are shown in boldface. The Youden Index is shown with the 95% CI and the threshold value between brackets.

N.D., not determined, as SPSS was unable to compute these values.

Table 3: Resuscitation fluid given at the emergency department or in the first 24 hours of admission, separated for the groups with an IAP ≤20 mmHg and >20 mmHg

Variable	Overall (N=567)	IAP ≤ 20 (N=509)	IAP > 20 (N=58)	P-value	OR (95% CI)	H-L Test (Chi-square)	AUC	Youden Index (95% CI; threshold)
Volume given at ED (L)	1.5 (0.4 - 2.5)	1.5 (0.2 - 2.5)	2.4 (1.0 - 3.5)	0.001	1.04 (0.97-1.11)	11.92 (0.064)	0.63	0.24 (0.10-0.33; >1.5)
Volume given <24h (L)[A]	6.0 (4.3 - 8.5)	6.0 (4.0 - 8.2)	9.5 (6.3 – 13.3)	<0.001	**1.17 (1.11-1.24)**	11.79 (0.161)	0.72	0.41 (0.22-0.58; >8.3)
Volume Crystalloids given <24h (L)[B]	4.5 (3.0 - 6.0)	4.2 (3.0 - 6.0)	6.0 (4.3 - 7.6)	<0.001	**1.20 (1.11-1.30)**	11.93 (0.154)	0.67	0.33 (0.17-0.42; >5.2)
Volume Colloids given <24h (L)[C]	1.5 (0.5 - 3.0)	1.5 (0.0 - 2.9)	2.5 (1.5 - 5.0)	<0.001	**1.21 (1.11-1.32)**	**19.23 (0.007)**	0.69	0.33 (0.22-0.39; >1.2)
Packed Red Cells given <24h (Units)[B]	2 (0 - 10)	2 (0 - 8)	17 (8 - 33)	<0.001	**1.08 (1.06-1.10)**	**22.90 (<0.001)**	0.84	0.57 (0.47-0.66; >6)

AUC, Area under the receiver operating characteristic (ROC) curve. H-L, Hosmer-Lemeshow goodness of fit test; IAP, Intra-Abdominal Pressure (mmHg); ED, Emergency Department; OR, Odds Ratio.

Descriptive data are shown as median with the P_{25} - P_{75} between brackets or as number with the percentage between brackets.

P-values are calculated using a Mann-Whitney U-test.

[A]Data were missing for 4 patients (3 in the ≤20mmHg group and 1 in the >20mmHg group); [B]Data were missing for 2 patients (1 in each group); [C]Data were missing for 3 patients (3 in the ≤20mmHg group and 0 in the >20mmHg group).

Odds Ratios are determined using a binary logistic regression and are given with the 95% confidence interval (CI) between brackets. The H-L statistic is given with the p-value between brackets. Statistically significant OR's and H-L values are shown in boldface. The Youden Index is shown with the 95% CI and the threshold value between brackets.

Table 4: Mortality, length of stay at ICU and hospital separated for the groups with an IAP ≤20 mmHg and >20 mmHg

Variable	Overall (N=567)	IAP ≤ 20 (N=509)	IAP > 20 (N=58)	P-value
Mortality	77 (13.6%)	62 (12.2%)	15 (25.9%)	0.012[A]
LOS ICU (days)	2 (0 - 6)	1 (0 - 4)	15 (8 - 27)	<0.001
LOS Hospital (days)	10 (6 - 20)	9 (6 - 17)	44 (15 - 65)	<0.001

IAP, Intra-Abdominal Pressure (mmHg); LOS, Length of Stay.

Data are shown as median with the P_{25} - P_{75} between brackets or as number with the percentage between brackets.

P-values are calculated using Mann-Whitney U-test and [A]Fisher's exact test.

REFERENCES

1. CDC WISQARS: web-based injury statistics query and reporting system. Available at www.cdc.gov/injury/wisqars/LeadingCauses.html Accessed March 5, 2013.
2. Nishijima DK, Simel DL, Wisner DH, Holmes JF. Does this adult patient have a blunt intra-abdominal injury? *JAMA*. 2012;307(14):1517-27.
3. Ertel W, Oberholzer A, Platz A, Stocker R, Trentz O. Incidence and clinical pattern of the abdominal compartment syndrome after "damage-control" laparotomy in 311 patients with severe abdominal and/or pelvic trauma. *Crit Care Med*. 2000;28(6):1747-1753.
4. Offner PJ, de Souza AL, Moore EE, Biffl WL, Franciose RJ, Johnson JL, Burch JM. Avoidance of abdominal compartment syndrome in damage-control laparotomy after trauma. *Arch Surg*. 2001;136(6):676-681.
5. Moore AF, Hargest R, Martin M, Delicata RJ. Intra-abdominal hypertension and the abdominal compartment syndrome. *Br J Surg*. 2004;91(9):1102-1110.
6. Malbrain ML, Cheatham ML, Kirkpatrick A, Sugrue M, Parr M, De Waele J, Balogh Z, Leppaniemi A, Olvera C, Ivatury R, et al. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. I. Definitions. *Intensive Care Med*. 2006;32(11):1722-1732.
7. De Laet IE, Ravyts M, Vidts W, Valk J, De Waele JJ, Malbrain ML. Current insights in intra-abdominal hypertension and abdominal compartment syndrome: open the abdomen and keep it open! *Langenbecks Arch Surg*. 2008;393(6):833-847.
8. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, Duchesne J, Bjorck M, Leppaniemi A, Ejike JC, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med*. 2013;39(7):1190-1206.
9. Scott BG, Welsh FJ, Pham HQ, Carrick MM, Liscum KR, Granchi TS, Wall MJ, Jr., Mattox KL, Hirshberg A. Early aggressive closure of the open abdomen. *J Trauma*. 2006;60(1):17-22.

10. Cheatham ML, Safcsak K, Llerena LE, Morrow CE, Jr., Block EF. Long-term physical, mental, and functional consequences of abdominal decompression. *J Trauma*. 2004;56(2):237-241; discussion 241-232.
11. Hatch QM, Osterhout LM, Podbielski J, Kozar RA, Wade CE, Holcomb JB, Cotton BA. Impact of closure at the first take back: complication burden and potential overutilization of damage control laparotomy. *J Trauma*. 2011;71(6):1503-1511.
12. Montalvo JA, Acosta JA, Rodriguez P, Alejandro K, Sarraga A. Surgical complications and causes of death in trauma patients that require temporary abdominal closure. *Am Surg*. 2005;71(3):219-224.
13. Shapiro MB, Jenkins DH, Schwab CW, Rotondo MF. Damage control: collective review. *J Trauma*. 2000;49(5):969-978.
14. Liverpool Hospital, Sydney. Available at www.trauma.org Accessed March 5, 2013.
15. South Western Area Health Service. Available at http://www.sswahs.nsw.gov.au/ Accessed March 5, 2013.
16. Niles SE, McLaughlin DF, Perkins JG, Wade CE, Li Y, Spinella PC, Holcomb JB. Increased mortality associated with the early coagulopathy of trauma in combat casualties. *J Trauma*. 2008;64(6):1459-1463; discussion 1463-1455.
17. Madigan MC, Kemp CD, Johnson JC, Cotton BA. Secondary abdominal compartment syndrome after severe extremity injury: are early, aggressive fluid resuscitation strategies to blame? *J Trauma*. 2008;64(2):280-285.
18. Balogh Z, McKinley BA, Holcomb JB, Miller CC, Cocanour CS, Kozar RA, Valdivia A, Ware DN, Moore FA. Both primary and secondary abdominal compartment syndrome can be predicted early and are harbingers of multiple organ failure. *J Trauma*. 2003;54(5):848-859; discussion 859-861.
19. Malbrain ML, Chiumello D, Pelosi P, Bihari D, Innes R, Ranieri VM, Del Turco M, Wilmer A, Brienza N, Malcangi V, et al. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. *Crit Care Med*. 2005;33(2):315-322.
20. Neal MD, Hoffman MK, Cuschieri J, Minei JP, Maier RV, Harbrecht BG, Billiar TR, Peitzman AB, Moore EE, Cohen MJ, et al. Crystalloid to packed red blood cell transfusion ratio in the massively transfused patient: when a little goes a long way. *J Trauma Acute Care Surg*. 2012;72(4):892-898.

21. Annane D, Siami S, Jaber S, Martin C, Elatrous S, Declere AD, Preiser JC, Outin H, Troche G, Charpentier C, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. *JAMA*. 2013;310(17):1809-1817.
22. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367(20):1901-1911.
23. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, Madsen KR, Moller MH, Elkjaer JM, Poulsen LM, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367(2):124-134.
24. Miller RS, Morris JA, Jr., Diaz JJ, Jr., Herring MB, May AK. Complications after 344 damage-control open celiotomies. *J Trauma*. 2005;59(6):1365-1371; discussion 1371-1364.
25. Dubose JJ, Scalea TM, Holcomb JB, Shrestha B, Okoye O, Inaba K, Bee TK, Fabian TC, Whelan J, Ivatury RR, et al. Open abdominal management after damage-control laparotomy for trauma: a prospective observational American Association for the Surgery of Trauma multicenter study. *J Trauma Acute Care Surg*. 2013;74(1):113-120; discussion 1120-1122.
26. Balentine C, Subramanian A, Palacio CH, Sansgiry S, Berger DH, Awad SS. AVAS Best Clinical Resident Award (Tied): management and outcomes of the open abdomen in nontrauma patients. *Am J Surg*. 2009;198(5):588-592.
27. Demetriades D. Total management of the open abdomen. *Int Wound J*. 2012;9 Suppl 1:17-24.

Chapter 4

Prevalence and outcome of abdominal compartment syndrome in trauma patients; a systematic review

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ABSTRACT

Background: Abdominal Compartment Syndrome (ACS) in severely injured patients is associated with high morbidity and mortality. Many efforts have been made to improve outcome of patients with ACS. A treatment algorithm for ACS patients was introduced on January 1, 2005 by the World Society of the Abdominal Compartment Syndrome (WSACS). The aim of this study was to estimate prevalence and mortality of ACS among severely injured patients, and to compare these before and after January 1, 2005 using a systematic literature review and meta-analysis.

Method: Databases of Embase, Medline (OvidSP), Web-of-science, CINAHL, CENTRAL, PubMed publisher and Google Scholar were searched for terms related to severely injured patients and ACS. Original studies reporting ACS in trauma patients were considered eligible. Data on study design, population, definitions, and outcomes were extracted. Estimates of overall prevalence and mortality of ACS among severely injured patients were calculated using inversed variance weighting assuming a random effects model. Tests for heterogeneity were applied.

Results: A total of 81 publications were included. The overall prevalence of ACS among severely injured patients was 4.5% (95% Confidence Interval, CI, 3.5-5.7%; N= 33,455). Prevalence among severely injured patients admitted to the ICU was 1.1% (95% CI: 0.6-1.7%; N= 6,985), 2.8% (95% CI: 1.6-4.4%; N= 3,803) among patients with visceral injuries, and 5.0% (95% CI: 2.8-7.7%; N= 4,200) among patients who underwent trauma laparotomy. The overall mortality rate among severely injured patients with ACS was 48.3% (95% CI, 41.5-55.2%; N= 967). Whereas prevalence has decreased by 1.5% (p=0.016) since January 1, 2005, an effect on mortality could not be shown.

Conclusion: The pooled prevalence of ACS among severely injured patients is 4.5%. The pooled mortality rate of these patients is 48.3%. Modern trauma resuscitation and introduction of evidence-based treatment algorithms resulted in decreased prevalence of ACS among severely injured patients.

INTRODUCTION

Abdominal compartment syndrome (ACS) is a serious complication in severely injured patients. ACS was initially recognized as a typical complication among trauma populations, although it is also described in many other critically ill patient groups. It is a result of major tissue injury, traumatic shock and massive fluid resuscitation, with or without abdominal injury or abdominal surgery. The diagnosis of ACS is confirmed if the intra-abdominal pressure (IAP) exceeds 20 mmHg (*i.e.*, high grade intra-abdominal hypertension; IAH) in combination with splanchnic hypoperfusion and subsequent organ dysfunction. ACS is associated with a high risk of mortality; the full blown syndrome without decompression is uniformly lethal (1-4).

Efforts during the past decades to improve the outcome of severely injured patients include the introduction of damage control surgery, damage control resuscitation, and the development of vacuum assisted temporary abdominal closure devices (TAC). Although aimed at improving outcome after trauma, these developments may also have changed the risk and outcome of post injury ACS (5). The World Society of the Abdominal Compartment Syndrome (WSACS) critically reviewed literature regarding these developments and subsequently introduced the Consensus Statements and Recommendations using the GRADE methodology. These statements serve as guidelines for the treatment of patients at risk for IAH/ACS and were first implemented on January 1, 2005 (but published in 2006) (6). An updated version of these guidelines provides physicians with easy-to-use treatment algorithms (7).

The application of these algorithms has resulted in a decrease of ACS mortality in a mixed population of trauma and non-trauma patients (8). It is however unclear to what extent these developments have affected the ACS prevalence and ACS mortality among severely injured patients. The aim of this study was to determine the prevalence and mortality rate of ACS among severely injured patients, and to assess to what extent developments described above have affected this.

METHODS

This systematic literature review was conducted and reported according to the standards set out in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (9). The protocol was predefined, but is not available online.

Ethics statement

The current study used secondary data, extracted from readily available literature; therefore, obtaining research ethics approval was not necessary.

Search Strategy

Databases of Embase, Medline (OvidSP), Web-of-science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL), PubMed publisher and Google Scholar were searched from database inception until February 15, 2015. Searched items consisted of terms related to injury and terms related to abdominal compartment syndrome (Table 1**)**. Reference lists of review articles and eligible studies were reviewed for additional studies that may have been missed.

Manuscript selection and eligibility criteria

Titles and abstracts were screened independently by two reviewers (SGS and RAV) for presence of trauma populations. Inconsistencies were resolved by discussion and consensus. Studies were included if they met the following inclusion criteria: 1) design: original reports with primary data; 2) population: presence of injured patients, and 3) outcome: description of ACS prevalence or ACS mortality numbers or data from which prevalence or mortality rates among injured patients could be calculated. No language criterion was used. Studies were excluded if no full text version was available after contacting corresponding authors. Also, studies restricted to thermally injured patients were excluded, as a systematic review on prevalence and outcome of IAH and ACS among severely burned patients is already available (10). No specific definitions for injured patients or ACS were used as eligibility criterion.

Scientific Level of Evidence

Study classification according to Mahid *et al.* and the prospective- and retrospective nature of the studies were collected in order to assess the type and level of evidence of publications; randomized controlled trials (RCTs), cohort studies, and case series were found to be eligible (11). The patient groups of RCTs were taken together, the pooled study population was considered one cohort over which prevalence or mortality rate was calculated.

Risk of bias assessment

Two reviewers (SGS and EMMVL) independently assessed the methodological quality of the studies using the MINORs (Methodological Index for Non-Randomized Studies) scale (12). The MINORs scale yields a maximum score of 16 for non-comparative cohort studies and a maximum of 24 for comparative cohort studies.

Data collection process and data items

Data extraction was done independently in duplicate by three reviewers (SGS, OJFVW and AVVB) using a standardized data sheet. Discordance was resolved by the reviewers rechecking their extracted data until data sheets corresponded. The following data were extracted for each publication: name of first author, publication year, years the inclusion period started and ended, population size (N), type of population, age of population, mean or median injury severity score (ISS), definition used for ACS, number of ACS patients (or ACS rate), and mortality rate of ACS patients. Publications using the same patient database in overlapping periods were identified. Only data from 1) the largest or 2) most recent cohorts were used.

Data synthesis and statistical analysis

ACS prevalence and mortality rates were computed for each study; they were transformed using a double arcsine transformation in order to ensure normal distribution (13). Next, the transformed rates and 95% confidence intervals were transformed back to prevalence and mortality rate estimates. Forest plots were constructed with 95% confidence interval for all studies to show the variation in ACS prevalence and mortality in severely injured patients across the included studies.

The Cochrane Chi-squared (χ^2) Q-test was applied in order to test for heterogeneity (significance set at $p < 0.10$), and the I^2 statistic was calculated in order to quantify the degree of between-study heterogeneity. This defines the variability percentage in effect estimates that is due to heterogeneity rather than to chance (14, 15). An I^2 statistic greater than 40% was considered to represent significant heterogeneity.

Data were pooled using a random-effects model for binomial data (DerSimonian–Laird) (16). A random-effects model was planned a priori, due to the degree of anticipated heterogeneity among the eligible studies. If significant heterogeneity was present, subgroup analyses were planned. Patients were categorized based on the source population, being 'severely injured patients admitted to the ICU', 'patients with visceral injuries' and 'patients who had undergone emergent trauma laparotomy'. These groups are not unique, as overlap to a certain degree is likely. For example, patients in the trauma laparotomy group may very well be admitted to the ICU, and vice versa.

For the secondary analysis the populations were divided into two groups, using January 1, 2005 (the date of first introduction of the WSACS guideline) as cut-off date (8). The first groups consisted of studies that stopped enrolling before January 1, 2005, and the second group started enrolling after this date. Studies without specified enrolment period as well as studies with enrolment periods that included this date were excluded from this sub-analysis. Differences in ACS prevalence and mortality rates between the two time periods were tested using an unpaired Student's *t* test. A p-value below 0.05 was considered statistically significant.

Analyses was performed using MetaXL software (Version 2.2; Epigear International Pty Ltd, Australia; 2011-2015). Student's *t* test was calculated using the GraphPad QuickCalcs web site (http://graphpad.com/quickcalcs/ttest1/?Format=SEM).

RESULTS

Trial identification

The search yielded 5,899 publications. After eliminating duplicates, 3,755 publications remained. These were reviewed for inclusion and exclusion criteria, and reference lists of reviews and eligible studies were examined for additional publications. A total of 80 publications was included in this analysis, including three randomized controlled trials, 12 prospective cohort studies, 40 retrospective cohort studies, and 25 case series (Figure 1) (1, 2, 8, 17-94).

The within-study quality according to the MINORS score ranged from 1 to 13 points out of a maximum of 16 points. The mean score was 7 points. Extracted data of included publications are listed in (Table 2)

The search identified no systematic reviews or meta-analysis regarding prevalence and mortality rate of ACS among injured patients. Only one previously published literature review listed prevalence and outcome of ACS among trauma patients in 2009. This study, however, did not describe a systematic search method (95). One publication reported sufficient data to calculate annual prevalence between 2002 and 2007 (8). The annual prevalences of this publication were pooled in a group before January 1, 2005 and a group after that date.

Prevalence of ACS in severely injured patients

The prevalence of ACS for 33,455 severely injured patients in 60 publications ranged from 0.0% to 36.4% (Figure 2). Prevalence of studies that finished enrolling patients before January 1, 2005 ranged from 0.5% to 36.4% (pooled value of 5.2%; 95% CI 3.7-7.0%; I2 95%; 17,689 patients; 33 publications). Prevalence reported after that date ranged from 0.0% to 28.0% (pooled value of 3.7%; 95% CI 1.7-6.4%; I2 90%; 4,752 patients; 12 publications; Table 3).

Given the large heterogeneity, subgroup analyses were performed (Figure 3). For severely injured patients admitted to the ICU, the prevalence ranged from 0.0% to 5.3% (6,985 patients; 8 publications). The reported prevalence before January 1, 2005 ranged from 0.5% to 1.3% (pooled value of 1.0%, 95% CI 0.7-1.3%; I2 27%; 6,678 patients; 6 publications). Only one study (81 patients) was found for the second period and contained no cases of ACS.

For patients with visceral injuries, ACS prevalence ranged from 0.2% to 20.0% (3,803; 18 publications). Prevalence ranged from 1.0% to 20.0% (pooled value 4.3%; 95% CI 1.6-8.1%; I2 78%; 892 patients; 8 publications) before January 1, 2005. The only study after January 1, 2005 reported an ACS prevalence of 11.1% (9 patients).
For patients who underwent trauma laparotomy, the ACS prevalence ranged from 0.9% to 36.4% (4,200 patients; 11 publications). The prevalence before January 1, 2005 ranged from 0.9% to 36.4% (pooled value 5.4; 95% CI 2.3-9.7%; I2 93%; 2,058 patients; 8 publications). Two studies after January 1, 2005 reported ACS prevalence of 2.3% and 13.2%, respectively.

Mortality of severely injured patients with ACS

The mortality for 967 severely injured patients with ACS in 42 publications ranged from 0.0% to 100.0% (Table 4). The mortality reported before January 1, 2005 ranged from 0.0% to 100.0% (pooled value 47.1%; 95% CI 39.3-54.9%; I2 64%; 484 patients; 28 publications). After that date, mortality ranged from 0.0% to 100.0% (pooled value 53.1%; 95% CI 0.0-100.0%; I2 85%; 39 patients; 4 publications).

DISCUSSION

The overall prevalence of ACS among trauma patients ranged from 0.0% to 36.4% with a pooled prevalence of 5.2% and 3.7% before and after January, 2005, respectively. The mortality ranged from 0.0% to 100.0% with a pooled value of 47.1% before and 53.1% after January 1, 2005. These values should be interpreted with care given the large statistical and clinical heterogeneity. Therefore, no causal relation with improved trauma care and the introduction of the Consensus Statements and Recommendations by the WSACS can be concluded.

The ACS prevalence was lowest in a general trauma ICU population and highest in patients who underwent a trauma laparotomy. This was not surprising. Damage control surgery keeps the most severely shocked patients alive with a packed abdomen with or without cross-clamping, increasing the risk of massive intestinal edema and reperfusion injury. (5). The current systematic review has certain limitations resulting from the inherent biases of the included studies. As stated above, the findings should be interpreted with caution. The studies had different study designs (i.e., RCT, longitudinal cohort study, or case series), diverse populations, and used different definitions of ACS. It is unclear to what extent this has biased the pooled values. It may also explain the large between-study heterogeneity and outlines the need for more rigorous and uniform definitions in future studies. Assuming that the WSACS guidelines are effective, it is notable that its use is not frequently described in included publications. Even definitions of ACS are still not uniformly applied in modern literature (83).

The current systematic review has certain limitations resulting from the inherent biases of the included studies. As stated above, the findings should be interpreted with caution. The studies had different study designs (i.e., RCT, longitudinal cohort study, or case series), diverse populations, and used different definitions of ACS. It is unclear to what extent this has biased the pooled values. It may also explain the large between-study heterogeneity and outlines the need for more rigorous and uniform definitions in future studies. Assuming that the WSACS guidelines are effective, it is notable that its use is not frequently described in included publications. Even definitions of ACS are still not uniformly applied in modern literature.

In conclusion, the overall prevalence of ACS ranged from 0.0% to 36.4% and the mortality ranged from 0.0% to 100.0%. Future studies are needed to measure the effect of improved trauma care and effectiveness of the WSACS Consensus Statements.

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Table 1: Search strategy

Database	Query	Hits	Unique
Embase	('abdominal compartment syndrome'/exp OR 'intraabdominal hypertension'/exp OR 'abdominal pressure'/exp OR ('compartment syndrome'/exp AND ('abdominal injury'/exp OR 'abdominal disease'/exp OR 'abdomen'/exp)) OR 'abdominal hypertension'/exp OR 'abdominal decompression'/exp OR 'lower body negative pressure'/exp OR (((abdomin* OR intraabdomin*) NEXT/1 (compartment* OR hypertens* OR pressure* OR decompressi*)) OR 'visceral edema' OR 'visceral oedema')) AND (injury/exp OR traumatology/exp OR 'emergency ward'/exp OR 'emergency medicine'/exp OR emergency/exp OR 'emergency surgery'/exp OR 'emergency health service'/exp OR 'emergency treatment'/exp OR (injur* OR wound* OR trauma* OR penetrat* OR emergen*):ab,ti) NOT ([animals]/lim NOT [humans]/lim)	2,808	2,785
Medline (OvidSP)	('abdominal compartment syndrome'/exp OR 'intraabdominal hypertension'/exp OR 'abdominal pressure'/exp OR ('compartment syndrome'/exp AND ('abdominal injury'/exp OR 'abdominal disease'/exp OR 'abdomen'/exp)) OR 'abdominal hypertension'/exp OR 'abdominal decompression'/exp OR 'lower body negative pressure'/exp OR (((abdomin* OR intraabdomin*) NEXT/1 (compartment* OR hypertens* OR pressure* OR decompressi*)) OR 'visceral edema' OR 'visceral oedema')) AND (injury/exp OR traumatology/exp OR 'emergency ward'/exp OR 'emergency medicine'/exp OR emergency/exp OR 'emergency surgery'/exp OR 'emergency health service'/exp OR 'emergency treatment'/exp OR (injur* OR wound* OR trauma* OR penetrat* OR emergen*):ab,ti) NOT ([animals]/lim NOT [humans]/lim)	1,207	245
Web-of-science	TS=(((((abdomin* OR intraabdomin*) NEAR/1 (compartment* OR hypertens* OR pressure* OR decompressi*)) OR "visceral edema" OR "visceral oedema")) AND ((injur* OR wound* OR trauma* OR penetrat* OR emergen*)) NOT ((animal* OR porcine OR swine OR pig OR rat OR mouse OR mice OR rats OR murine OR dog OR dogs OR rabbit* OR horse* OR equin* OR cat OR cats OR cow OR cows OR bovine) NOT (human* OR patient*)))	1,330	569
CINAHL	(MH "Abdominal Compartment Syndrome+" OR (MH "Compartment Syndromes+" AND (MH "Abdominal Injuries+" OR MH abdomen+)) OR (((abdomin* OR intraabdomin*) N1 (compartment* OR hypertens* OR pressure* OR decompressi*)) OR "visceral edema" OR "visceral oedema")) AND (MH "Wounds and Injuries+" OR MH Traumatology+ OR MH "Emergency Medical Services+" OR MH "emergency medicine+" OR MH emergencies+ OR MH "Emergency Treatment (Non-Cinahl)+" OR (injur* OR wound* OR trauma* OR penetrat* OR emergen*)) NOT (MH animals+ NOT MH humans+)	297	79
CENTRAL	((((abdomin* OR intraabdomin*) NEXT/1 (compartment* OR hypertens* OR pressure* OR decompressi*)) OR 'visceral edema' OR 'visceral oedema')) AND ((injur* OR wound* OR trauma* OR penetrat* OR emergen*):ab,ti)	36	1

PubMed publisher	(Intra-Abdominal Hypertension[mh] OR (Compartment Syndromes[mh] AND (Abdominal Injuries[mh] OR abdomen[mh])) OR intraabdominal compartment*[tiab] OR intra abdominal compartment*[tiab] OR intraabdominal hypertens*[tiab] OR intra abdominal hypertens*[tiab] OR intraabdominal pressure*[tiab] OR intra abdominal pressure*[tiab] OR "visceral edema"[tiab] OR "visceral oedema"[tiab]) AND ("Wounds and Injuries"[mh] OR injuries[sh] OR Traumatology[mh] OR Emergency Medical Services[mh] OR emergency medicine[mh] OR emergencies[mh] OR Emergency Treatment[mh] OR (injur*[tiab] OR wound*[tiab] OR trauma*[tiab] OR penetrat*[tiab] OR emergen*[tiab])) NOT (animals[mh] NOT humans[mh]) AND publisher[sb]	12	9
Google scholar	"abdominal|intraabdominal compartment|hypertension|pressure|decompression"|"visceral edema|oedema" injury|injuries|wound|wounds|trauma|penetrating|emergency|emergencies	200[#]	58
Hand search	Reference lists	9	9
Total		5,899	3,755

[#]First 200 hits.

Databases searched on February 15, 2015

Figure 1: Flowchart

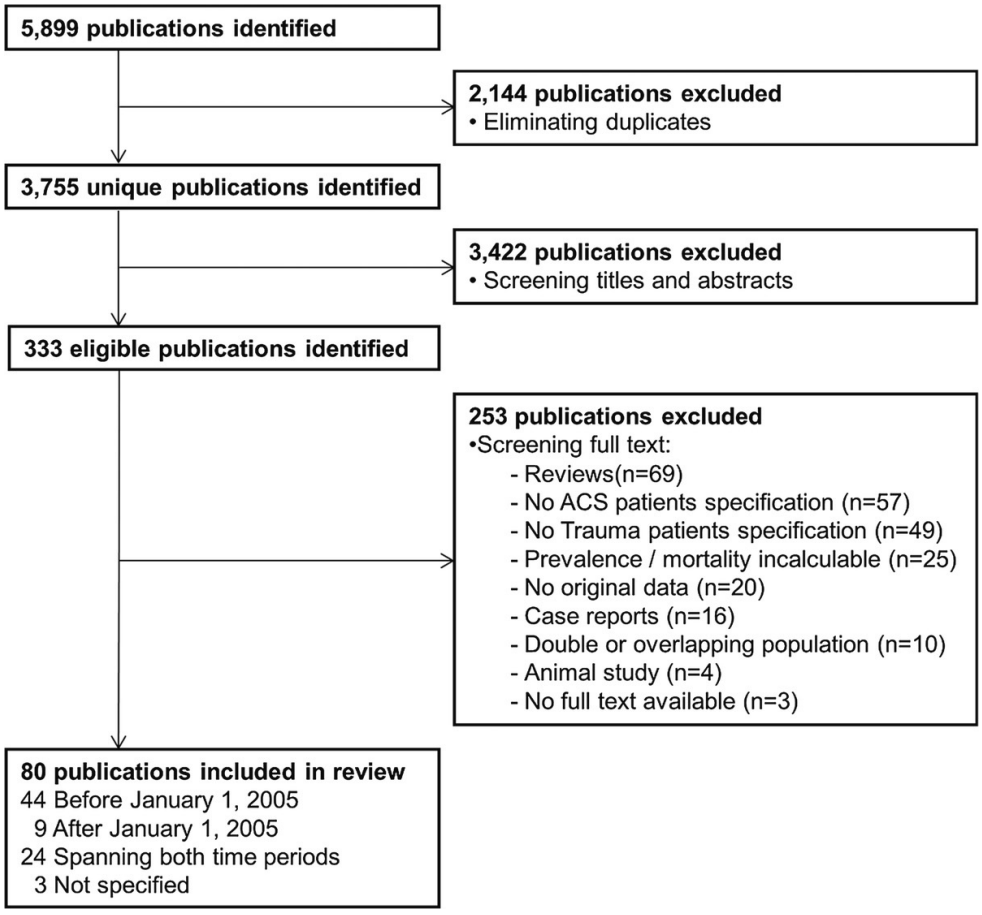


Table 2: Data overview of included studies on prevalence and mortality of abdominal compartment syndrome in trauma patients

Publication	Study period	LOE	Pro/Retro	MINOR Score	N	Population [Type]	Population [Age]*	ISS**	ACS [definition]	ACS [prevalence]	ACS [mortality]
Smith (1992) (17)	1988-1990	5	Retro	3	16	Laparostomy	32 (19-51)	29 (16-57)	Massive visceral edema	N.S.	4 (25%)
Morris (1993) (18)	1984-1992	3	Retro	2	107	DCS	32	33	Tense abdomen + OD	16 (15%)	10 (63%)
Bender (1994) (19)	1986-1991	5	Retro	6	17	ACS	35 (16-58)	34.2 (25-75)	Not able to close abdomen	N.S.	3 (18%)
Widergren (1994) (20)	1987-1993	3	Retro	1	2,5	ACS	35 (±18)	30 (±12)	Elevated IAP + OD	46 (2%)	19 (41%)
Howdieshell (1995) (21)	1988-1992	3	Retro	6	36	TL	Range 13-75	30 (13-50)	IAP + renal failure	6 (17%)	N.S.
Torrie (1996) (22)	1988-1993	5	Retro	2	15	Trauma ACS	N.S.	34 (19-50)	Not able to close abdomen	N.S.	6 (40%)
Eddy (1997) (23)	1984-1996	5	Retro	2	34	ACS	30 (±12) (16-58)	33 (±11)	Tense abdomen + OD	N.S.	23 (68%)
Mayberry (1997) (24)	1989-1996	3	Retro	7	805	TL	37 (±17); 38 (±15)	34 (±13); 30 (±14)	Elevated IAP + OD	18 (2%)	N.S.
Meldrum (1997) (25)	1994-1995	3	Pro	11	145	ISS >15	39 (±9) (17-59)	26 (±6)	IAP >20 mmHg + OF	21 (14%)	6 (28%)
Behrman (1998) (26)	1994-1996	3	Retro	4	171	TL	30	30 (±7); 21 (±10)	IAP >25 mmHg	3 (2%)	N.S.
Chang (1998) (27)	1995-1996	5	Pro	7	13	IAH	37 (±20)	27 (±13)	IAP >25 mmHg OD	N.S.	8 (62%)
Ivatury (1998) (28)	1992-1996	3	Retro	13	70	Penetrating injury	28 (±9)	22 (±9)	IAH + OD	2 (3%)	N.S.
Letoublon (1999) (30)	1985-1998	3	Retro	6	130	Blunt hepatic injury	32 (±14) (7-74)	N.S.	N.S.	2 (2%)	N.S.
Maxwell (1999) (31)	1997-1998	5	Retro	4	1,216	Trauma ICU	36 (±7) (15-63)	25 (±3)	Laparostomy. no abd. injury	6 (1%)	4 (67%)
Barker (2000) (32)	1992-1999	3	Retro	6	112	TL	39 (±17) (5-80)	28 (±14) (5-75)	Elevated IAP + OD	1 (1%)	N.S.
Cheatham (2000) (33)	1997-1999	5	Retro	6	73	ICU and IAH	51 (±19)	33 (±16)	IAP ≥25 mmHg + OD	N.S.	53 (73%)
Ertel (2000) (34)	1991-1998	3	Pro+Retro	9	311	DCL	38 (±1)	30 (±0.7)	Tense abdomen + OD	17 (6%)	6 (35%)
Kopelman (2000) (35)	N.S.	5	Retro	2	6	ACS	46 (±6)	17	N.S.	N.S.	4 (67%)
Paunescu (2000) (36)	1992-1999	3	Retro	2	1,456	Polytrauma	N.S.	N.S.	N.S.	33 (2%)	23 (68%)
Beck (2001) (1)	1994-1999	5	Pro	9	406	Pediatric ICU	0; 2; 3	N.S.	IAP >15 mmHg + OD	3 (1%)	3 (100%)
Chen (2001) (37)	1998-1999	5	Pro	7	25	Blunt hepatic injury	30 (±9) (15-54)	20 (±5) (9-41)	IAP >25cmH2O	5 (20%)	0 (0%)
Garner (2001) (38)	1999-2000	3	Retro	6	698	Trauma ICU	41 (±4.7)	24 (±1.0)	Decompression	5 (1%)	N.S.
Raeburn (2001) (39)	1996-2000	3	Pro	7	77	DCS	35 (15-77)	29 (±2)	IAP >20 mmHg + OD	28 (36%)	12 (43%)
Tremblay (2001) (40)	1997-2000	5	Retro	8	12	Laparostomy	36 (±17) (7-81)	24 (±11)	Elevated IAP + OD	N.S.	7 (58%)
Balogh (2002) (41)	1997-2001	3	Retro	11	128	Shock resuscitation	41 (±5)	28 (±3)	Laparostomy. no abd injury	11 (9%)	6 (55%)
Gracias (2002) (42)	1999-2000	5	Retro	6	5	Laparostomy	35 (±10)	33 (±19)	IAH + OF	N.S.	3 (60%)
Hong (2002) (43)	1998-1999	3	Pro	9	706	Trauma ICU	42 (14-90)	18 (1-75)	Decompression	6 (1%)	3 (50%)
Miller (2002) (44)	1996-2011	3	Retro	7	646	TL	40	32	Decompression	26 (4%)	N.S.
Arvieux (2003) (45)	1990-2001	3	Retro	7	109	DCS	34 (±16)	32 (±15)	Intestinal edema	11 (10%)	4 (36%)
Balogh (2003) (46)	1999-2002	3	Retro	9	152	Severe injury	39 (±1); 41 (±2)	27 (±1); 28 (±2)	IAP >25 mmHg + OD	23 (15%)	N.S.
Gao (2003) (47)	1988-2000	3	Retro	5	225	Hepatic injury	28 (7-73)	27 (4-75)	N.S.	4 (2%)	N.S.
Goldman (2003) (48)	1995-2000	3	Retro	7	192	Blunt hepatic injury	30 (±9)	25 (±15)	Decompression	2 (1%)	N.S.
Mayberry (2003) (49)	1993-1998	5	Retro	9	9	Severely injured patient	47 (20-57)	24 (±9)	Decompression	N.S.	2 (22%)
Mohr (2003) (50)	1995-2002	3	Retro	8	37	Hepatic injury + NOM	33 (16-85)	25	Decompression	1 (3%)	N.S.
Velmahos (2003) (51)	1999-2001	3	Pro	11	78	Hepatic injury	35 (±12); 35 (±17)	25 (±11); 19 (±10)	N.S.	2 (3%)	N.S.
Cothren (2004) (52)	1996-2003	3	Retro	6	2,762	ICU and ISS >15	36 (±4)	33 (±4)	IAP >25 mmHg + OD	36 (1%)	14 (39%)
Miller (2004) (53)	2001-2003	3	Pro	9	212	TL	36 (±15)	34 (±12)	N.S.	8 (4%)	N.S.
Pleva (2004) (54)	1999-2002	5	Retro	4	436	Polytrauma	N.S.	N.S.	IAP >25mmHg + OD	8 (2%)	2 (25%)
Stone (2004) (55)	2000-2002	3	Retro	7	890	Trauma ICU	N.S.	25 (±9) (9-45)	N.S.	10 (1%)	6 (60%)
Britt (2005) (56)	1997-2003	5	Retro	7	10	ACS	40	N.S.	IAH + OD	N.S.	6 (60%)
Miller (2005) (57)	1995-2002	3	Retro	9	344	TL	36 (±16)	35 (±14)	Elevated IAP + OD	115 (33%)	N.S.
Prince (2005) (58)	1989-1998	3	Retro	9	920	TL	32 (±16)	22 (±15)	Tense abdomen + OD	12 (1%)	N.S.
Rodas (2005) (59)	2002-2004	5	Retro	6	5	ACS	32 (±7)	21 (±4)	Decompr. improved OD	N.S.	0 (0%)
Kozar (2006) (60)	2000-2006	3	Retro	8	699	Blunt hepatic injury	33 (14-90)	27 (±11); 25 (±11)	N.S.	5 (1%)	N.S.
Reed (2006) (61)	2004-2005	5	Retro	8	226	Trauma ICU	36 (±16)	22	IAP ≥20mmHg	12 (5%)	5 (42%)
Nicol (2007) (62)	1996-2004	3	Retro	8	72	Hepatic injury + packing	30 (14-68)	N.S.	N.S.	12 (17%)	N.S.

Scalea (2007) (63)	2001-2004	3	Retro	9	102	Blunt trauma + brain inj.	30 (±12)	34 (±13)	Laparostomy. no abd. injury	24 (24%)	N.S.
Dissanaike (2008) (64)	2004-2007	3	Pro	8	1,001	Blunt injury	40 (±17); 39 (±18)	34 (±13); 36 (±14)	WSACS	43 (4%)	31 (72%)
Letoublon (2008) (65)	1994-2005	3	Retro	7	186	Blunt hepatic injury + NOM	33 (7-81)	N.S.	N.S.	4 (2%)	N.S.
Madigan (2008) (66)	2001-2005	5	Retro	8	48	ACS	41 (±17)	26 (±9)	WSACS	N.S.	29 (60%)
Parsak (2008) (67)	1998-2005	5	Pro	10	29	IAP >10mmHg	56 (±16) (20-88)	N.S.	WSACS	N.S.	10 (35%)
Wei (2008) (68)	2001-2006	3	Retro	9	87	Splenic injury	38 (±14); 47 (±19)	34 (±12); 29 (±11)	N.S.	1 (1%)	N.S.
Cotton (2009) (69)	2004-2008	2	Pro	12	266	Massive transfusion	39 (±18); 36 (±16)	28 (±16) 33 (±16)	IAP >25mmHg + OF	14 (5%)	N.S.
Koss (2009) (70)	2004-2007	3	Retro	5	23	ACS	40 (±21) (13-85)	32 (±11) (9-50)	N.S.	N.S.	5 (22%)
Nellensteijn (2009) (71)	1990-2008	3	Retro	5	80	U18 + blunt hepatic injury	12 (2-18)	[illegible] 41)	N.S.	1 (1%)	N.S.
Cheatham (2010) (8)	2002-2007	3	Retro	12	4,938	Laparostomy	40 (±17); 49 (±19)	23 (±11); 30 (±14)	WSACS	95 (2%)	47 (45%)
Duchesne (2010) (72)	2009-2009	5	Pro	7	5	ACS	36 (±17)	29 (±9)	WSACS	N.S.	0 (0%)
Khan (2010) (2)	2006-2007	3	Pro	10	38	TL	35 (±15) (18-85)	N.S.	WSACS	5 (13%)	5 (100%)
Balogh (2011) (73)	2007-2009	3	Pro	12	81	ICU and ISS >15	41 (±2)	29 (±1)	WSACS	0 (0%)	N.S.
Giladi (2011) (74)	2004-2006	3	Retro	8	4,294	Trauma ICU	39 (±18); 40 (±17)	21 (±12.6); 20 (±12.3)	IAP >25mmHg + OF	74 (2%)	N.S.
James (2011) (75)	2007-2011	2	Pro	10	109	Massive transfusion	27.6; 35.6; 33.0; 35.7	18; 16; 29.5; 18	N.S.	3 (3%)	N.S.
Parks (2011) (76)	2002-2009	3	Retro	10	591	Blunt hepatic injury	N.S.	Stratified	N.S.	1 (<1%)	N.S.
Saltzherr (2011) (77)	1995-2008	3	Retro	8	177	Hepatic injury	29 (19-38)	22 (10-34)	N.S.	1 (<1%)	N.S.
Shekhei (2011) (78)	N.S.	5	Pro	7	28	ACS	N.S.	N.S.	N.S.	N.S.	23 (82%)
Al-sharif (2012) (79)	2006-2011	3	Retro	4	139	[illegible] hemorrhage	14 (10-16)	24 (16-30)	N.S.	0 (0%)	N.S.
Ding (2012) (80)	N.S.	5	Retro	4	39	Laparostomy	N.S.	N.S.	Decompression	N.S.	8 (21%)
Harrell (2012) (81)	2004-2009	5	Retro	8	87	ACS	N.S.	N.S.	WSACS	N.S.	58 (67%)
Maung (2012) (82)	2007-2010	3	Retro	10	309	Trauma ventilation	46 (±18); 45 (±20)	21 (±11); 18 (±11)	WSACS	7 (2%)	N.S.
Neal (2012) (83)	2003-2008	3	Pro	10	452	Massive transfusion	41 (±17)	34 (25-43)	IAP >25cmH2O + OF	68 (15%)	N.S.
Ordonez (2012) (84)	2003-2010	3	Pro	12	311	Gunshot wounds	30 (±10); 30 (±10)	25 (18-34); 16 (9-25)	N.S.	35 (11%)	N.S.
Pando (2012) (85)	2005-2010	3	Retro	6	9	Hepatic injury + NOM	N.S.	26 (±8)	N.S.	1 (11%)	0 (0%)
Ali (2013) (86)	2010-2011	3	Pro	6	100	Abd. injury + pelvic fracture	27 (5-50)	N.S.	WSACS	28 (28%)	23 (82%)
Divarci (2013) (87)	2009-2010	3	Retro	7	14	U18 Abdominal trauma	N.S.	N.S.	IAP >15 mmHg + OD	2 (14%)	N.S.
Fiard (2013) (88)	2004-2012	3	Retro	3	27	Renal injury treated + NOM	27(13-63)	N.S.	N.S.	1 (4%)	N.S.
Guidry (2013) (89)	2007-2012	3	Retro	4	258	Vascular injury	Stratified	Stratified	N.S.	8 (3%)	N.S.
Kasotakis (2013) (90)	2003-2011	3	Retro	10	1,754	Blunt injury	44 (± 18)	32 (± 13) (1-75)	N.S.	103 (6%)	N.S.
Mahmood (2013) (91)	2009-2011	3	Pro	12	117	Hemorrhagic shock	35 (± 14)	23 (± 10)	WSACS	1 (1%)	N.S.
Rencuzogullari (92)	N.S.	2	Pro	12	40	ACS	N.S.	N.S.	N.S.	N.S.	12 (30%)
Asfar (2014) (93)	2003-2012	3	Pro	9	117	Blunt hepatic injury	29 (±12) (7-63)	N.S.	N.S.	4 (3 %)	N.S.
Joseph (2014) (94)	2006-2011	3	Retro	8	799	TL	34 (±17)	20	WSACS	18 (2%)	N.S.

ACS, Abdominal Compartment Syndrome; ICU, Intensive Care Unit; IAH, Intra-Abdominal Hypertension; IAP, Intra-Abdominal Pressure; ISS, Injury Severity Score; LOE, level of evidence (1 = systematic review with or without meta-analysis, 2 = randomized controlled trial, 3 = Cohort study, 4 = Case-control study, 5 = case series, 6 = case report, 7 = opinion); MINOR score, Methodological Index for NOn-Randomized studies; N.S., Not Specified; OD, Organ Dysfunction; OF, Organ Failure; Pro, prospective; Retro, Retrospective; SDC, Supplemental Digital Content; Stratified, population is stratified in multiple groups with differing ISS or age; TL, Trauma Laparotomy; U18, pediatric population under 18 years of age; WSACS, (according to definitions of the) World Society of the Abdominal Compartment Syndrome. *Age (mean or median) is shown in years with corresponding standard deviation (SD) or ranges. **ISS is shown as mean or median with corresponding SD or ranges unless indicated otherwise. Prevalence and mortality rates are shown as number with corresponding percentage.

Table 3: Pooled prevalence of abdominal compartment syndrome in severely injured patients before and after January 1, 2005

			Heterogeneity				Prevalence	
	Population (N)*	Studies (N)	Cochran's Q	*p* Value	I^2 (%)	95% CI	Pooled value	95% CI
Overall								
< 2005	17,689	33	699	<0.001	95	94-96	5.2%	3.7-7.0%
≥ 2005	4,752	12	109	<0.001	90	84-94	3.7%	1.7-6.4%
ICU patients								
< 2005	6,678	6	7	<0.001	27	0-70	1.0%	0.7-1.3%
≥ 2005	81	1	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Visceral injuries								
< 2005	892	8	32	<0.001	78	58-89	4.3%	1.6-8.1%
≥ 2005	9	1	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Trauma laparotomy								
< 2005	2,558	8	101	0.074	93	89-96	5.4%	2.3-9.7%
≥ 2005	837	2	8	0.005	87	51-97	6.4%	0.0-20.0%

*Total population in which the pooled prevalence of ACS was calculated. Data were pooled using a random-effects model for binomial data.

ACS, Abdominal Compartment Syndrome; ICU, Intensive Care Unit; N.D., Not Determined, 95% CI, 95% Confidence Interval.

Table 4: Pooled mortality rate of abdominal compartment syndrome in severely injured patients before and after January 1, 2005

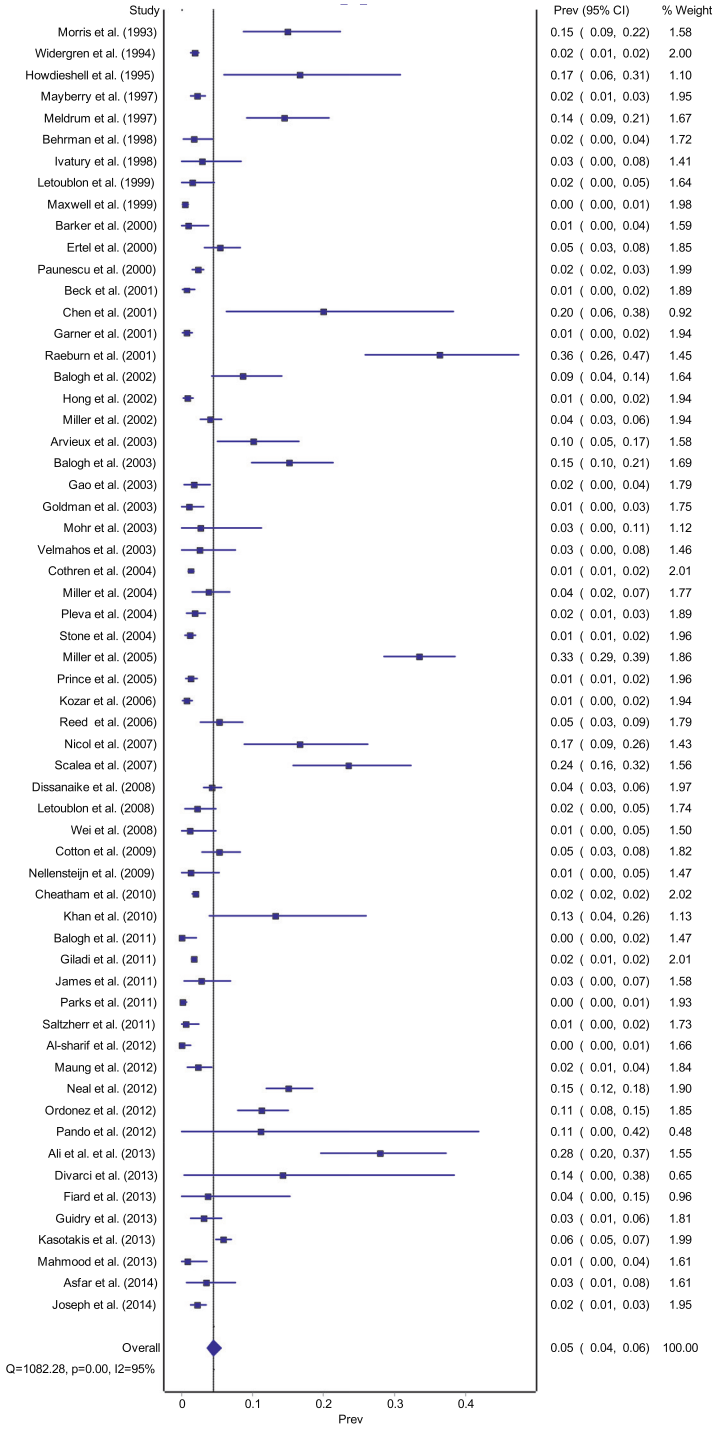
			Heterogeneity				Mortality	
	Population (N)*	Studies (N)	Cochran's Q	*p* Value	I^2 (%)	95% CI	Pooled value	95% CI
Overall								
< 2005	484	28	74	<0.001	64	45-76	47.1%	39.3-54.9%
≥ 2005	39	4	20	<0.001	85	64-94	53.1%	0.0-100.0%

*Total population in which the pooled prevalence of ACS was calculated.

Pooled mortality rate was calculated using inverse variance weighting and assuming a random effects model. Double arcsine transformation according to Freeman-Tukey was applied.

95% CI, 95% Confidence Interval

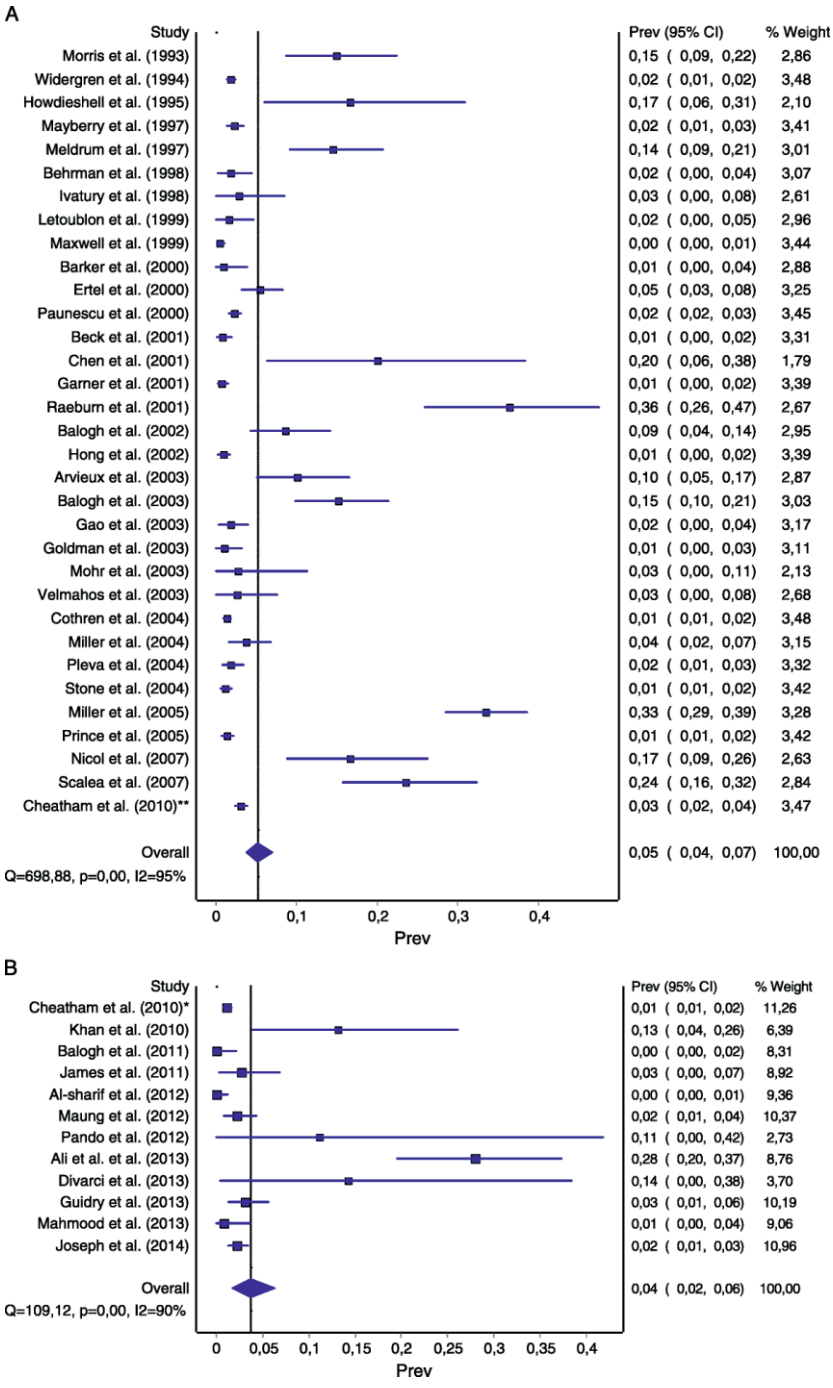
Figure 2: Forest plot of overall prevalence of ACS among severely injured patients



I2, I^2-statistic for study heterogeneity; Prev, Prevalence; Q, Cochrans Q-statistic for study heterogeneity, 95% CI, 95% Confidence Interval

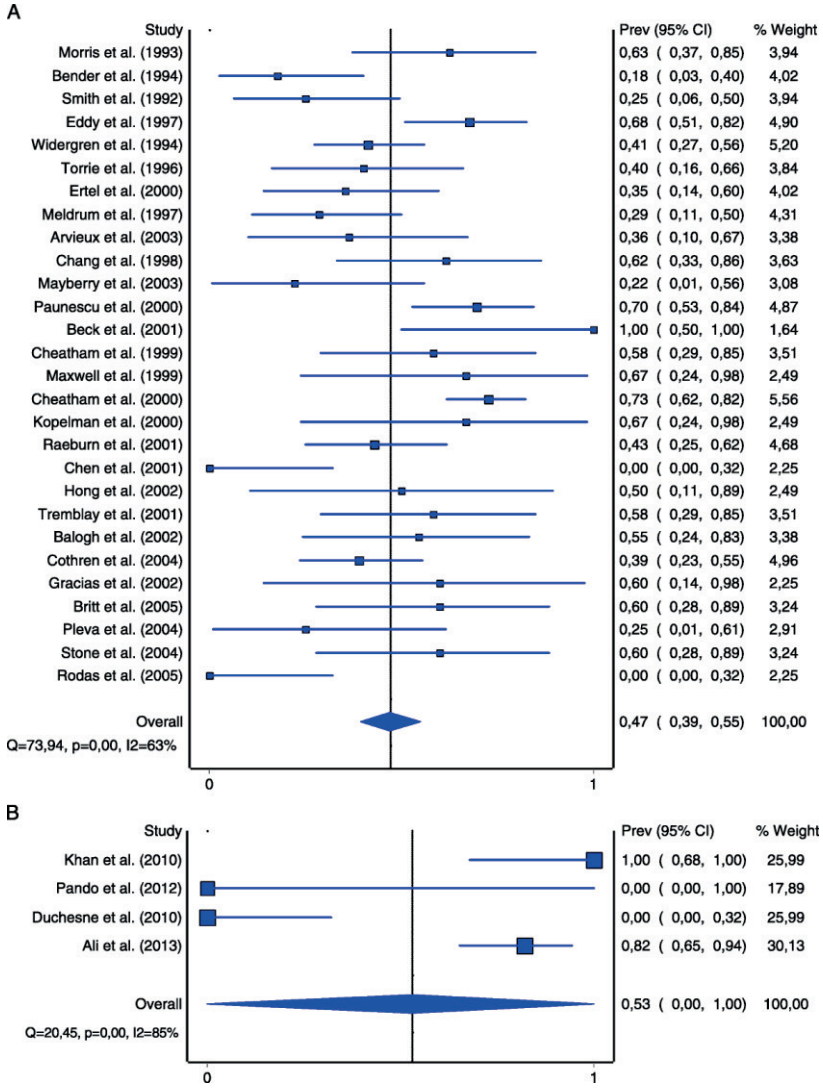
Studies are listen based upon publication year on the y-axis on the left hand side. Prevalence is shown on the x-axis as fraction. The individual study prevalence and corresponding 95% Confidence Intervals and study weight as used in the pooled analysis are listen on the y-axis on the right hand side.

Figure 2: Forest plot of prevalence of ACS among severely injured patients before (A) and after (B) January 1, 2005.



Studies are listed based upon publication year on the y-axis on the left hand side. Prevalence is shown on the x-axis as fraction. The individual study prevalence and corresponding 95% confidence intervals and study weight as used in the pooled analysis are listed on the y-axis on the right hand side.
I2, I2 statistic for study heterogeneity; Prev, prevalence; Q, Cochran's Q-statistic for study heterogeneity; 95% CI, 95% confidence interval.

Figure 3: Forest plot of ACS mortality among severely injured patients before (A) and after (B) January 1, 2005.



Studies are listed based upon publication year on the y-axis at the left hand side. Mortality rate is shown at the x-axis as fraction. The individual study mortality and corresponding 95% confidence intervals and study weight as used in the pooled analysis are listed on the y-axis at the right hand side.

I2, I2 statistic for study heterogeneity; Prev, prevalence of mortality; Q, Cochran's Q-statistic for study heterogeneity; 95% CI, 95% confidence interval.

REFERENCES

1. Beck R, Halberthal M, Zonis Z, Shoshani G, Hayari L, Bar-Joseph G. Abdominal compartment syndrome in children. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2001;2(1):51-6.
2. Khan S, Verma AK, Ahmad SM, Ahmad R. Analyzing intra-abdominal pressures and outcomes in patients undergoing emergency laparotomy. Journal of emergencies, trauma, and shock. 2010;3(4):318-25.
3. Cheatham ML, White MW, Sagraves SG, Johnson JL, Block EF. Abdominal perfusion pressure: a superior parameter in the assessment of intra-abdominal hypertension. J Trauma. 2000;49(4):621-6; discussion 6-7.
4. Hirshberg A, Wall MJ, Jr., Mattox KL. Planned reoperation for trauma: a two year experience with 124 consecutive patients. J. Trauma. 1994;37(3):365-9.
5. Balogh ZJ, Lumsdaine W, Moore EE, Moore FA. Postinjury abdominal compartment syndrome: From recognition to prevention. Lancet. 2014;384(9952):1466-75.
6. Malbrain ML, Cheatham ML, Kirkpatrick A, Sugrue M, Parr M, De Waele J, et al. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. I. Definitions. Intensive Care Med. 2006;32(11):1722-32.
7. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain MLNG, De Keulenaer B, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: Updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med. 2013;39(7):1190-206.
8. Cheatham ML, Safcsak K. Is the evolving management of intra-abdominal hypertension and abdominal compartment syndrome improving survival? Critical Care Medicine. 2010;38(2):402-7.

9. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS medicine. 2009;6(7):e1000100.
10. Strang SG, Van Lieshout EM, Breederveld RS, Van Waes OJ. A systematic review on intra-abdominal pressure in severely burned patients. Burns. 2014;40(1):9-16.
11. Mahid SS, Hornung CA, Minor KS, Turina M, Galandiuk S. Systematic reviews and meta-analysis for the surgeon scientist. Br J Surg. 2006;93(11):1315-24.
12. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg. 2003;73(9):712-6.
13. Freeman MF, Tukey JW. Transformations related to the angular and the square root. The Annals of Mathematical Statistics. 1950;21(4):607-11.
14. Cochran WG. The combination of estimates from different experiments. Biometrics. 1954;10(1):101-29.
15. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002;21(11):1539-58.
16. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials. 1986;7(3):177-88.
17. Smith PC, Tweddell JS, Bessey PQ. Alternative approaches to abdominal wound closure in severely injured patients with massive visceral edema. The Journal of trauma. 1992;32(1):16-20.
18. Morris JA, Jr., Eddy VA, Blinman TA, Rutherford EJ, Sharp KW. The staged celiotomy for trauma. Issues in unpacking and reconstruction. Annals of Surgery. 1993;217(5):576-84; discussion 84-6.
19. Bender JS, Bailey CE, Saxe JM. The technique of visceral packing: recommended management of difficult fascial closure in trauma patients. Journal of Trauma …. 1994.
20. Widergren JT, Battistella FD, Holcroft JW. The open abdomen: treatment for intra-abdominal compartment syndrome. 1994.
21. Howdieshell TR, Yeh KA, Hawkins ML, Cue JI, Ledgerwood AM. Temporary abdominal wall closure in trauma patients: Indications, technique, and results. World Journal of Surgery. 1995;19(1):154-8.

22. Torrie J, Hill AA, Streat S. Staged abdominal repair in critical illness. Anaest Intensive Care. 1996;24(3):368-74.
23. Eddy V, Nunn C, Morris JA, Jr. Abdominal compartment syndrome. The Nashville experience. The Surgical clinics of North America. 1997;77(4):801-12.
24. Mayberry JC, Mullins RJ, Crass RA, Trunkey DD. Prevention of abdominal compartment syndrome by absorbable mesh prosthesis closure. Archives of surgery (Chicago, Ill: 1960). 1997;132(9):957-61; discussion 61-2.
25. Meldrum DR, Moore FA, Moore EE, Franciose RJ, Sauaia A, Burch JM. Prospective characterization and selective management of the abdominal compartment syndrome. American Journal of Surgery. 1997;174(6):667-72; discussion 72-3.
26. Behrman SW, Bertken KA, Stefanacci HA, Parks SN. Breakdown of intestinal repair after laparotomy for trauma: incidence, risk factors, and strategies for prevention. The Journal of trauma. 1998;45(2):227-31; discusion 31-3.
27. Chang MC, Miller PR, D'Agostino R, Jr., Meredith JW. Effects of abdominal decompression on cardiopulmonary function and visceral perfusion in patients with intra-abdominal hypertension. The Journal of trauma. 1998;44(3):440-5.
28. Ivatury RR, Porter JM, Simon RJ, Islam S, John R, Stahl WM. Intra-abdominal hypertension after life-threatening penetrating abdominal trauma: prophylaxis, incidence, and clinical relevance to gastric mucosal pH and abdominal compartment syndrome. The Journal of trauma. 1998;44(6):1016-21; discussion 21-3.
29. Cheatham ML, Safcsak K, Block EF, Nelson LD. Preload assessment in patients with an open abdomen. The Journal of trauma. 1999;46(1):16-22.
30. Letoublon C, Lachachi F, Arvieux C, Lavagne P, Amroun H, Delannoy P, et al. Current treatment of closed injuries of the liver: benefits and pitfalls. Chirurgie; memoires de l'Academie de chirurgie. 1999;124(1):20-30.
31. Maxwell RA, Fabian TC, Croce MA, Davis KA. Secondary abdominal compartment syndrome: an underappreciated manifestation of severe hemorrhagic shock. The Journal of trauma. 1999;47(6):995-9.
32. Barker DE, Kaufman HJ, Smith LA, Ciraulo DL, Richart CL, Burns RP. Vacuum pack technique of temporary abdominal closure: a 7-year experience with 112 patients. The Journal of trauma. 2000;48(2):201-6; discussion 6-7.

33. Cheatham ML, White MW, Sagraves SG, Johnson JL, Block EF. Abdominal perfusion pressure: a superior parameter in the assessment of intra-abdominal hypertension. The Journal of trauma. 2000;49(4):621-6; discussion 6-7.
34. Ertel W, Oberholzer A, Platz A, Stocker R, Trentz O. Incidence and clinical pattern of the abdominal compartment syndrome after "damage-control" laparotomy in 311 patients with severe abdominal and/or pelvic trauma. Critical Care Medicine. 2000;28(6):1747-53.
35. Kopelman T, Harris C, Miller R, Arrillaga A. Abdominal compartment syndrome in patients with isolated extraperitoneal injuries. The Journal of trauma. 2000;49(4):744-7; discussion 7-9.
36. Paunescu V, Popescu C. Acute abdominal compartment syndrome in politraumatised patients. Proceedings Eurosurgery 2000. 40128 Bologna: Medimond S R L; 2000. p. 295-7.
37. Chen RJ, Fang JF, Chen MF. Intra-abdominal pressure monitoring as a guideline in the nonoperative management of blunt hepatic trauma. The Journal of trauma. 2001;51(1):44-50.
38. Garner GB, Ware DN, Cocanour CS, Duke JH, McKinley BA, Kozar RA, et al. Vacuum-assisted wound closure provides early fascial reapproximation in trauma patients with open abdomens. American Journal of Surgery. 2001;182(6):630-8.
39. Raeburn CD, Moore EE, Biffl WL, Johnson JL, Meldrum DR, Offner PJ, et al. The abdominal compartment syndrome is a morbid complication of postinjury damage control surgery. American Journal of Surgery. 2001;182(6):542-6.
40. Tremblay LN, Feliciano DV, Schmidt J, Cava RA, Tchorz KM, Ingram WL, et al. Skin only or silo closure in the critically ill patient with an open abdomen. American Journal of Surgery. 2001;182(6):670-5.
41. Balogh Z, McKinley BA, Cocanour CS, Kozar RA, Holcomb JB, Ware DN, et al. Secondary abdominal compartment syndrome is an elusive early complication of traumatic shock resuscitation. American Journal of Surgery. 2002;184(6):538-43; discussion 43-4.
42. Gracias VH, Braslow B, Johnson J, Pryor J, Gupta R, Reilly P, et al. Abdominal compartment syndrome in the open abdomen. Archives of surgery (Chicago, Ill: 1960). 2002;137(11):1298-300.

43. Hong JJ, Cohn SM, Perez JM, Dolich MO, Brown M, McKenney MG. Prospective study of the incidence and outcome of intra-abdominal hypertension and the abdominal compartment syndrome. The British journal of surgery. 2002;89(5):591-6.
44. Miller PR, Thompson JT, Faler BJ, Meredith JW, Chang MC. Late fascial closure in lieu of ventral hernia: the next step in open abdomen management. The Journal of trauma. 2002;53(5):843-9.
45. Arvieux C, Cardin N, Chiche L, Bachellier P, Falcon D, Letoublon C, et al. Damage control laparotomy for haemorragic abdominal trauma. A retrospective multicentric study about 109 cases. Annales De Chirurgie. 2003;128(3):150-8.
46. Balogh Z, McKinley BA, Cocanour CS, Kozar RA, Cox CS, Moore FA. Patients with impending abdominal compartment syndrome do not respond to early volume loading. American Journal of Surgery. 2003;186(6):602-7; discussion 7-8.
47. Gao JM, Du DY, Zhao XJ, Liu GL, Yang J, Zhao SH, et al. Liver trauma: Experience in 348 cases. World Journal of Surgery. 2003;27(6):703-8.
48. Goldman R, Zilkoski M, Mullins R, Mayberry J, Deveney C, Trunkey D. Delayed celiotomy for the treatment of bile leak, compartment syndrome, and other hazards of nonoperative management of blunt liver injury. American Journal of Surgery. 2003;185(5):492-7.
49. Mayberry JC, Welker KJ, Goldman RK, Mullins RJ. Mechanism of acute ascites formation after trauma resuscitation. Archives of surgery (Chicago, Ill: 1960). 2003;138(7):773-6.
50. Mohr AM, Lavery RF, Barone A, Bahramipour P, Magnotti LJ, Osband AJ, et al. Angiographic embolization for liver injuries: low mortality, high morbidity. The Journal of trauma. 2003;55(6):1077-81; discussion 81-2.
51. Velmahos GC, Toutouzas K, Radin R, Chan L, Rhee P, Tillou A, et al. High success with nonoperative management of blunt hepatic trauma: the liver is a sturdy organ. Archives of surgery (Chicago, Ill: 1960). 2003;138(5):475-80; discussion 80-1.
52. Cothren CC, Moore EE, Ciesla DJ, Johnson JL, Moore JB, Haenel JB, et al. Postinjury abdominal compartment syndrome does not preclude early enteral feeding after definitive closure. American Journal of Surgery. 2004;188(6):653-8.

53. Miller PR, Meredith JW, Johnson JC, Chang MC. Prospective evaluation of vacuum-assisted fascial closure after open abdomen: planned ventral hernia rate is substantially reduced. Annals of Surgery. 2004;239(5):608-14; discussion 14-6.
54. Pleva L, Sir M, Mayzlik J. Abdominal compartment syndrome in polytrauma. Biomedical papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia. 2004;148(1):81-4.
55. Stone PA, Hass SM, Flaherty SK, DeLuca JA, Lucente FC, Kusminsky RE. Vacuum-assisted fascial closure for patients with abdominal trauma. Journal of Trauma - Injury, Infection and Critical Care. 2004;57(5):1082-6.
56. Britt RC, Gannon T, Collins JN, Cole FJ, Weireter LJ, Britt LD. Secondary abdominal compartment syndrome: risk factors and outcomes. The American surgeon. 2005;71(11):982-5.
57. Miller RS, Morris JA, Jr., Diaz JJ, Jr., Herring MB, May AK. Complications after 344 damage-control open celiotomies. The Journal of trauma. 2005;59(6):1365-71; discussion 71-4.
58. Prince RA, Hoffman CJ, Scanlan RM, Mayberry JC. The distinct and secondary harmful effect of pelvic and extremity injury on the outcome of laparotomy for trauma. The Journal of surgical research. 2005;124(1):3-8.
59. Rodas EB, Malhotra AK, Chhitwal R, Aboutanos MB, Duane TM, Ivatury RR. Hyperacute abdominal compartment syndrome: an unrecognized complication of massive intraoperative resuscitation for extra-abdominal injuries. The American surgeon. 2005;71(11):977-81.
60. Kozar RA, Moore FA, Cothren CC, Moore EE, Sena M, Bulger EM, et al. Risk factors for hepatic morbidity following nonoperative management: Multicenter study. Arch Surg. 2006;141(5):451-9.
61. Reed SF, Britt RC, Collins J, Weireter L, Cole F, Britt LD. Aggressive surveillance and early catheter-directed therapy in the management of intra-abdominal hypertension. The Journal of trauma. 2006;61(6):1359-63; discussion 63-5.
62. Nicol AJ, Hommes M, Primrose R, Navsaria PH, Krige JEJ. Packing for control of hemorrhage in major liver trauma. World Journal of Surgery. 2007;31(3):569-74.
63. Scalea TM, Bochicchio GV, Habashi N, McCunn M, Shih D, McQuillan K, et al. Increased intra-abdominal, intrathoracic, and intracranial pressure after severe

brain injury: multiple compartment syndrome. J TRAUMA. 2007;62(3):647-56; discussion 56.

64. Dissanaike S, Pham T, Shalhub S, Warner K, Hennessy L, Moore EE, et al. Effect of Immediate Enteral Feeding on Trauma Patients with an Open Abdomen: Protection from Nosocomial Infections. Journal of the American College of Surgeons. 2008;207(5):690-7.

65. Letoublon C, Chen Y, Arvieux C, Voirin D, Morra I, Broux C, et al. Delayed celiotomy or laparoscopy as part of the nonoperative management of blunt hepatic trauma. World J Surg. 2008;32(6):1189-93.

66. Madigan MC, Kemp CD, Johnson JC, Cotton BA. Secondary abdominal compartment syndrome after severe extremity injury: are early, aggressive fluid resuscitation strategies to blame? The Journal of trauma. 2008;64(2):280-5.

67. Parsak CK, Seydaoglu G, Sakman G, Acarturk TO, Karakoc E, Hanta I, et al. Abdominal compartment syndrome: current problems and new strategies. World Journal of Surgery. 2008;32(1):13-9.

68. Wei B, Hemmila MR, Arbabi S, Taheri PA, Wahl WL. Angioembolization reduces operative intervention for blunt splenic injury. Journal of Trauma - Injury, Infection and Critical Care. 2008;64(6):1472-7.

69. Cotton BA, Au BK, Nunez TC, Gunter OL, Robertson AM, Young PP. Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. The Journal of trauma. 2009;66(1):41-8; discussion 8-9.

70. Koss W, Ho HC, Yu M, Edwards K, Ghows M, Tan A, et al. Preventing loss of domain: a management strategy for closure of the "open abdomen" during the initial hospitalization. Journal of Surgical Education. 2009;66(2):89-95.

71. Nellensteijn D, Porte RJ, Van Zuuren W, Ten Duis HJ, Hulscher JBF. Paediatric blunt liver trauma in a Dutch level 1 trauma center. European Journal of Pediatric Surgery. 2009;19(6):358-61.

72. Duchesne JC, Howell MP, Eriksen C, Wahl GM, Rennie KV, Hastings PE, et al. Linea alba fasciotomy: a novel alternative in trauma patients with secondary abdominal compartment syndrome. The American surgeon. 2010;76(3):312-6.

73. Balogh ZJ, Martin A, van Wessem KP, King KL, Mackay P, Havill K. Mission to eliminate postinjury abdominal compartment syndrome. Archives of surgery (Chicago, Ill: 1960). 2011;146(8):938-43.
74. Giladi AM, Dossett LA, Fleming SB, Abumrad NN, Cotton BA. High-dose antioxidant administration is associated with a reduction in post-injury complications in critically ill trauma patients. Injury. 2011;42(1):78-82.
75. James MFM, Michell WL, Joubert IA, Nicol AJ, Navsaria PH, Gillespie RS. Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). British Journal of Anaesthesia. 2011;107(5):693-702.
76. Parks NA, Davis JW, Forman D, Lemaster D. Observation for nonoperative management of blunt liver injuries: How long is long enough? Journal of Trauma - Injury, Infection and Critical Care. 2011;70(3):626-9.
77. Saltzherr TP, Van Der Vlies CH, Van Lienden KP, Beenen LFM, Ponsen KJ, Van Gulik TM, et al. Improved outcomes in the non-operative management of liver injuries. HPB. 2011;13(5):350-5.
78. Shekhei RA, Heydari M, Shahbazi S. Comparison of intra-abdominal pressure measurement and physical exam for diagnosis of surgery indication in patients with abdominal compartment syndrome due to blunt trauma. Journal of Kerman University of Medical Sciences. 2011;18(3):271-8.
79. Al-Sharif A, Thakur V, Al-Farsi S, Singh RN, Kornecki A, Seabrook JA, et al. Resuscitation volume in paediatric non-haemorrhagic blunt trauma. Injury-International Journal of the Care of the Injured. 2012;43(12):2078-82.
80. Ding LA, Niu DG, Shao CC, Cheng HG. Laparostomy for treating severe abdominal infection and truma - 39 cases report and literature review. Journal of gastroenterology and hepatology. 2012;27(Journal Article):295.
81. Harrell BR, Melander S. Identifying the association among risk factors and mortality in trauma patients with intra-abdominal hypertension and abdominal compartment syndrome. Journal of trauma nursing : the official journal of the Society of Trauma Nurses. 2012;19(3):182-9.

82. Maung AA, Schuster KM, Kaplan LJ, Ditillo MF, Piper GL, Maerz LL, et al. Compared to conventional ventilation, airway pressure release ventilation may increase ventilator days in trauma patients. The journal of trauma and acute care surgery. 2012;73(2):507-10.
83. Neal MD, Hoffman MK, Cuschieri J, Minei JP, Maier RV, Harbrecht BG, et al. Crystalloid to packed red blood cell transfusion ratio in the massively transfused patient: when a little goes a long way. The journal of trauma and acute care surgery. 2012;72(4):892-8.
84. Ordonez CA, Badiel M, Pino LF, Salamea JC, Loaiza JH, Parra MW, et al. Damage control resuscitation: Early decision strategies in abdominal gunshot wounds using an easy "aBCD" mnemonic. Journal of Trauma and Acute Care Surgery. 2012;73(5):1074-8.
85. Pando E, Ferrer J, Burrel M, Gobbo GDD, Barrufet M, Real MI, et al. Evaluation of the efficacy of angioembolization in the management of severe liver trauma. Hospital clinic barcelona case studies. HPB. 2012;14:530.
86. Ali SR, Mohammad H, Sara S. Evaluation of the relationship between pelvic fracture and abdominal compartment syndrome in traumatic patients. Journal of emergencies, trauma, and shock. 2013;6(3):176-9.
87. Divarci E, Ergun O, Karapinar B, Yalaz M, Celik A. Can increased intra-abdominal pressure (IAP) be treated more effectively with intravesical pressure measurement in high-risk patients? Ulusal travma ve acil cerrahi dergisi = Turkish journal of trauma & emergency surgery : TJTES. 2013;19(6):559-63.
88. Fiard G, Terrier N, Sengel C, Chodez M, Descotes JL, Rambeaud JJ, et al. Indications, successes and complications of arterial embolization in renal trauma. Eur Urol Suppl. 2013;12(1):e564.
89. Guidry C, DellaVope J, Simms E, Heaney JB, Guice J, McSwain Jr N, et al. Impact of inverse ratios on patients with exsanguinating vascular injuries: Should more be the new paradigm? Journal of Trauma and Acute Care Surgery. 2013;74(2):403-10.

90. Kasotakis G, Sideris A, Yang Y, De Moya M, Alam H, King DR, et al. Aggressive early crystalloid resuscitation adversely affects outcomes in adult blunt trauma patients: An analysis of the Glue Grant database. Journal of Trauma and Acute Care Surgery. 2013;74(5):1215-22.
91. Mahmood I, Mahmood S, Parchani A, Kumar S, El-Menyar A, Zarour A, et al. Intra-abdominal hypertension in the current era of modern trauma resuscitation. Anz Journal of Surgery. 2013(Journal Article).
92. Rencuzogullari A, Yalav O, Dalci K, Eray IC, Parsak CK, Seydaoglu G. Comparison of early surgical alternatives in the management of open abdomen: A randomized controlled study. European Surgical Research. 2013;50(Journal Article):155.
93. Asfar S, Khoursheed M, Al-Saleh M, Alfawaz AA, Farghaly MM, Nur AM. Management of liver trauma in Kuwait. Medical Principles and Practice. 2014;23(2):160-6.
94. Joseph B, Zangbar B, Pandit V, Vercruysse G, Aziz H, Kulvatunyou N, et al. The conjoint effect of reduced crystalloid administration and decreased damage-control laparotomy use in the development of abdominal compartment syndrome. The journal of trauma and acute care surgery. 2014;76(2):457-61.
95. Balogh ZJ, Van Wessem K, Yoshino O, Moore FA. Postinjury abdominal compartment syndrome: Are we winning the battle? World J Surg. 2009;33(6):1134-41.

Chapter 5

A systematic review on intra-abdominal pressure in severely burned patients

BURNS.
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ABSTRACT

Objective: Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) are complications that may occur in severe burn patients. Evidenced based medicine for these patients is in its early development. The aim of this study was to provide an overview of literature regarding IAH and ACS in severe burn patients.

Methods: A systematic search was performed in Cochrane Central Register of Controlled Trials, PubMed, Embase, Web of Science and CINAHL on October 1, 2012. These databases were searched on 'burn', 'intra-abdominal hypertension', 'abdominal compartment syndrome', synonyms and abbreviations. Studies reporting original data on mortality, abdominal decompression or abdominal pressure related complications were included.

Results: Fifty publications met the criteria, reporting 1616 patients. The prevalence of ACS and IAH in severe burn patients is 4.1-16.6 % and 64.7-74.5%, respectively. The mean mortality rate for ACS in burn patients is 74.8%. The use of plasma and hypertonic lactated resuscitation may prevent IAH or ACS. Despite colloids decrease resuscitation volume needs, no benefit in preventing IAH was proven. Escharotomy, peritoneal catheter drainage, and decompression laparotomy are effective intra-abdominal pressure (IAP) diminishing treatments in burn patients. Markers for IAP-related organ damage might be superior to IAP measurement itself.

Conclusion: ACS and IAH are frequently seen devastating complications in already severely injured burn patients. Prevention is challenging but can be achieved by improving fluid resuscitation strategies. Surgical decompression measures are effective and often unavoidable. Timing is essential since decompression should prevent progression to ACS rather than limit its effects. Prognosis of ACS remains poor, but options for care improvement are available in literature.

INTRODUCTION

Severely injured burn patients are at risk for elevated intra-abdominal pressure (IAP). The World Society of Abdominal Compartment Syndrome (WSACS) defines burn injury as an independent risk factor for abdominal compartment syndrome (ACS). ACS is a syndrome of new organ failure resulting from a sustained or repeated IAP >20 mmHg (1). A sustained or repeated IAP ≥12 mmHg without signs of organ failure is termed Intra-Abdominal Hypertension (IAH). IAH and ACS are detrimental complications in the critically ill, even more in severely burned patients. However, evidenced based medicine for these severely injured patients is still in its early development.

Greenhalgh *et al.* were the first to describe the occurrence and effects of elevated IAP among four cases of burn injury in children in 1994 (2). In a prospective analysis of 30 severe burn patients, they demonstrated that an IAP ≥30 mmHg is associated with a 3 to 4 times increased sepsis and mortality rates. This publication initiated an increase of awareness of IAP-related complications and its devastating effects. It took until 1999 before Ivy *et al.* (3) reported on intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) in adult burn patients. IAH and ACS are diagnosed using various IAP measuring techniques, measurements can be continuous and direct or indirect intra-vesical; this last method is included in the guidelines of WSACS and is accurate in burn patients as well (4-6)

IAH and ACS result from large fluid resuscitation volumes in combination with severe systemic inflammatory response syndrome (SIRS) (7). Both resuscitation volume and SIRS are dependent of the burn injury severity (8). Even though the most commonly used Parkland-Baxter formula states a use of 4mL/kg/% of (burned) total body surface area (TBSA), larger volumes are often given (9, 10). This may lead to a phenomenon called ‘fluid creep’ which gives rise to excessive edema formation and ‘third spacing’ of the fluid excess (11). This is swift process; intra-abdominal edema and ascites leading to IAH can emerge within only a few hours after sustaining the burn injury (12). SIRS in these patients becomes a self-perpetuating process caused by accumulation of pro-inflammatory cytokines in the resulting ascites fluid (13).

The second main factor that leads to IAH in burn patients are compliance decreasing burns of the abdominal or thoracic wall. The compliance curve of a healthy human abdomen

shows it can easily contain 3L extra volume without a significant increase in IAP (14). When local burn injury is present, the abdominal volume capacity is smaller. Truncal burn and increased intra-abdominal volume can raise IAP independently, but when an inauspicious combination of these conditions occurs, patients can deteriorate fast. In that case, IAP can be relieved rapidly by longitudinal skin incision (escharotomy) of the truncal burns or eschars (15, 16).

ACS related new organ failure typically presents itself as oliguria or ventilation difficulties. They result from the body's inability to compensate and overcome the intra-abdominal pressures which gives rise to tissue ischemia. Compensatory ability is strongly patient dependent, therefore measuring IAP alone is not sufficient in determining the patient's threat. Abdominal perfusion pressure (APP) defined as the mean arterial pressure (MAP) minus the IAP, is more suitable measurement (1, 17). To restore adequate perfusion pressures in ACS patients, decompression is needed. Early ACS recognition is of decisive importance for prompting such a decompression. Even when early recognition is achieved, ACS has a poor prognosis. Mortality rates of 44% up to 100% are reported for burn patients with ACS (18, 19).

Even though IAP-related complications in severe burn patients are dangerous, they occur quite common. Prevention of IAH and ACS should receive high priority in severe burn patients. Unfortunately resuscitation of burn patients with respect to IAH and ACS is based on limited evidence (9, 20, 21). In order to identify the treatment elements that improve outcome for these patients, a concise overview of available evidence is needed. The aim of this systematic review was to provide a detailed overview of literature regarding epidemiology, therapy, and outcome of rising IAP related complications in major burn patients.

METHODS

A systematic search was conducted in Cochrane Central Register of Controlled Trials, PubMed, Embase, Web of Science and CINAHL on October 1, 2012. Databases were searched for the following terms: “burn” and synonyms combined with “abdominal compartment syndrome” or “intra-abdominal hypertension” and synonyms or abbreviations (Table 1). Reference lists of all manuscripts were reviewed to identify additional literature. Articles were screened on [title] and [abstract] for the exclusion criteria; no burn in combination with IAH or ACS, reviews, comments, animal studies, and questionnaire surveys. When no full-text was available after several attempts and when a double population was suspected, manuscripts were excluded too. The remaining articles were screened in full text and included when original patient data were present. No language criterion was used.

The level of evidence was determined according to Mahid *et al.* (22). Data regarding risk factors, diagnosis, treatment and outcome of these studies were extracted; conclusions of individual studies are discussed.

RESULTS

The primary search resulted in 500 hits. After applying the inclusion and exclusion criteria, 50 manuscripts remained (Figure 1); 21 case-reports or case series and 29 cohort studies. Especially the first publications used a variety of definitions and cut points for intra-abdominal hypertension and abdominal compartment syndrome. Since WSACS stated unambiguous definitions for IAH and ACS in 2006, literature became more uniform and comparable (1). The heterogeneity in study populations and collected data and the lack of details on the IAP measurement techniques across studies made pooled analysis impossible.

Prevalence

By approximation, IAH prevalence according to WSACS guidelines (≥12 mmHg) is 64.7-74.5% among patients with ≥20% of TBSA burned or having inhalation injury (Table 2). The prevalence of ACS among patients with ≥15% TBSA burned ranged from 4.1% to 16.6% (Table 3). Seven of nine manuscripts reported ACS rates between 4% and 16.6 % independent of their variety in cutoff burn size.

Outcome

In 21 case reports and series, a mortality rate of 50% among 58 burn ACS patients was seen (2, 3, 5, 12, 16, 23-38) (Table 4). Nine cohort studies (N=132 total) report mortality rates between 44%-100%, with a weighted average of 74.8% (18, 19, 39-45) (Table 5). No improving trend in mortality can be demonstrated over recent years.

Risk factors

Several obvious risk factors for ACS in burn patients exist. Decreased abdominal wall compliance (caused by local burns) is generally considered to contribute to the development of IAH. However, truncal burns are not a prerequisite per se for IAH in burn patients (3). Resuscitation volume is the second risk factor for IAH. A small prospective case series of nine patients showed that fluid resuscitation volume of 0.25L/kg in the early post burn period resulted in an IAP of 24.4 mmHg (27). Exceeding this volume (also described as 'Ivy score'), is a suggested independent risk factor for developing IAH/ACS. Oda *et al.* noted that a resuscitation volume larger 0.3L/kg in the first 24h post burn were at risk for ACS (46).

Greenhalgh *et al.* described sepsis, oliguria, hypoventilation and hypotension as specific signs for IAH or ACS, apart from sepsis evidence was insufficient to determine whether these risk factors are independent (1, 2). Additionally, injury severity (in % TBSA burned), seems linearly associated with ACS incidence (47). A burn size of ≥40% TBSA proved to be an independent risk factor for ACS (25). Electrical etiology of burn injury is another possible risk factor; in a matched case control study the ACS prevalence in electrical burns patients was 4% vs. 1.5% in thermally injured patients (48). Nonetheless sample size was too small to reach statistical significance. The last risk factor is skeletal immaturity; in a retrospective study of 1014 patients, six out of 10 cases that developed ACS (mean TBSA burned 72%) were non-adults with a mean age of six years (41).

Resuscitation

Large volumes of resuscitation fluid are needed to maintain appropriate hemodynamics in severely burned patients. However, excessive fluid resuscitation may increase the IAP level in burn patients (2, 3, 27). Similarly, pediatric burn patient prove to be at risk for excessive chylous ascites accumulation as a result of large resuscitation fluid volumes leading to ACS (35). A multivariable linear regression analysis of 72 burn patients (mean TBSA burned 44.5%), showed percentage TBSA burned, age, weight, and intubation before admission to a burn center to significantly influence fluid requirements in the first 24 hours after burn injury (49).

Implementation of standardized military volume limiting burn resuscitation guidelines resulted in a decrease of a composite endpoint of ACS and mortality (50). Decreasing

resuscitation volume of the Parkland formula from 4 to 3 ml/kg/%TBSA is proposed in a case report of a pediatric burn patient who developed ACS and died as a result of 'fluid creep' (36). The use of a modified Brooke formula (2ml/kg/%TBSA) proved to be a good alternative as well (51). A statistically significant reduction of resuscitation volumes ($p=0.005$) and peak IAP ($p=0.0001$) was achieved by using plasma instead of crystalloid resuscitation fluid (52). In a randomized trial, a statistically significantly lower resuscitation volume ($p<0.01$) and IAP after 24h ($p<0.05$) was demonstrated in severe burn patients without inhalation injury after resuscitation with hypertonic lactated saline (HLS) compared lactated Ringer's (53). Using colloids to reduce resuscitation volumes was not associated with worse outcome in burn patients when compared with the standard Parkland formula (54).

Decompression laparotomy

Decompression laparotomy is the most used and accepted abdominal decompressive measure. Even in children this is an adequate therapy without specified adverse effects (19). Although indications for decompression laparotomy are usually straight forward, some nuances can be made. Since burn patients have already lost the protective barrier of normal skin, there is diversion in opinion whether decompression laparotomy might induce unacceptable morbidity. Although hemodynamic parameters in burn patients rapidly improve after decompression laparotomy, it does not decrease rates of acute lung injury and multi organ dysfunction syndrome (MODS) (55). Acute lung injury and multi organ dysfunction syndrome may be more severe after decompression laparotomy than before ($p<0.05$ and $p<0.01$, respectively) and more severe than in similar severely injured burn patients without IAH ($p<0.05$ and $p<0.05$, respectively). Similarly, open abdominal decompression is associated with higher mortality rates among patients aged 80 years or older (81%) than among younger patients (30-50%) (56). If possible, surgeons should consider avoiding decompression laparotomy in fragile patient categories.
Alternative IAP lowering techniques which can be applied prior to decompression laparotomy include escharotomy of circumferential abdominal burn wounds, percutaneous catheter decompression, bowel care, nasogastric tube decompression, flushing the bladder catheter to ensure patency, pharmacologic paralysis, and sedation (41).

Escharotomy

When large burns of the trunk are present, abdominal and thoracic wall escharotomy is the appropriate early decompressive measure. Thoracoabdominal escharotomy is mostly performed in a standardized pattern; an incision in the anterior axillary line bilaterally, one along the lower margin of the rib cage and two symmetric longitudinal cuts at the anterior abdomen. A small cohort study proved abdominal escharotomy to decrease mean bladder pressure significantly in low grade IAH ($p<0.001$) (16). Another 8-patients cohort study demonstrated that escharotomy statistical significantly reduces IAP from 38 to 19 mmHg ($p<0.01$) and results in a direct improvement of cardiovascular parameters in high grades of IAH (57). Patients of both studies presented themselves within 2-6 hours after burn injury and developed IAH requiring decompressive escharotomy within 24 hours after the injury. This endorses the need for early IAP measurement in standard burn care, especially when burn injury of the trunk is present.

Percutaneous catheter decompression

IAH in burn patients can occur as a result of accumulation of ascites and bowel edema. Percutaneous catheter decompression decompresses the abdomen by releasing the ascites without influencing the edema. When ascites is present, placement of a peritoneal dialysis catheter or angiocatheter (depending on patient size) and leaving it sutured in place is generally sufficient. In a small study, this minimally invasive measure decreased the IAP by 14 mmHg, with a rapid improve in hemodynamic parameters (26). A 13-patient cohort study concluded percutaneous catheter decompression to be effective in patients with <80% TBSA burned with concomitant inhalation injury. More severely injured patients required decompression laparotomy and died (44). The effectiveness of percutaneous catheter decompression with respect to abdominal perfusion pressure (APP) was confirmed in a case report (32). Lastly, a retrospective case-control study determined percutaneous catheter decompression to be a safe decompression alternative (43). Nonetheless, when no signs of ascites are present, this technique is obsolete. Peritoneal catheter decompression is indicated when escharotomy has failed (40), beware of non-functioning catheters.

Temporary abdominal closure

When faced with an open abdomen after decompression laparotomy, the question raises how to close it. Closing an open abdomen is especially difficult in patients with abdominal burns. In order to prevent complications of the open abdomen, temporary abdominal closure device can be used. Temporary abdominal closure devices again cause additional damage to the already injured abdominal wall and are associated with infectious complications such as abscess and fistula formation. In a six-patient cohort study, four burn patients died of sepsis with MODS after applying a vacuum-assisted TAC (42).
To bridge the period unto definitive abdominal closure, visceral coverage should be preferred over vacuum assisted temporary abdominal closure devices until proven to be safe in burn patients. The possibility for early partial abdominal closure should be regularly assessed in order to prevent persistent dehiscence. The component separation technique of Ramirez is a primary closure technique which does not use foreign materials (34, 58). In a series of burn patients with ACS, two patients survived more than 30 days after abdominal closure with this technique (34). No intra-abdominal abscess and entero-cutaneous fistula formations were observed in this study.

The danger for ACS remains after temporal abdominal closure (23). Recurrent or tertiary ACS endorses the need for continued IAP monitoring after temporary closure

Management

IAH in burn patients is frequently a result of large resuscitation volumes, but this may lead to other complications such as acute ischemic optic neuropathy as well (33). This 'fluid creep' is a dangerous condition of which IAH (and ACS) is only a single expression. Acute kidney injury, a possible complication of IAH/ACS, does not help in draining this volume overload. Acute kidney injury is found in 40% of severely burned patients with ACS, and is associated with 50% mortality rate (59). Burn patients with AKI require dialysis, which is associated with high mortality rates as well. Renal deterioration in burn patients can be reduced by diminishing the use of nephro-toxic medication (60). If IAH emerges, one should be aware of this other severe non-surgical or systemic complications. These complex multi-system complications require a multi-disciplinary approach, in which intensivists, surgeons, anesthesiologists, and nutritionists can play a crucial role in patient survival (37, 61, 62).

DISCUSSION

This systematic review listed best literature regarding prevalence, treatment and outcome of IAH and ACS in severe burn patients, and provides more clarity regarding occurrence and mortality of ACS in burn patients. There are several shortcomings of the individual reports, the most obvious being the limited level of scientific evidence. Moreover, most papers do not mention clearly whether the diagnosis IAH was made based upon a one time "peak" measurement or on repeated sequential measurements. Nevertheless, some amendments can be made for this review as well. For example, the broad range of interest of this search aims at most important findings of the available literature regarding IAP-related complications in severe burn patients. Subsequently, minor details were not mentioned in this report. Much literature is available regarding burn care or ACS and IAH, but little and often poor evidence is found on the combination of conditions. More research is needed to decrease IAP related morbidity and mortality. A promising clue for this can be found in the following. Even though a large increase in use in abdominal decompressions is seen, no decrease in laparotomies for IAH related non-occlusive intestinal ischemia was seen over recent years (45). This ischemia induces massive inflammatory response which creates a vicious circle which indirectly leads to the development of ACS. Tools for early recognition of IAP related splanchnic ischemia are not available, but are probably more important than the measurement of IAP or APP itself (19, 38).

CONCLUSION

Abdominal compartments syndrome and especially intra-abdominal hypertension are frequently seen devastating complications in the already severely injured burn patients. IAH prevalence is 64.7-74.5% among patients with ≥20% TBSA burned or with inhalation injury. ACS is seen in 4.1-16.6% of patients with ≥15% of TBSA burned. IAH or ACS can be prevented by decreasing resuscitation volume. Strict monitoring of urine output or hemodynamic parameters to prevent 'fluid creep' is of great importance. Using the modified Brooke formula, plasma, hypertonic lactated or colloid resuscitation is preferred over crystalloid use, especially in more severely injured, older and heavier patients intubated prior to admission on a burn unit.

Truncal burns in ACS patients require immediate escharotomy and should be followed by increasingly invasive decompression measures if no relieve is achieved. Timing of decompression is essential since it should rather prevent progression to abdominal compartment syndrome than limiting its effects.

Prognosis of abdominal compartments syndrome is very poor with a mean mortality rate of 74.8%. IAH/ACS-burn patient outcome can be further improved by superior resuscitation regimes, better understanding of the inflammatory response after burn injury and tools for early recognition of splanchnic ischemia.

Figure 1: Flowchart of literature search

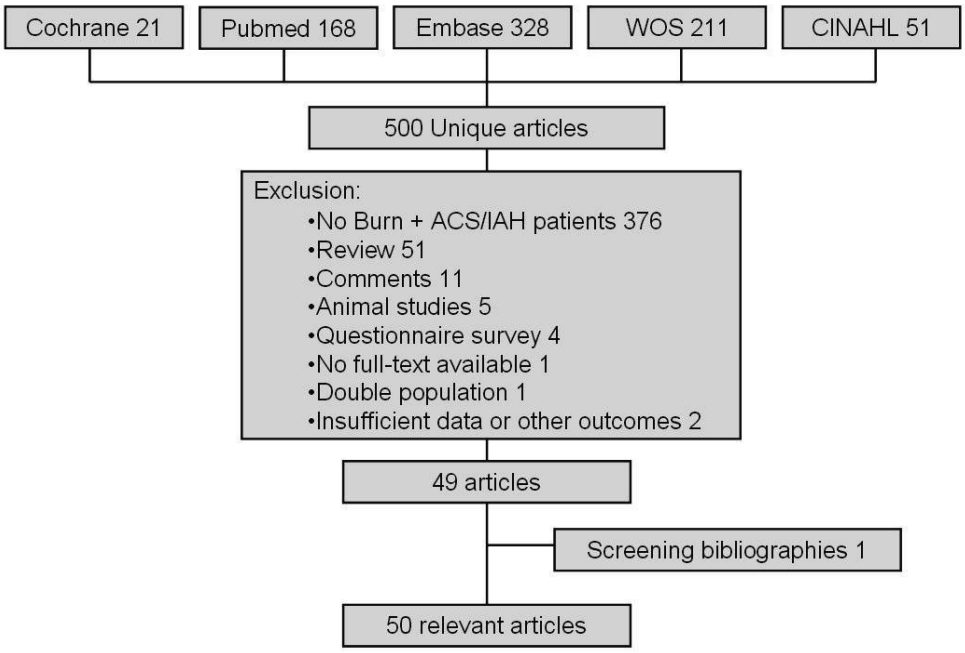

Table 1: Search query

(burn OR burns OR burning OR burnings OR burned OR burnt OR scald OR scalds OR scalding OR scorch OR scorching OR singe OR singed OR blaze OR blazed OR “blast injury” OR “blast injuries”) AND (“abdominal compartment syndrome” OR ACS OR “abdominal compartment syndromes” OR “abdominal compartmental syndrome” OR “abdominal compartmental syndromes” OR “abdominal hypertension” OR “intra-abdominal hypertension” OR “IAH” OR “intra abdominal hypertension” OR “abdominal pressure” OR “intra-abdominal pressure” OR “intra abdominal pressure” OR “IAP”)

Table 2: Prevalence of IAH among burn patients

Author	LOE	Burn cutoff	IAH cutoff	N=	Prevalence
Oda et al. (2006) (53)	2	≥40% TBSA	≥22mmHg*	36	36%*
Sanchez et al. (2009) (63)	5	Mech. Vent.	≥12mmHg	33	64.7%
Malbrain et al (2010) (64)	3	Mech. Vent.	≥12mmHg	55	74.5%

*WSACS stated IAH cutoff pressure at 12 mmHg, therefore this number is of less relevance.

LOE, Level Of Evidence according to Mahid et al (22)

Table 3: Prevalence of ACS among burn patients

Author	LOE	Cutoff point	N=	Prevalence
Hobson et al. (2002) (41)	3	'Acute burn'	1014	1%
Markel et al (2009) (47)	3	'Acute burn'	51	1.8%
Oda et al (2006) (46)	3	≥40% TBSA	48	16.6%
Ennis et al (2008) (50)	3	≥30% TBSA	118	11%
Mosier et al (2011) (61)	3	≥20% TBSA	153	4.6%
Klein et al (2007) (49)	3	≥20% TBSA	72	4.2%
Yenikomshian et al (2011) (62)	3	≥20% TBSA	50	8%
Cartotto et al (2010) (18)	3	≥15% TBSA	194	4.1%
Dulhunty et al (2008) (54)	3	≥15% TBSA	80	16%

Seven of nine cohort studies reported ACS prevalence of 4.1-16 % among patients burned ≥15% TBSA

TBSA, Total Body Surface Area burned; LOE, Level Of Evidence according to Mahid et al (22)

Table 4: Mortality of severe burn patients with ACS in case descriptions

Author	N	Mortality
Greenhalgh et al (1994) (2)	4	3 (75%)
Ivy et al (1999) (3)	3	3 (100%)
Ivy et al (2000)(27)	10	2 (20%)
Mayes et al (2000) (31)	2	1 (50%)
Corcos et al (2001) (26)	3	2 (67%)
Wilson et al (2001) (38)	1	0 (0%)
Blinderman et al (2002) (24)	1	1 (100%)
Tsoutsos et al (2003) (16)	10	4 (40%)
Pirson et al (2004) (33)	1	0 (0%)
Britt et al (2005) (25)	4	4 (100%)
Rodas et al (2005) (12)	1	0 (0%)
Ball et al (2006) (23)	1	0 (0%)
Jensen et al (2006) (28)	3	2 (67%)
Levis et al (2006) (30)	4	3 (75%)
Parra et al (2006) (32)	1	0 (0%)
Muangman et al (2007) (5)		N/A
Poulakidis et al (2009) (34)	3	2 (67%)
Thamm et al (2009) (37)	1	0 (0%)
Lamb et al (2010) (29)		N/A
Rogers et al (2010) (36)	1	1 (100%)
Rocourt et al (2011) (35)	2	0 (0%)
Total	**56**	**28 (50%)**

Table 5: Mortality of severe burn patients with ACS in cohort studies

Author	LOE	N	Mortality
Hobson et al (2002) (41)	3	10	6 (60%)
Latenser et al (2002) (44)	5	4	4 (100%)
Hershberger et al (2007) (40)	5	25	22 (88%)
Chung JY et al (2007) (39)	5	9	5 (56%)
O'Mara et al (2007) (19)	5	16	7 (44%)
Latenser et al (2008) (43)	4	9	4 (44%)
Keremati et al (2008) (42)	5	6	4 (67%)
Cartotto et al (2010) (18)	3	8	8 (100%)
Van Niekerk et al (2010) (45)	3	45	39 (87%)
Total		**132**	**74.8%**

LOE, level of evidence according to Mahid et al (22)

REFERENCES

1. Malbrain ML, Cheatham ML, Kirkpatrick A, Sugrue M, Parr M, De Waele J*, et al.* Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. I. Definitions. Intensive Care Med. 2006;32(11):1722-32.
2. Greenhalgh DG, Warden GD. The importance of intra-abdominal pressure measurements in burned children. J Trauma. 1994;36(5):685-90.
3. Ivy ME, Possenti PP, Kepros J, Atweh NA, D'Aiuto M, Palmer J*, et al.* Abdominal compartment syndrome in patients with burns. J Burn Care Rehabil. 1999;20(5):351-3.
4. World Society of the Abdominal Compartment Syndrome. Available at http://www.wsacs.org/consensus_summary.php; Accessed Dec. 1, 2012.
5. Muangman P, Muangman S, Suvanchote S, Benjathanung R. Abdominal compartment syndrome monitoring in major burn patients with Siriraj device catheter. J Med Assoc Thai. 2007;90(2):384-90.
6. Waes OF, Jaquet J, Hop WJ, Morak MM, Ijzermans J, Koning J. A Single-Lumen Central Venous Catheter for Continuous and Direct Intra-abdominal Pressure Measurement. European Journal of Trauma and Emergency Surgery. 2009;35(6):532-7.
7. Kirkpatrick AW, Ball CG, Nickerson D, D'Amours SK. Intraabdominal hypertension and the abdominal compartment syndrome in burn patients. World J Surg. 2009;33(6):1142-9.
8. Evers LH, Bhavsar D, Mailander P. The biology of burn injury. Exp Dermatol. 2010;19(9):777-83.
9. Tricklebank S. Modern trends in fluid therapy for burns. Burns. 2009;35(6):757-67.
10. Baxter CRMD. Guidelines For Fluid Resuscitation. [Miscellaneous]. J Trauma. 1981;21(Supplement 8):687-9.
11. Saffle JI. The phenomenon of "fluid creep" in acute burn resuscitation. J Burn Care Res. 2007;28(3):382-95.

12. Rodas EB, Malhotra AK, Chhitwal R, Aboutanos MB, Duane TM, Ivatury RR. Hyperacute abdominal compartment syndrome: an unrecognized complication of massive intraoperative resuscitation for extra-abdominal injuries. Am Surg. 2005;71(11):977-81.
13. Kowal-Vern A, Ortegel J, Bourdon P, Chakrin A, Latenser BA, Kimball D*, et al.* Elevated cytokine levels in peritoneal fluid from burned patients with intra-abdominal hypertension and abdominal compartment syndrome. Burns. 2006;32(5):563-9.
14. Shay S, Schreiber M, Richter J. Compliance curves during peritoneal dialysate infusion are like a distensible tube and are similar at multiple UGI sites. Am J Gastroenterol. 1999;94(4):1034-41.
15. Orgill DP, Piccolo N. Escharotomy and decompressive therapies in burns. J Burn Care Res. 2009;30(5):759-68.
16. Tsoutsos D, Rodopoulou S, Keramidas E, Lagios M, Stamatopoulos K, Ioannovich J. Early escharotomy as a measure to reduce intraabdominal hypertension in full-thickness burns of the thoracic and abdominal area.World J Surg. 2003;27(12):1323-8.
17. Cheatham ML, White MW, Sagraves SG, Johnson JL, Block EF. Abdominal perfusion pressure: a superior parameter in the assessment of intra-abdominal hypertension. J Trauma. 2000;49(4):621-6; discussion 6-7.
18. Cartotto R, Zhou A. Fluid creep: the pendulum hasn't swung back yet! J Burn Care Res. 2010;31(4):551-8.
19. O'Mara MS, Reed N, Palmieri TL, Greenhalgh DG. Immediate and long-term outcomes of decompressive laparotomy for abdominal compartment syndrome in pediatric burn patients... American Burn Association 39th Annual Meeting, March 20-23, 2007, Manchester Grand Hyatt, San Diego, California. Journal of Burn Care & Research. 2007;28(2):S137-S.
20. Berger MM, Bernath MA, Chiolero RL. Resuscitation, anaesthesia and analgesia of the burned patient. Curr Opin Anaesthesiol. 2001;14(4):431-5.
21. Azzopardi EA, McWilliams B, Iyer S, Whitaker IS. Fluid resuscitation in adults with severe burns at risk of secondary abdominal compartment syndrome--an evidence based systematic review. Burns. 2009;35(7):911-20.

22. Mahid SS, Hornung CA, Minor KS, Turina M, Galandiuk S. Systematic reviews and meta-analysis for the surgeon scientist. Br J Surg. 2006;93(11):1315-24.
23. Ball CG, Kirkpatrick AW, Karmali S, Malbrain ML, Gmora S, Mahabir RC*, et al.* Tertiary abdominal compartment syndrome in the burn injured patient. J Trauma. 2006;61(5):1271-3.
24. Blinderman C, Lapid O, Shaked G. Abdominal compartment syndrome in a burn patient. Isr Med Assoc J. 2002;4(10):833-4.
25. Britt RC, Gannon T, Collins JN, Cole FJ, Weireter LJ, Britt LD. Secondary abdominal compartment syndrome: risk factors and outcomes. Am Surg. 2005;71(11):982-5.
26. Corcos AC, Sherman HF. Percutaneous treatment of secondary abdominal compartment syndrome. J Trauma. 2001;51(6):1062-4.
27. Ivy ME, Atweh NA, Palmer J, Possenti PP, Pineau M, D'Aiuto M. Intra-abdominal hypertension and abdominal compartment syndrome in burn patients. J Trauma. 2000;49(3):387-91.
28. Jensen AR, Hughes WB, Grewal H. Secondary abdominal compartment syndrome in children with burns and trauma: a potentially lethal complication. J Burn Care Res. 2006;27(2):242-6.
29. Lamb CM, Berry JE, DeMello WF, Cox C. Secondary abdominal compartment syndrome after military wounding. J R Army Med Corps. 2010;156(2):102-3.
30. Levis C, Ali F. Significance of early diagnosis of abdominal compartment syndrome in major burns. Can J Plast Surg. 2006;14(3):175-8.
31. Mayes T, Gottschlich MM, Warden GD. Nutrition intervention in pediatric patients with thermal injuries who require laparotomy. J Burn Care Rehabil. 2000;21(5):451-6; discussion 0-1.
32. Parra MW, Al-Khayat H, Smith HG, Cheatham ML. Paracentesis for resuscitation-induced abdominal compartment syndrome: an alternative to decompressive laparotomy in the burn patient. J Trauma. 2006;60(5):1119-21.
33. Pirson J, Zizi M, Jacob E, Deleuze JP. Acute ischemic optic neuropathy associated with an abdominal compartment syndrome in a burn patient. Burns. 2004;30(5):491-4.
34. Poulakidas S, Kowal-Vern A. Component separation technique for abdominal wall reconstruction in burn patients with decompressive laparotomies. J Trauma. 2009;67(6):1435-8.

35. Rocourt DV, Hall M, Kenney BD, Fabia R, Groner JI, Besner GE. Respiratory failure after pediatric scald injury. J Pediatr Surg. 2011;46(9):1753-8.
36. Rogers AD, Karpelowsky J, Millar AJ, Argent A, Rode H. Fluid creep in major pediatric burns. Eur J Pediatr Surg. 2010;20(2):133-8.
37. Thamm OC, Leitsch S, Spanholtz TA, Perbix W, Spilker G. Complicated course of a burned patient with severe inhalation injury: A case report. Perioperative Med. 2009;1(4):224-7.
38. Wilson MD, Dziewulski P. Severe gastrointestinal haemorrhage and ischaemic necrosis of the small bowel in a child with 70% full-thickness burns: a case report. Burns. 2001;27(7):763-6.
39. Chung JY, Latenser BA, Burke BA, Lewis RW, II, Wibbenmeyer LA. Pilot study: percutaneous drainage prevents abdominal compartment syndrome in significant thermal injury... American Burn Association 39th Annual Meeting, March 20-23, 2007, Manchester Grand Hyatt, San Diego, California. Journal of Burn Care & Research. 2007;28(2):S146-S.
40. Hershberger RC, Hunt JL, Arnoldo BD, Purdue GF. Abdominal compartment syndrome in the severely burned patient. J Burn Care Res. 2007;28(5):708-14.
41. Hobson KG, Young KM, Ciraulo A, Palmieri TL, Greenhalgh DG. Release of abdominal compartment syndrome improves survival in patients with burn injury. J Trauma. 2002;53(6):1129-33; discussion 33-4.
42. Keramati M, Srivastava A, Sakabu S, Rumbolo P, Smock M, Pollack J*, et al.* The Wittmann Patch(trademark) as a temporary abdominal closure device after decompressive celiotomy for abdominal compartment syndrome following burn. Burns. 2008;34(4):493-7.
43. Latenser BA, Beins NT, Born JM, Chung JY. Closed percutaneous drainage is definitive treatment of abdominal compartment syndrome in burn patients... Proceedings of the American Burn Association: 40th Annual Meeting, Tuesday through Friday, April 29 - May 2, 2008, Hyatt Regency Chicago, Chicago, Illinois. Journal of Burn Care & Research. 2008;29(2):S112-S.

44. Latenser BA, Kowal-Vern A, Kimball D, Chakrin A, Dujovny N. A pilot study comparing percutaneous decompression with decompressive laparotomy for acute abdominal compartment syndrome in thermal injury. J Burn Care Rehabil. 2002;23(3):190-5.
45. Van Niekerk W, Markell KW, Cancio L. Abdominal surgery in burn patients: The rise of abdominal compartment syndrome has not eclipsed dead gut. Intensive Care Med. 2010;36:S382.
46. Oda J, Yamashita K, Inoue T, Harunari N, Ode Y, Mega K*, et al.* Resuscitation fluid volume and abdominal compartment syndrome in patients with major burns. Burns. 2006;32(2):151-4.
47. Markell KW, Renz EM, White CE, Albrecht ME, Blackbourne LH, Park MS*, et al.* Abdominal complications after severe burns. J Am Coll Surg. 2009;208(5):940-7; discussion 7-9.
48. Handschin AE, Vetter S, Jung FJ, Guggenheim M, Kunzi W, Giovanoli P. A case-matched controlled study on high-voltage electrical injuries vs thermal burns. J Burn Care Res. 2009;30(3):400-7.
49. Klein MB, Hayden D, Elson C, Nathens AB, Gamelli RL, Gibran NS*, et al.* The association between fluid administration and outcome following major burn: a multicenter study. Ann Surg. 2007;245(4):622-8.
50. Ennis JL, Chung KK, Renz EM, Barillo DJ, Albrecht MC, Jones JA*, et al.* Joint Theater Trauma System implementation of burn resuscitation guidelines improves outcomes in severely burned military casualties. J Trauma. 2008;64(2 Suppl):S146-51; discussion S51-2.
51. Chung KK, Wolf SE, Cancio LC, Alvarado R, Jones JA, McCorcle J*, et al.* Resuscitation of severely burned military casualties: fluid begets more fluid. J Trauma. 2009;67(1529-8809 (Electronic)):231-7.
52. O'Mara MS, Slater H, Goldfarb IW, Caushaj PF. A prospective, randomized evaluation of intra-abdominal pressures with crystalloid and colloid resuscitation in burn patients. J Trauma. 2005;58(5):1011-8.
53. Oda J, Ueyama M, Yamashita K, Inoue T, Noborio M, Ode Y*, et al.* Hypertonic lactated saline resuscitation reduces the risk of abdominal compartment syndrome in severely burned patients. J Trauma. 2006;60(1):64-71.

54. Dulhunty JM, Boots RJ, Rudd MJ, Muller MJ, Lipman J. Increased fluid resuscitation can lead to adverse outcomes in major-burn injured patients, but low mortality is achievable. Burns. 2008;34(8):1090-7.
55. Oda J, Yamashita K, Inoue T, Hosotsubo H, Aoki Y, Ode Y*, et al.* Acute lung injury and multiple organ dysfunction syndrome secondary to intra-abdominal hypertension and abdominal decompression in extensively burned patients. J Trauma. 2007;62(6):1365-9.
56. Cheatham ML, Safcsak K, Fiscina C, Ducoin C, Smith HG, Promes JT*, et al.* Advanced age may limit the survival benefit of open abdominal decompression. Am Surg. 2011;77(7):856-61.
57. Oda J, Ueyama M, Yamashita K, Inoue T, Harunari N, Ode Y*, et al.* Effects of escharotomy as abdominal decompression on cardiopulmonary function and visceral perfusion in abdominal compartment syndrome with burn patients. J Trauma. 2005;59(2):369-74.
58. Ramirez OM, Ruas E, Dellon AL. "Components separation" method for closure of abdominal-wall defects: an anatomic and clinical study. Plast Reconstr Surg. 1990;86(3):519-26.
59. Palmieri T, Lavrentieva A, Greenhalgh D. An assessment of acute kidney injury with modified RIFLE criteria in pediatric patients with severe burns. Intens Care Med. 2009;35(12):2125-9.
60. Soltani A, Karsidag S, Garner W. A ten-year experience with hemodialysis in burn patients at Los Angeles County + USC Medical Center. J Burn Care Res. 2009;30(5):832-5.
61. Mosier MJ, Pham TN, Klein MB, Gibran NS, Arnoldo BD, Gamelli RL*, et al.* Early enteral nutrition in burns: compliance with guidelines and associated outcomes in a multicenter study. J Burn Care Res. 2011;32(1):104-9.
62. Yenikomshian H, Reiss M, Nabavian R, Garner WL. Gastric feedings effectively prophylax against upper gastrointestinal hemorrhage in burn patients. J Burn Care Res. 2011;32(2):263-8.
63. Sanchez MS, Herrero E, Asensio MJ, Araujo P, Galvan B, Denia R*, et al.* Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) in critically burn patients. Burns. 2009;35((2009)):S46.

64. Malbrain ML, Jacobs A, De laet I, Van Regenmortel N, Schoonheydt K, Dits H. Incidence and prognosis of intra-abdominal hypertension and abdominal compartment syndrome in severely burned patients. Intens Care Med. 2010;36((2010)):S375.

Chapter 6

Prevalence of intra-abdominal hypertension and markers for associated complications in severe burn patients; a multicenter prospective cohort study (BURNIAH study)

SUBMITTED

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ABSTRACT

Background: Severely burned patients are at risk for intra-abdominal hypertension (IAH) and related complications such as organ failure, abdominal compartment syndrome (ACS), and death. The aim of this study was to determine the prevalence of IAH among severely burned patients. The secondary aim was to determine the value of urinary intestinal fatty acid binding protein (I-FABP) as an early marker for IAH-associated complications.

Methods: A prospective observational study of 58 adult patients with burn injuries ≥15% of total body surface area (TBSA) admitted in two burn centers in the Netherlands was conducted. Intra-abdominal pressure (IAP) and urinary I-FABP were measured every six hours during 72 hours. A linear mixed-effect model was used to determine the correlation between I-FABP levels and IAP. Diagnostic characteristics of urinary I-FABP levels were tested using receiver operating characteristics (ROC) analysis. Multi-level modeling was used to determine the prognostic role of repeated I-FABP.

Results: Thirty-one (53%) patients developed IAH, seventeen (29%) patients developed new organ failure, but no patients developed ACS. Patients had burn wounds of 29% (P_{25}-P_{75} 19%-24%) TBSA. Ln-transformed levels of urinary I-FABP and IAP were inversely correlated with an estimate of -0.06 (95% CI: -0.10 to -0.02; p=0.002). Maximal urinary I-FABP levels had a fair discriminatory ability for patients with IAH with an area under the ROC curve of 74% (p=0.001). Urinary I-FABP levels had no predictive value for IAH or new organ failure in severe burn patients.

Conclusions: The prevalence of IAH among patients with ≥15% TBSA burned was 53%. None of the patients developed ACS. In this population, a diagnostic or predictive value of urinary I-FABP levels for IAH and related organ failure could not be proven.

INTRODUCTION

Patients with severe burns are at risk for complications and sequelae resulting in morbidity and death. This risk increases with burn severity. Intra-abdominal hypertension (IAH) and subsequent abdominal compartment syndrome (ACS) are complications that occur in severely burned patients, both are associated with poor outcome. These complications result from massive fluid resuscitation and capillary leakage. Modern resuscitation regimes aim to prevent IAH and ACS from occurring. Although the risk has significantly decreased, these complications are still not completely preventable (1, 2). If IAH and ACS occur, keeping its consequences under control is the only thing left. Early identification of patients at risk for IAH and ACS facilitates decompressive treatment and thereby prevents associated morbidity and mortality (3). In order to improve this early identification, epidemiologic knowledge and diagnostic tools for that aim are needed.
Severe burn injury can lead to burn shock within 24 to 48 hours and is a result of a depression of cardiac output which is induced by cytokines and increased capillary permeability. This can lead to massive fluid shifts and hypotension requiring extensive fluid suppletion (4). The effect of fluid shift is called “third spacing” referring to an extra space to where the fluid shifts to. This space or compartment frequently concerns the abdomen. Increasing abdominal content results in IAH and can result in ACS. ACS can also occur in patients with circumferential trunk burn, which decreases abdominal compliance and requires acute escharotomy. Especially patients with both conditions are at risk. Diagnostic tools that predict which patient will develop such IAP-related complications are lacking.
Besides hyper-hydration and decreased abdominal wall compliance, indication for damage control laparotomy is another important risk factor for ACS (WSACS). These risk factors apply to a relevant number of patients admitted in burn centers. ACS associated mortality among severe burn patients is estimated at 75% (5). Early identification of patients at risk for ACS, IAH-related morbidity and mortality will likely benefit these patients. The current gold standard requires intra-bladder pressure measurements (6). This is a simple, non-invasive measuring technique, yielding immediate results. However, the level of IAP is neither an indicator for the timing of surgical therapy, nor is it a reliable indicator for clinical outcome (7).

In this context, Intestinal Fatty Acid Binding Protein (I-FABP) may be of interest. Evidence is accumulating that the intestines are central in the origin of posttraumatic sequelae (8-10). Loss of intestinal barrier integrity seems to be an early event in severe illness and trauma that plays a crucial role in the subsequent development of the systemic inflammatory response. The intestinal barrier is maintained by a lining of intestinal epithelial cells (enterocytes) and tight junctions that seal the paracellular space between adjacent enterocytes preventing toxins and bacteria from entering the circulation. Both enterocyte damage and tight junction loss can be triggered by IAH; these can be quantified by levels of I-FABP (11-12). This marker is rapidly released upon intestinal integrity loss and easily detectable in urine (13).

The primary aim of this study was to determine the prevalence of IAH an ACS in severe burn patients. The secondary aim was to determine the diagnostic value of urinary intestinal fatty acid binding protein (I-FABP) as an early marker for IAH-associated complications.

MATERIALS AND METHODS

This prospective, observational study was conducted in two burn centers. The study was approved by the Medical Research Ethics Committee (MREC) in the principal study hospital (reference number M012-021) and by the local hospital board in the participating center (reference number L2013-23). Signed informed consent by patient or proxy was obtained.

Patients

Adult patients (18 years or older) admitted between January 1, 2013 and December 31, 2016, with burn wounds with a total body surface area (TBSA) of at least 15% were included. Patients were enrolled as soon as possible, maximally within 48 hours after meeting the eligibility criteria. Patients in whom intra-bladder pressure measurement was contra-indicated or unreliable were excluded from the study.

Treatment

Upon admission, patients were treated according to local protocols. Patients in whom IAH or ACS was identified were treated using the international guidelines of the WSACS (6). The IAH/ACS Management Algorithm provides a decision tree for the follow-up of patients related to the IAP level.

Sample collection

During the first 72 hours after enrolment, a urine sample was collected every six hours. Samples were kept on ice, frozen at −80°C within two hours after collection, and stored until further analysis.

Data collection

Patient characteristics, ICU admission diagnosis, Simplified Acute Physiology Score (SAPS) II, Sequential Organ Failure Assessment score (SOFA, on day 1 to 4), Acute Physiology and Chronic Health Evaluation (APACHE) II scores, burn injury characteristics, presence of abdominal and thoracic burns, inhalation injury, intubation status and ventilation settings, hemodynamic parameters, intra-abdominal pressure (IAP), diuresis, serum levels of

lactate, lactate dehydrogenase (LDH), creatine kinase (CK), pH, base excess, C-reactive protein (CRP), albumine, and creatinine, colloid osmotic pressure, administered resuscitation volume (crystalloids and colloids), and administered transfusions were recorded from the patients' medical files. The administered volume of crystalloids above the predicted requirement according to Parklands formula (4 mL/kg body weight/% TBSA), and the Ivy score (exceeding the ratio of 0.25 L/kg administered volume during study period) were calculated (14).

Urinary concentrations of I-FABP were analyzed in duplicate using a highly specific, commercially available enzyme-linked immunosorbent assay (ELISA) that selectively detects human I-FABP (HyCult Biotechnology, Uden, The Netherlands). I-FABP levels in urine were adjusted to urinary creatinine levels. Intra-abdominal pressure was also measured every six hours during the first 72 hours after enrolment. Complications and events as well as any (secondary) intervention performed such as decompression laparotomy were recorded. Monitoring of occurrence and extent of new organ failure was based upon change in SOFA score. Furthermore, lengths of stay in the ICU and in-hospital mortality were registered.

Outcome parameters

Intra-abdominal pressure was measured using an intra-bladder technique according to Kron *et al*. (15) with an instilling volume of 20 mL of sodium chloride 0.9% solution. IAP was measured every six hours. Intra-abdominal hypertension and abdominal compartment syndrome were diagnosed in compliance with WSACS guidelines. For research purposes, IAH was determined if the average IAP of 4 consecutive measurements (thus during 24 hours) was ≥12 mmHg. New organ failure was diagnosed if the score in one of six SOFA sub-domains increased to ≥3, compared to a maximum score of 2 on the day before. ACS was diagnosed if an IAP above 20 mmHg and new organ failure occurred during the same follow-up window (of 24 hours) in which the SOFA score was calculated.

Statistical analysis

An overall population of 100 patients would be sufficient to detect a 0.5 SD increase to 26±10 ng/mL in I-FABP level in patients with IAH (two-sided test with an α level of 0.05) with at least 85% statistical power (5). Statistical analyses were performed using IBM SPSS statistics 22 (IBM, Armonk, NY, USA). Receiver operating characteristic (ROC) analysis and calculation of the Youden index associated criterions were performed with MedCalc Statistical Software version 17.4 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2017).

Normality of continuous data was assessed by the Shapiro Wilk test. Homogeneity of variances was tested using the Levene's test. Since all continuous data deviated from the standard normal distribution, they are presented as median and quartiles and compared using the Mann-Whitney U-test. Statistical significance was accepted at $p<0.05$.

A linear mixed-effect model was used to determine the correlation between I-FABP levels and IAP. For this analysis, restricted maximum likelihood method was used and a random intercept and slope were considered. BMI, age, gender, APACHE II score, TBSA, presence of abdominal and thoracic burns, and inhalation injury, resuscitation volume administered in first 8 hours and 24 hours, intra-abdominal pressure, mean arterial pressure, levels of lactate and CRP, base excess and time from baseline measurement were entered as covariates into the model in order to evaluate their effect on the correlation between I-FABP level and IAP.

Diagnostic characteristics of urinary I-FABP levels on the onset of IAH and new organ failure were tested using ROC analysis. The corresponding cut-off values and associated sensitivity and specificity were determined. Areas under the ROC curve are shown as measure of overall diagnostic performance.

The predictive value of I-FABP levels on IAH and organ failure was visualized by plotting re-aligned measurements of the biomarker on the moment (T=0) of peak IAP. Median (P_{25}-P_{75}) I-FABP levels were plotted separately for patients with the outcome of interest and control patients.

Since multiple IAP and I-FABP measurements of the same patient are more associated with each other than they are between patients, a multi-level model was used in order to determine the prognostic role of repeated I-FABP on development of IAH, new organ dysfunction, or ACS. A generalized linear mixed model (GLMM) framework with binomial logit link was chosen for that aim. For this analysis, the binary outcomes of IAH and new organ failure were used as dependent variables. Patient ID was used as a clustering variable as up to 13 measurements per patient were available. BMI, age, gender, APACHE II score, TBSA of burn, presence of abdominal and thoracic burns and inhalation injury, resuscitation volume administered in first 8 hours and 24 hours, intra-abdominal pressure (only for the analysis of organ failure), mean arterial pressure, levels of lactate and CRP, base excess, and time from baseline measurement were entered into the model as covariate in order to evaluate their effect on the relation between I-FABP level and outcome. Data points that occurred after the event of interest were removed from this analysis. A random intercept and slope were considered. Results were expressed as odds ratios with corresponding 95% confidence interval and p-values.

RESULTS

A total of 58 patients were included in two burn centers (Figure 1). Unexpected difficulties in obtaining informed consent and logistic difficulties resulted in a low inclusion rate. Therefore, the study was ended prematurely before the target number of 100 inclusions was met. No patients were lost to follow-up. Clinical baseline characteristics of 58 included patients are shown in Table 1. Patients had a median age of 48 years (P_{25}-P_{75} 30-58 years), a median APACHE-II score of 11 (P_{25}-P_{75} 8-17) and a median burned TBSA of 29% (P_{25}-P_{75} 19-24%). Thirty-six (62%) patients were male, 51 (88%) patients had a flame burn, 31 (53%) patients developed IAH and 17 (29%) patients developed new organ failure. None of the patients was diagnosed with ACS. BMI and lactate levels were significantly higher in patients who developed IAH than in patients who did not. Seven (12%) patients died during the study period, 5 (16%) patients had IAH and 2 (7%; p = 0.432) had no IAH.

The median urinary I-FABP levels (uncorrected and corrected for creatinine excretion) at baseline were not statistically significant different between groups with or without IAH (Figure 2). Among patients with IAH, baseline levels of I-FABP between groups with and without new organ failure during the study period were not different either. Median levels of repeated urinary I-FABP measurements (uncorrected, corrected for creatinine excretion, untransformed, as well as logarithmic transformed) in patients with or without IAH and organ failure are shown in Figure 3. Although all median urinary I-FABP levels (corrected for creatinine excretion) seemed higher in patients who developed new organ failure than in patients who did not, none of the differences reached statistical significance (Figure 3D).
Realigned measurements of I-FABP (corrected for creatinine excretion; realignment according to peak levels of IAP during study period) demonstrated no statistically significant peaks prior to the peak value of IAP (Figure 4). Similarly as described above, the median I-FABP levels seamed consistently higher in patients with new organ failure than in patients without, but never reached statistical significance.

Univariate correlation analysis between intra-abdominal pressure and I-FABP level showed an unexpected inverse correlation of IAP with both uncorrected and corrected Ln-

transformed urinary I-FABP levels, with an estimate of -0.06 (p=0.001 and p=0.002, respectively). This effect was more pronounced in the subgroup analysis of patients with IAH; here the correlation estimates within the subgroup were -0.08 (p<0.001) and -0.09 (p<0.001) for uncorrected and corrected Ln-transformed urinary I-FABP, respectively (Table 2). Multivariable analysis confirmed statistically significant inverse correlation for corrected, Ln-transformed urinary I-FABP levels (*i.e.*, corrected for creatinine excretion; p=0.048 for all patients and p=0.043 for patients with IAH) and IAP.

The maximal I-FABP levels per patients showed to be indicative for IAH with a sensitivity of 75% and a specificity of 70% for uncorrected I-FABP levels and a sensitivity of 75% and specificity of 74% for I-FABP levels corrected for creatinine excretion. The overall accuracy was fair with an area under ROC curve 0.74 in both cases (p=0.001 and p=0.002 respectively; Table 3). Other expressions of urinary I-FABP showed no significant discriminatory ability between patients with or without IAH or organ failure.

Unadjusted generalized linear mixed model analysis demonstrated no statistically significantly predictive value of repeated I-FABP measurements for the development of IAH or new organ failure (Table 4). Adjusting for covariates did not improve any of the prediction models in this study.

DISCUSSION

The prevalence of intra-abdominal hypertension in patients ≥15% TBSA burned was 53%. None of these patients developed abdominal compartment syndrome. In this population, a diagnostic or predictive value of urinary I-FABP levels for IAH and related organ failure could not be proven.

The prevalence of IAH in severely burned patients as found in this study is comparable with findings from previous studies. A systematic review published in 2013 reported a pooled prevalence of 65-75% in severely burned patients, but the studies used various cut off values for the percentage of TBSA burned (5). A more recent African study reported an IAH-prevalence of 58% in a group of 64 adults and children with a TBSA burned of 25% and 20%, respectively (2). As opposed to the IAH prevalence, the absence of ACS cases in the current study contrasts literature. An observational study included 56 mechanically ventilated patients with severe burn injuries between 2007 and 2009 and reported that 16 patients developed ACS (29%). It is known that reduction of crystalloid resuscitation volume, early use of albumin and vasopressors reduces the risk of ACS (16). Reduction of IAH and ACS prevalence is confirmed in several studies and has uniformly been attributed to modern restrained resuscitation regimes as promoted by the WSACS guidelines (17, 18). The present study is the first epidemiological study of severe burn patients that reports no cases of ACS. Most likely, both IAP monitoring, leading to increased awareness of IAP related problems, and restrictive resuscitation regimes have contributed to the absence of ACS cases in this series. It seems unlikely however that the problem of secondary ACS (due to large resuscitation volumes) is now solved, as the prevalence of IAH is still very high. Although not specifically studied, our results suggest that the WSACS guidelines are efficient in the prevention of ACS in patients at risk.
The value of urinary intestinal fatty acid binding protein (I-FABP) levels as an early marker for IAH-associated complications was limited in this study. High I-FABP levels were hypothesized to be indicative for imminent ACS and subsequent early treatment would benefit outcome. As no cases of ACS have been observed, this hypothesis could not be tested. Nevertheless, an inverse correlation between IAP and I-FABP levels was demonstrated. This inverse correlation between IAP and I-FABP was unexpected.

Especially since increased IAP causes reduced blood flow which theoretically induces intestinal ischemia and subsequently increased levels of I-FABP (19-22). The inverse correlation seemingly suggests that increased IAP would rather be protective for intestinal mucosa, though a causal relation could not be demonstrated. Also, data of the yet unpublished I-Fabulous study confirmed a positive correlation between IAP and I-FABP in ICU patients with two or more risk factors for IAH (23).

This study has several limitations. First, the study was ended prematurely as it turned out to be more difficult to obtain informed consent than anticipated. Whether or not that was due to the nature and severity of the injuries is unknown. After a period of 48 months, 58 patients were included without any abdominal compartment syndrome had emerged. Formally, this study is underpowered as a result of this inclusion number. But even after the inclusion of the calculated 100 patients, we believe that the rate of abdominal compartment syndrome would still be too low to draw statistically sound conclusions. A second limitation is that this series consists of non-consecutive patients with a TBSA ≥15%. For epidemiological purposes, a consecutive series of patients would be preferred. The non-consecutive series was due to unexpected difficulties in obtaining informed consent. This may have led to either an underestimation or an overestimation of the prevalence of IAH and ACS. As a final limitation, it remains challenging to relate the definition of organ failure to that of ACS. Each patient with ACS suffers from organ failure, but not each organ failure is caused by ACS. Organ failure is best determined using the SOFA score, but this is normally determined only once a day. This is not ideal since an abdominal compartment syndrome can develop within a few hours. Diagnosing ACS, and specifically at what moment ACS emerged, remains quite subjective. The hypothesis that the I-FABP biomarker can provide a more objective measure for this diagnosis could not be confirmed. For future research D-lactate and ischemia modified albumin (IMA) or combinations of markers may be of interest (24).

CONCLUSION

The prevalence of IAH among severely burned patients with a TBSA ≥15% is 53%. None of the patients developed abdominal compartment syndrome. In this population, a diagnostic or predictive value of urinary I-FABP levels for IAH and related organ failure could not be proven.

Figure 1: Flow chart

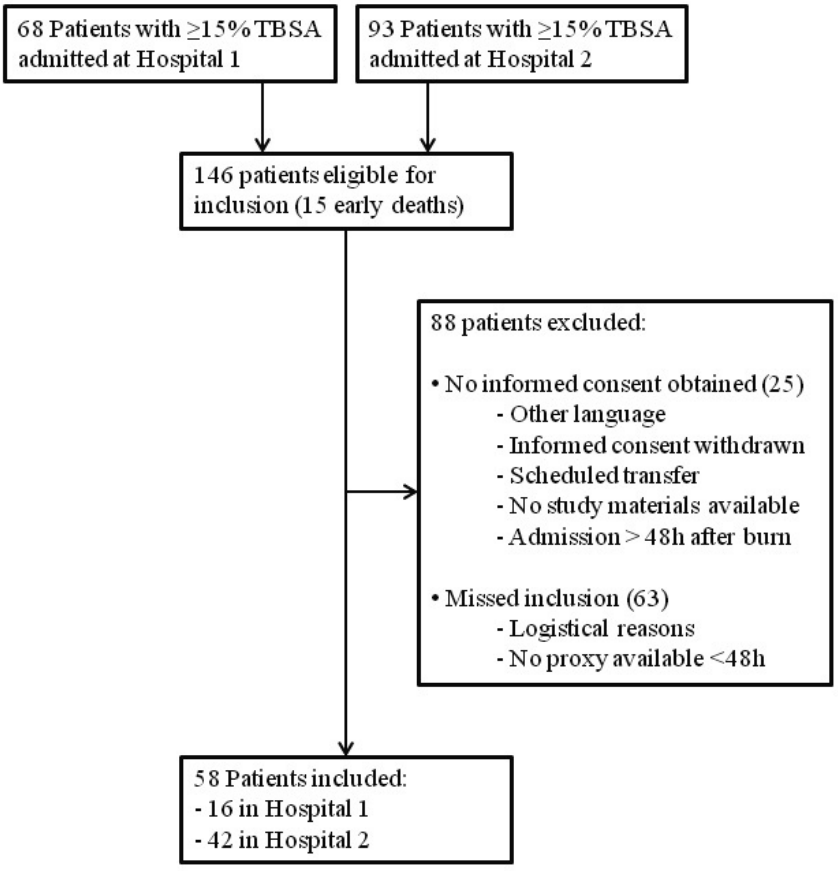


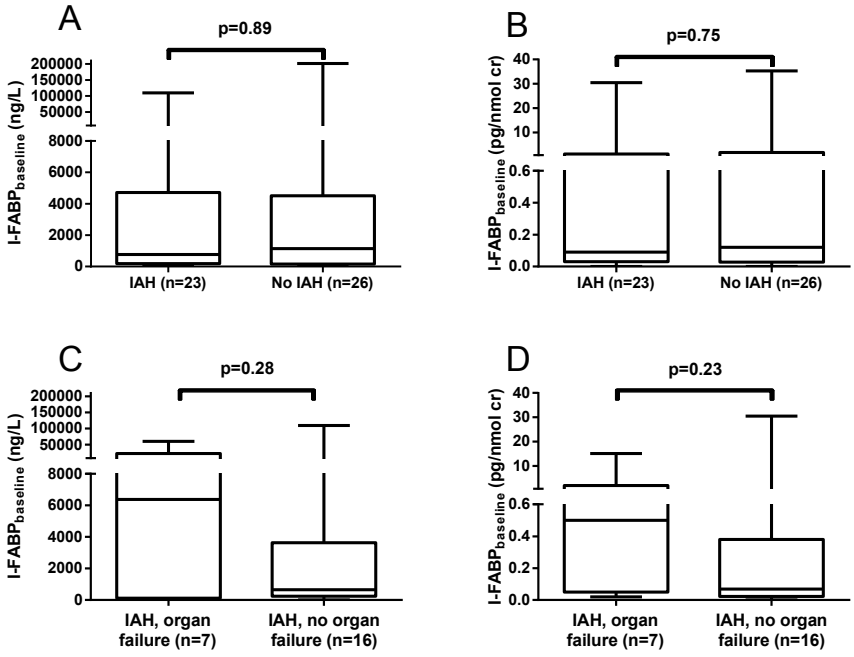
Table 1: Baseline characteristics for patients with and without intra-abdominal hypertension

	All N=58	IAH N=31 (53%)	No IAH N=27 (47%)	P-value
Age (years)	48 (30-58)	51 (38-59)	42 (28-54)	0.085
Male	36 (62%)	19 (61%)	17 (63%)	1.000
BMI (kg/m^2)	26 (23-29)	28 (24-31)	24 (23-27)	0.007
ASA classification I	29 (50%)	12 (39%)	17 (63%)	0.214*
ASA classification II	17 (29%)	11 (36%)	6 (22%)	
ASA classification III	10 (17%)	6 (19%)	4 (15%)	
ASA classification IV	2 (3%)	2 (7%)	0 (0%)	
No co-morbidity	19 (33%)	8 (26%)	11 (41%)	0.270
APACHE II score	11 (8-17)	12 (8-17)	10 (7-14)	0.223
SAPS II score	26 (22-34)	30 (23-36)	26 (20-31)	0.085
SOFA score	4 (2-6)	4 (2-5)	3 (2-6)	0.937
TBSA (%)	29 (19-42)	21 (18-45)	30 (22-40)	0.235
Flame burn	51 (88%)	29 (94%)	22 (82%)	0.233
Scald burn	7 (12%)	2 (6%)	5 (18%)	
Abdominal burns	41 (71%)	21 (68%)	20 (74%)	0.773
Circular abdominal burns	8 (20%)	4 (19%)	4 (20%)	1.000
Inhalation injury	28 (48%)	16 (52%)	12 (44%)	0.610
Crystalloid <8h (L)	5.9 (3.9-10.1)	6.0 (4.0-11.0)	5.8 (3.1-9.2)	0.895
Colloid <8h (mL)	106 (63-440)	440 (58-474)	98 (63-131)	0.482
Crystalloid <24h (L)	11.7 (8.1-15.8)	13.3 (8.2-15.8)	10.9 (7.7-16.4)	0.691
Colloid <24h (mL)	0 (0-0)	0 (0-0)	0 (0-563)	0.616
Ivy Score	211 (148-304)	210 (150-307)	215 (127-289	0.797
Exceeding Parkland formula	34 (59%)	18 (58%)	16 (59%)	1.000
IAP (mmHg)	10 (7-14)	13 (11-15)	6 (4-8)	<0.001
MAP (mmHg)	82 (72-93)	82 (72-100)	73 (73-90)	0.598
PEEP (cmH_2O)	7 (5-8)	7 (5-9)	8 (5-8)	0.917
I-FABP urine (pg/nmol cr)	0.1 (0.0-1.4)	0.1 (0.0-1.2)	0.1 (0.0-1.7)	0.749
Lactate (mmol/L)	2.2 (1.5-3.4)	2.6 (1.9-3.8)	2.1 (1.2-2.5)	0.045
Serum creatiine (µmol/L)	69 (55-86)	75 (57-91)	66 (54-85)	0.321
Mortality	7 (12%)	5 (16%)	2 (7%)	0.432

Data are presented as median (P_{25} - P_{75}), or number with corresponding percentage (%). P-values were calculated using a Mann Whitney U-test, Fisher exact test or *Pearson Chi Square test.

APACHE, Acute Physiology and Chronic Health Evaluation; ASA, American Society of Anesthesiologists physical status classification system; BMI, body mass index; Cr, creatinine; IAH, intra-abdominal hypertension; IAP, intra-abdominal pressure; Ivy Score, fluid resuscitation volume during study period per kilogram body weight; MAP, Mean Arterial Pressure; N.D., not determined; PEEP, positive end expiratory pressure; SAPS, Simplified Acute Physiology Score; SOFA, sequential organ failure assessment; TBSA, total body surface area burned.

Figure 2: I-FABP levels at baseline in patients who developed IAH (A and B) or organ failure (C and D)

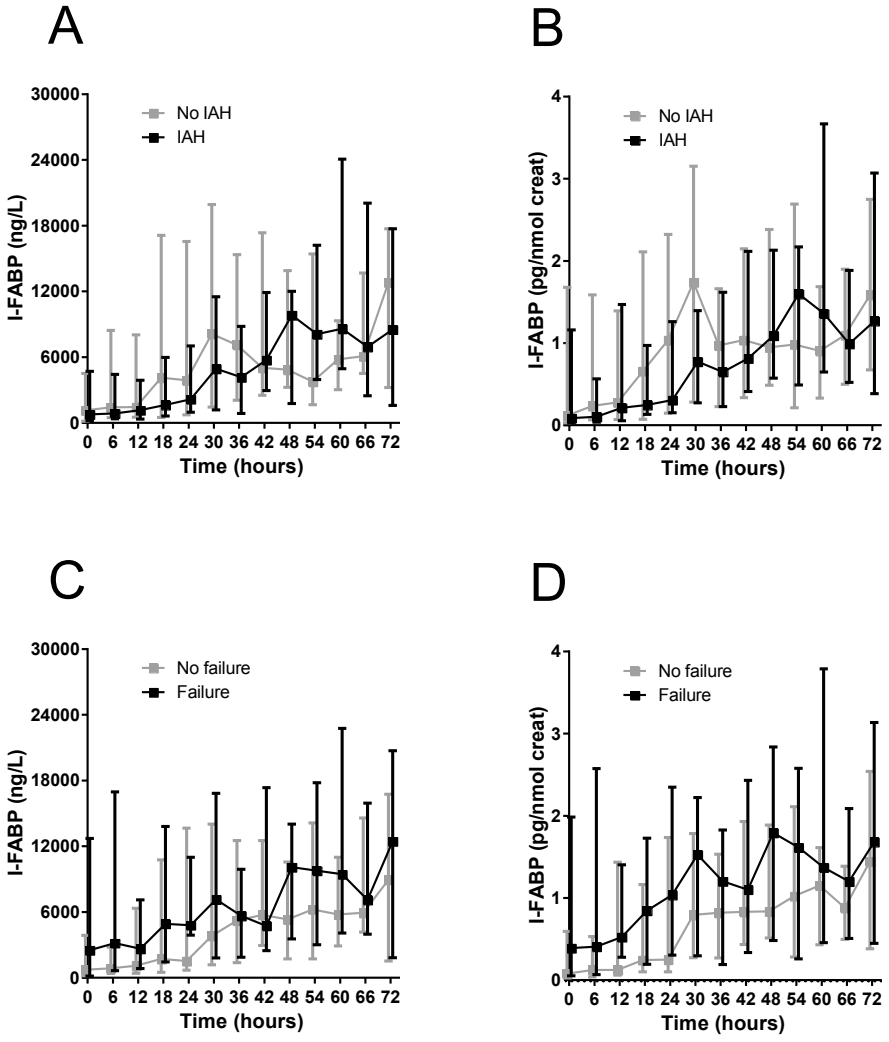


Data are shown as median (P_{25} - P_{75}) I-FABP levels, uncorrected (A and C) and corrected (B and D) for creatinine excretion.

Cr, creatinine; IAH, intra-abdominal hypertension; I-FABP, intestinal fatty acid binding protein.

P-values are calculated using Mann-Whitney test.

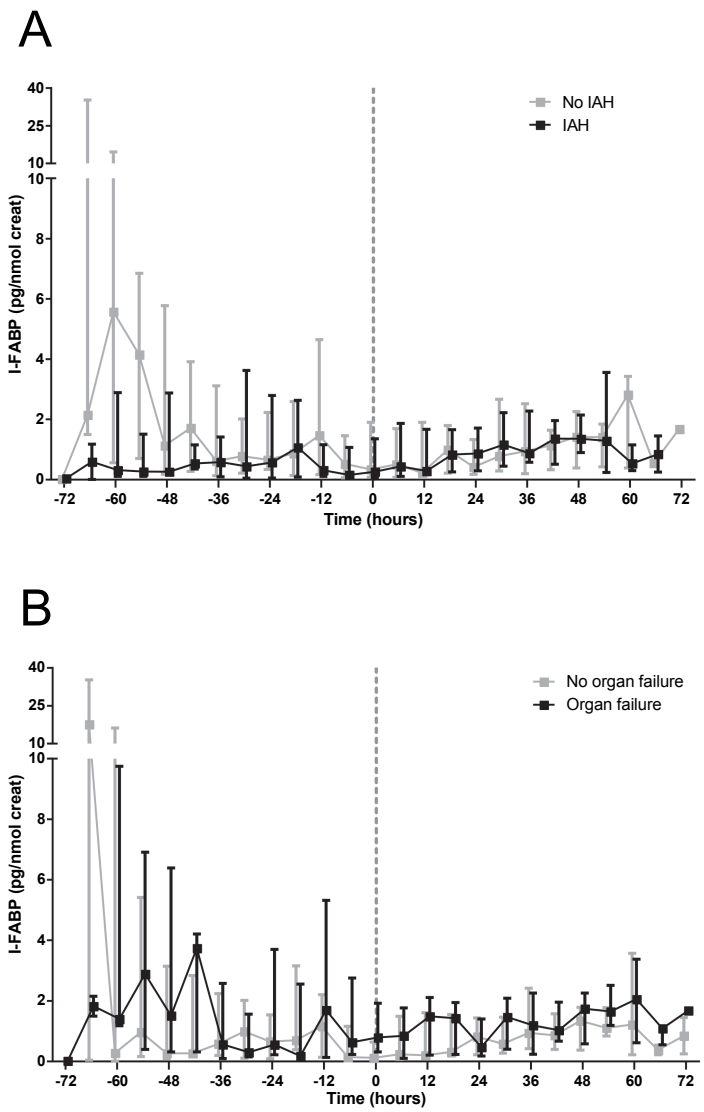
Figure 3: Changes in I-FABP levels over time in patients with or without intra-abdominal hypertension (A and B) or new organ failure (C and D)



Data are shown as median (P_{25} - P_{75}) I-FABP levels, uncorrected (A and C) and corrected (B and D) for creatinine excretion.

Creat, creatinine; IAH, intra-abdominal hypertension; I-FABP, intestinal fatty acid binding protein.

Figure 4: Time course of I-FABP levels before and after peak values of IAP, for patients with or without IAH (A) or new organ failure (B)



Data are represented as median with P_{25}-P_{75}. Zero denotes the moment of peak value of IAP.

Creat, creatinine; IAH, intra-abdominal hypertension; IAP, intra-abdominal pressure; I-FABP, intestinal fatty acid binding protein.

Table 2: Univariate and multivariable correlation between I-FABP level and intra-abdominal pressure

	Urinary I-FABP (ng/L)			Urinary I-FABP (pg/nmol creat)		
	N	Estimate (95% CI)	P	N	Estimate (95% CI)	P
UNTRANSFORMED I-FABP						
Unadjusted linear mixed model						
All patients	479	-275.25 (-587.60 – 37.09)	0.084	477	-0.02 (-0.10 – 0.06)	0.557
Only patients with IAH	242	-290.52 (-562.85 – -18.18)	**0.037**	240	-0.03 (-0.13 – 0.07)	0.583
Adjusted linear mixed model						
All patients	124	-243.83 (-775.14 – 287.48) [A]	0.338	123	0.16 (-0.14 – 0.45) [A]	0.285
Only patients with IAH	72	-360.18 (-851.07 – 130.71) [B]	0.147	71	0.002 (-0.23 – 0.23) [B]	0.983
Ln-TRANSFORMED I-FABP						
Unadjusted linear mixed model						
All patients	478	-0.06 (-0.10 – -0.03)	**0.001**	477	-0.06 (-0.10 – -0.02)	**0.002**
Only patients with IAH	241	-0.08 (-0.13 – -0.04)	**<0.001**	240	-0.09 (-0.14 – -0.05)	**<0.001**
Adjusted linear mixed model						
All patients	167	-0.05 (-0.10 – 0.00) [C]	0.077	166	-0.05 (-0.10 – 0.00) [E]	**0.048**
Only patients with IAH	72	-0.04 (-0.12 – 0.05) [D]	0.389	84	-0.06 (-0.11 – -0.00) [E]	**0.043**

The coefficient estimates for the linear mixed models are shown with 95% confidence interval between brackets.

CI, confidence interval; creat, creatinine; IAH, intra-abdominal hypertension; I-FABP, intestinal fatty acid binding protein; N, number of samples (this number includes multiple samples of same patients).

[A] Adjusted for lactate level and TBSA; [B] Adjusted for BMI, lactate level and SOFA score at baseline; [C] Adjusted for CRP and resuscitation volume of crystalloids given in first 8 hours; [D] Adjusted for lactate and resuscitation volume of crystalloids given in first 8 hours; [E] Adjusted for CRP, MAP, and resuscitation volume of crystalloids given in first 8 hours.

Table 3: Diagnostic performance of I-FABP levels for intra-abdominal hypertension and organ failure

All patients		**Event**	**N**	**AUC** (95% CI)	**P**	**Cut-off value** (95% CI)	**Sensitivity (%)** (95% CI)	**Specificity (%)** (95% CI)
Maximum I-FABP	(ng/L)	IAH	51	0.74 (0.60-0.85)	**0.001**	8,337 (1,385-22,672)	75 (53-90)	70 (50-86)
	(pg/nmol)		51	0.74 (0.59-0.85)	**0.002**	1.16 (0.06-1.99)	75 (53-90)	74 (54-89)
Median I-FABP	(ng/L)	IAH	51	0.61 (0.47-0.75)	0.185	1,712 (770-22,311)	67 (45-84)	67 (46-84)
	(pg/nmol)		51	0.64 (0.49-0.77)	0.102	0.52 (0.11-3.64)	75 (53-90)	59 (39-78)
Maximum I-FABP	(ng/L)	Organ failure	54	0.55 (0.41-0.68)	0.571	24,009 (15,098-60,396)	81 (54-96)	34 (20-51)
	(pg/nmol)		54	0.52 (0.38-0.66)	0.821	2.89 (1.86-35.27)	75 (48-93)	42 (26-59)
Median I-FABP	(ng/L)	Organ failure	54	0.54 (0.40-0.68)	0.598	2,939 (651-11,001)	69 (41-89)	55 (38-71)
	(pg/nmol)		54	0.55 (0.41-0.69)	0.545	0.87 (0.20-3.64)	44 (20-70)	71 (54-85)
Only patients with IAH								
Maximum I-FABP	(ng/L)	Organ failure	27	0.55 (0.35-0.74)	0.705	12,900 (265-27,951)	63 (25-92)	63 (38-84)
	(pg/nmol)		27	0.54 (0.34-0.73)	0.763	1.58 (0.06-2.89)	75 (35-97)	53 (29-76)
Median I-FABP	(ng/L)	Organ failure	27	0.63 (0.43-0.81)	0.334	2,939 (196-8,525)	75 (35-97)	63 (38-84)
	(pg/nmol)		27	0.60 (0.39-0.78)	0.462	0.87 (0.29-1.69)	50 (16-84)	79 (54-94)

Data were analyzed using ROC analysis.

ACS, abdominal compartment syndrome; AUC, area under the receiver operating characteristics curve; CI, confidence interval; creat, creatinine; IAH, intra-abdominal hypertension; IAP, intra-abdominal pressure; I-FABP, intestinal fatty acid binding protein; N, number of patients; ROC, receiver operating characteristic.

Table 4: Prognostic role of I-FABP levels on development of intra-abdominal hypertension, abdominal compartment syndrome, and organ failure

		Event	Unadjusted analysis			Adjusted analysis		
All patients			**N**	**OR (95% CI)**	**P**	**N**	**OR (95% CI)**	**P**
Urinary I-FABP	(ng/L)	IAH	333	1.000 (1.000-1.000)	0.884	321	1.000 (1.000-1.000)[A]	0.794
	(pg/nmol creat)		333	1.048 (0.907-1.211)	0.525	321	1.015 (0.853-1.207)[A]	0.869
	(ng/L) (Ln-transformed)		333	0.845 (0.569-1.257)	0.405	321	0.806 (0.524-1.238)[A]	0.323
	(pg/nmol creat) (Ln-transformed)		333	0.832 (0.567-1.220)	0.346	321	0.801 (0.529-1.212)[A]	0.292
Urinary I-FABP	(ng/L)	Organ failure	457	1.000 (1.000-1.000)	0.907	457	1.000 (1.000-1.000)[B]	0.898
	(pg/nmol creat)		455	1.012 (0.835-1.225)	0.906	455	0.991 (0.696-1.411)[B]	0.961
	(ng/L) (Ln-transformed)		456	1.093 (0.699-1.709)	0.697	456	1.041 (0.566-1.913)[B]	0.897
	(pg/nmol creat) (Ln-transformed)		455	1.112 (0.711-7.139)	0.641	455	1.010 (0.554-1.842)[B]	0.975
Only patients with IAH			**N**	**OR (95% CI)**	**P**	**N**	**OR (95% CI)**	**P**
Urinary I-FABP	(ng/L)	Organ failure	223	1.000 (1.000-1.000)	0.723	223	1.000 (1.000-1.000)[C]	0.723
	(pg/nmol creat)		221	1.030 (0.800-1.328)	0.817	221	1.030 (0.800-1.328)[C]	0.817
	(ng/L) (Ln-transformed)		222	1.161 (0.603-2.238)	0.654	222	1.161 (0.603-2.238)[C]	0.654
	(pg/nmol creat) (Ln-transformed)		221	1.133 (0.588-2.185)	0.707	221	1.133 (0.588-2.185)[C]	0.707

Data were analyzed using a generalized linear mixed model.

ACS, abdominal compartment syndrome; CI, confidence interval; creat, creatinine; IAH, intra-abdominal hypertension; I-FABP, intestinal fatty acid binding protein; N, number of samples (this number includes multiple samples of same patients); OR, odds ratio. [A]Adjusted for BMI; [B]Adjusted for inhalation, TBSA and resuscitation volume of crystalloids <24h; [C]Adjusting for covariates did not significantly improve the model, therefore unadjusted OR with 95% confidence intervals and P-values are shown.

REFERENCES

1. Bjorck M, Petersson U, Bjarnason T, Cheatham ML. Intra-abdominal hypertension and abdominal compartment syndrome in nontrauma surgical patients. Am Surg. 2011;77 Suppl 1:S62-6.
2. Mbiine R, Alenyo R, Kobusingye O, Kuteesa J, Nakanwagi C, Lekuya HM, Kituuka O, Galukande M. Intra-abdominal hypertension in severe burns: prevalence, incidence and mortality in a sub-Saharan African hospital. Int J Burns Trauma. 2017;7(6):80-7.
3. Ramirez JI, Sen S, Palmieri TL, Greenhalgh DG. Timing of Laparotomy and Closure in Burn Patients with Abdominal Compartment Syndrome: Effects on Survival. J Am Coll Surg. 2018;226(6):1175-80.
4. Evers LH, Bhavsar D, Mailander P. The biology of burn injury. Exp Dermatol. 2010;19(9):777-83.
5. Strang SG, Van Lieshout EMM, Breederveld RS, Van Waes OJF. A systematic review on intra-abdominal pressure in severely burned patients. Burns. 2014;40(1):9-16.
6. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, Duchesne J, Bjorck M, Leppaniemi A, Ejike JC*, et al.* Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med. 2013;39(7):1190-206.
7. Reintam Blaser A, Regli A, De Keulenaer B, Kimball EJ, Starkopf L, Davis WA, Greiffenstein P, Starkopf J, Incidence RF, Outcomes of Intra-Abdominal Study I. Incidence, Risk Factors, and Outcomes of Intra-Abdominal Hypertension in Critically Ill Patients-A Prospective Multicenter Study (IROI Study). Crit Care Med. 2019;47(4):535-42.
8. Fink MP, Delude RL. Epithelial barrier dysfunction: a unifying theme to explain the pathogenesis of multiple organ dysfunction at the cellular level. Crit Care Clin. 2005;21(2):177-96.
9. Moore FA. The role of the gastrointestinal tract in postinjury multiple organ failure. Am J Surg. 1999;178(6):449-53.

10. Rotstein OD. Pathogenesis of multiple organ dysfunction syndrome: gut origin, protection, and decontamination. Surg Infect (Larchmt). 2000;1(3):217-23; discussion 23-5.
11. de Haan JJ, Lubbers T, Derikx JP, Relja B, Henrich D, Greve JW, Marzi I, Buurman WA. Rapid development of intestinal cell damage following severe trauma: a prospective observational cohort study. Crit Care. 2009;13(3):R86.
12. Gollin G, Marks C, Marks WH. Intestinal fatty acid binding protein in serum and urine reflects early ischemic injury to the small bowel. Surgery. 1993;113(5):545-51.
13. Pelsers MM, Hermens WT, Glatz JF. Fatty acid-binding proteins as plasma markers of tissue injury. Clin Chim Acta. 2005;352(1-2):15-35.
14. Ivy ME, Atweh NA, Palmer J, Possenti PP, Pineau M, D'Aiuto M. Intra-abdominal hypertension and abdominal compartment syndrome in burn patients. J Trauma. 2000;49(3):387-91.
15. Kron IL, Harman PK, Nolan SP. The measurement of intra-abdominal pressure as a criterion for abdominal re-exploration. Ann Surg. 1984;199(1):28-30.
16. Park SH, Hemmila MR, Wahl WL. Early albumin use improves mortality in difficult to resuscitate burn patients. J Trauma Acute Care Surg. 2012;73(5):1294-7.
17. Ruiz-Castilla M, Barret JP, Sanz D, Aguilera J, Serracanta J, Garcia V, Collado JM. Analysis of intra-abdominal hypertension in severe burned patients: the Vall d'Hebron experience. Burns. 2014;40(4):719-24.
18. Sanchez-Sanchez M, Garcia-de-Lorenzo A, Herrero E, Asensio MJ, Galvan B, Cachafeiro L. Prevalence of intra-abdominal hypertension (IAH) among patients with severe burns. Burns. 2014;40(3):533.
19. Kanda T, Tsukahara A, Ueki K, Sakai Y, Tani T, Nishimura A, Yamazaki T, Tamiya Y, Tada T, Hirota M*, et al.* Diagnosis of ischemic small bowel disease by measurement of serum intestinal fatty acid-binding protein in patients with acute abdomen: a multicenter, observer-blinded validation study. J Gastroenterol. 2011;46(4):492-500.
20. Sun DL, Cen YY, Li SM, Li WM, Lu QP, Xu PY. Accuracy of the serum intestinal fatty-acid-binding protein for diagnosis of acute intestinal ischemia: a meta-analysis. Sci Rep. 2016;6:34371.

21. Thuijls G, van Wijck K, Grootjans J, Derikx JP, van Bijnen AA, Heineman E, Dejong CH, Buurman WA, Poeze M. Early diagnosis of intestinal ischemia using urinary and plasma fatty acid binding proteins. Ann Surg. 2011;253(2):303-8.
22. Vermeulen Windsant IC, Hellenthal FA, Derikx JP, Prins MH, Buurman WA, Jacobs MJ, Schurink GW. Circulating intestinal fatty acid-binding protein as an early marker of intestinal necrosis after aortic surgery: a prospective observational cohort study. Ann Surg. 2012;255(4):796-803.
23. Strang SG, Van Waes OJF, Van der Hoven B, Ali S, Verhofstad MHJ, Pickkers P, Van Lieshout EMM. Intestinal fatty acid binding protein as a marker for intra-abdominal pressure-related complications in patients admitted to the intensive care unit; study protocol for a prospective cohort study (I-Fabulous study). Scand J Trauma Resusc Emerg Med. 2015;23:6.
24. Montagnana M, Danese E, Lippi G. Biochemical markers of acute intestinal ischemia: possibilities and limitations. Ann Transl Med. 2018;6(17):341.

PART III - MARKERS FOR ADVERSE OUTCOME

Chapter 7

Intestinal fatty acid binding protein as a marker for intra-abdominal pressure-related complications in patients admitted to the Intensive Care Unit; study protocol for a prospective cohort study (I-Fabulous study)

Chapter 8

Intestinal fatty acid binding protein as a marker for intra-abdominal pressure-related complications in patients admitted to the Intensive Care Unit; a prospective cohort study (I-Fabulous study)

Chapter 9

Relation between intra-abdominal pressure and early intestinal ischemia in rats.

Chapter 7

Intestinal fatty acid binding protein as a marker for intra-abdominal pressure-related complications in patients admitted to the intensive care unit; study protocol for a prospective cohort study (I-Fabulous study)

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ABSTRACT

Background: Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) have detrimental effects on all organ systems and are associated with increased morbidity and mortality in critically ill patients admitted to an intensive care unit. Intra-bladder measurement of the intra-abdominal pressure (IAP) is currently the gold standard. However, IAH is not always indicative of intestinal ischemia, which is an early and rapidly developing complication. Sensitive biomarkers for intestinal ischemia are needed to be able to intervene before damage becomes irreversible. Gut wall integrity loss, including epithelial cell disruption and tight junctions breakdown, is an early event in intestinal damage. Intestinal Fatty Acid Binding Protein (I-FABP) is excreted in urine and blood specifically from damaged intestinal epithelial cells. Claudin-3 is a specific protein which is excreted in urine following disruption of intercellular tight junctions. This study aims to investigate if I-FABP and Claudin-3 can be used as a diagnostic tool for identifying patients at risk for IAP-related complications.

Methods/Design: In a multicenter, prospective cohort study 200 adult patients admitted to the intensive care unit with at least two risk factors for IAH as defined by the World Society of the Abdominal Compartment Syndrome (WSACS) will be included. Patients in whom an intra-bladder IAP measurement is contra-indicated or impossible and patients with inflammatory bowel diseases that may affect I-FABP levels will be excluded. The IAP will be measured using an intra-bladder technique. During the subsequent 72 hours, the IAP measurement will be repeated every six hours. At these time points, a urine and serum sample will be collected for measurement of I-FABP and Claudin-3 levels. Clinical outcome of patients during their stay at the intensive care unit will be monitored using the Sequential Organ Failure Assessment (SOFA) score.

Discussion: Successful completion of this trial will provide evidence on the eventual role of the biomarkers I-FABP and Claudin-3 in predicting the risk of IAP-associated adverse outcome. This may aid early (surgical) intervention.

Trial registration: The trial is registered at the Netherlands Trial Register (NTR4638).

BACKGROUND

Patients undergoing major surgery or sustaining severe trauma are at risk of developing morbidity and mortality from postoperative or posttraumatic systemic inflammatory response syndrome, sepsis and multiple organ dysfunction. The development of such potentially lethal complications in otherwise healthy patients is poorly understood. Data from a prospective multicenter epidemiological study showed that intra-abdominal hypertension (IAH) is associated with increased morbidity and mortality rates in critically ill patients admitted to an intensive care unit (ICU) (1,2). Therefore, early identification of patients at risk for IAH-related morbidity and mortality can be potentially lifesaving.

Intra-abdominal pressure and intra-abdominal hypertension

Compliance of the abdominal wall together with the abdominal content determines the intra-abdominal pressure (IAP) level. Under physiologic situations, the IAP level is below 12 mmHg. Increased pressure in the abdomen is known as intra-abdominal hypertension (IAH). This is defined as a sustained IAP ≥12 mmHg (3). IAH results in reduced blood flow to most organs, with consequent dysfunction of the cardiovascular, respiratory, renal, gastrointestinal, and central nervous systems. An IAP >20 mmHg in combination with new organ dysfunction is indicative of an abdominal compartment syndrome (ACS). The ultimate treatment of ACS is a decompressive laparotomy. Risk factors for ACS include leakage of an aneurysm of the abdominal aorta, closing the abdomen under pressure after abdominal surgery, damage control laparotomy, hyper-hydration during hypovolemic shock, pancreatitis, and pulmonary contusion. These risk factors may apply to a majority of patients in the ICU. The mortality risk in patients with ACS may be as high as 80% (1). The current gold standard measurement tool as put forward by the World Society of the Abdominal Compartment Syndrome (WSACS; www.wsacs.org) is an intra-bladder pressure measurement. This is a simple, minimally invasive method, and the results are immediately available (3). From a clinical perspective, however, the IAP level does not always represent the presence of intestinal ischemia and as such is not a perfect indicator for clinical outcome nor surgical therapy. Sensitive biomarkers indicative of early (*i.e.*, reversible) organ dysfunction are therefore needed as additional diagnostic tool. The combination of increased IAP and a biomarker level that represents organ damage would support the need for and timing of decompressive measures to relieve the abdominal pressure.

Biomarkers released upon loss of small intestinal integrity

Evidence is accumulating that the intestines play a central role in the origin of postoperative and posttraumatic sequelae (4-6). Enterocyte damage and tight junction loss can be triggered by IAH, and both result in loss of intestinal integrity. As a consequence, toxins, bacteria, and undigested food particles may pass the enterocyte layer, enter the underlying vasculature, and trigger systemic inflammatory reactions that may progress to multiple organ dysfunction syndrome and even death. Peptides released upon enterocyte damage (*e.g.*, Intestinal Fatty Acid Binding protein; I-FABP) or tight junction loss (*e.g.*, Claudin-3) are potentially ideal biomarkers that will help identify patients with early IAH-induced intestinal damage.

I-FABP is a small (14–15 kDa) protein that is exclusively present in mature enterocytes of the small and large intestine. It is released into the circulation upon enterocyte membrane integrity loss and rapidly excreted into the urine (half-life 11 minutes). Elevated I-FABP levels have been found in plasma, serum, and urine in patients with intestinal ischemia, celiac disease, systemic inflammatory response syndrome and necrotizing enterocolitis (7-15). I-FABP levels can be measured sensitively in plasma, serum, and urine using an enzyme-linked immunosorbent assay (ELISA) (7, 8).

Claudins are small (22 kDa) tight junction proteins (4,16-19). Especially Claudin-3 is expressed in high quantities solely in the intestine (18). The amount of Claudin-3 in the intestine decreases after tight junction integrity loss (17). Breakdown of tight junctions by loss of Claudins (as measured on Western blots in urine) is an early event in intestinal damage, resulting in intestinal barrier loss (20).

The main aim of the current study is to investigate if urinary levels of I-FABP can be used as a diagnostic tool for identifying patients at risk for IAP-related complications. Secondary aims are to determine the same for serum levels of I-FABP and for urinary and serum levels of Claudin-3.

METHODS / DESIGN

Study design and setting

Multicenter prospective observational study of 200 patients admitted to the ICU of Erasmus MC, University Medical Center Rotterdam (Rotterdam, The Netherlands) or Radboud University Medical Center Nijmegen (Nijmegen, The Netherlands), who are at risk for developing IAH or ACS according to the definitions of the World Society of the Abdominal Compartment Syndrome (3). Since it was suggested that patients who have undergone liver transplantation should also be screened for IAH (21, 22), liver transplantation has been added to the list of risk factors. The study is registered at the Netherlands Trial Register (NTR4638).

Study population and eligibility criteria

All adult patients admitted to the ICU who have at least two risk factors for developing IAH or ACS according to the WSACS will be eligible for inclusion (3).

Patients meeting the following inclusion criteria will be eligible for enrolment:

1. Patients with at least two risk factors putting them at risk for IAH or ACS as agreed by the WSACS. Risk factors may be present already at admission, but also patients developing risk factors during ICU stay will be eligible from that moment onwards;
2. Age 18 or older, with no upper age limit;
3. Signed informed consent by patient or proxy.

If any of the following criteria applies, patients will be excluded:

1. Patients in whom intra-bladder pressure measurement is contra-indicated. This includes patients with bladder trauma or hematuria;
2. Patients in whom intra-bladder pressure measurements are not reliable due to intra-peritoneal adhesions, bladder oppressive pelvic hematoma, abdominal packs in situ, (previous) bladder tumor or previous bladder removal;
3. Patients with any inflammatory bowel disease that may affect I-FABP levels.

Exclusion of a patient because of enrolment in another ongoing drug or surgical intervention trial will be left to the discretion of the attending surgeon on a case-by-case basis.

Treatment

Patients with increased pressure determined by the intra-bladder pressure measurements will be treated in compliance with the algorithms for patient management as developed by the WSACS (www.wsacs.org/algorithms.php) (3). The IAH Assessment Algorithm describes all risk factors that every patient should be screened for upon intensive care unit admission and upon clinical deterioration leading to new organ dysfunction. The intra-bladder pressure will be measured in patients with two or more risk factors for IAH or ACS or in patients who have undergone a liver transplantation. Patients who do not have two or more risk factors at baseline but develop new risk factors during their ICU admission will be followed from that moment onwards. The reason for this is that the occurrence of IAH during intensive care stay is known to be an independent predictor for mortality, whereas presence of IAH at intensive care admission is not (23). Patients should be enrolled as soon as possible, but at least within 48 hours after meeting the eligibility criteria. The IAH/ACS Management Algorithm provides a decision tree for the follow-up of patients related to the IAP level. The IAH/ACS Medical Management Algorithm provides a stepwise approach of actions to be taken for achieving IAP pressure relief. In short, ICU management will be provided by the attending physicians and may consist of, among others, balanced intravenous fluid administration, correction of hypovolemia, electrolyte disturbances and/or anemia and analgesics.

Outcome measures

I-FABP levels will serve as primary outcome measure. Urinary and serum concentrations of I-FABP will be analyzed in duplicate using a highly specific, commercially available enzyme-linked immunosorbent assay (ELISA) that selectively detects human I-FABP (HyCult Biotechnology, Uden, The Netherlands). The ELISA will be performed following the supplier's protocol. I-FABP levels in urine will be adjusted to urinary creatinine levels. Claudin-3 levels will serve as secondary outcome measure. Urinary levels of Claudin-3 will be analyzed in duplicate either by ELISA (if available at time of analysis) or by Western blotting. Claudin-3 levels in urine will be adjusted to urinary creatinine levels. If analyzed from Western blots, equal amounts of each sample (adjusted to urinary creatinine levels) will be separated by sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE), transferred to a polyvinylidene fluoride (PVDF) membrane and probed using

primary antibody to Claudin-3 (Rabbit anti-claudin-3 (34–1700), Zymed Laboratories, San Francisco, CA). After incubation with goat anti rabbit HRP-conjugated secondary antibody (Jackson, West Grove, PA), a signal will be detected by supersignal west pico chemiluminescence substrate (Pierce, Etten-Leur, the Netherlands). Band intensities for each sample will be semi-quantitatively analyzed using Quantity One (Biorad, Hercules, CA). This is a straightforward approach for semi-quantitative assessment of protein levels. Urinary creatinine levels in the collected samples will be determined at the Clinical Chemistry department. The occurrence of (increasing) organ dysfunction will be based upon the SOFA score.

Baseline, disease and treatment-related data

In addition to the outcome variables mentioned above, the following data will be collected:

***Intrinsic variables (baseline data)*:**

- Age
- Gender
- Weight
- Height
- Comorbidity

Disease-related variables at admission:

- Reason of admission to the ICU (*i.e.*, type of disease or injury and type of intervention)
- Serum lactate concentration at baseline (sodium fluoride tube)
- IAP level at baseline
- Urinary creatinine level at baseline (sediment tube)
- Acute Physiology and Chronic Health Evaluation II (APACHE II) score at baseline; this is a validated and commonly applied severity of disease classification system (24). An integer score ranging from 0 to 71 is computed based upon 12 routine physiological measurements with a higher score implying a more severe disease and a higher risk of death.
- Acute Physiology and Chronic Health Evaluation IV (APACHE IV) score at baseline; this

standardized scoring metrics was developed in 2005 as an improved version of the APACHE II. The previously used set of equations were re-evaluated and improved where needed. The most important change involved the new categorization of disease groups (25).

- Simplified Acute Physiology Score II (SAPS II) at baseline; this score was designed to measure the severity of disease for patients admitted to Intensive care units aged 15 or more (26). The SAPS II score is calculated from 12 routine physiological measurements during the first 24 hours of ICU admission, information about previous health status and some information obtained at admission. The computed score has a range from 0 to 163 points and a predicted mortality between 0% and 100%. Higher scores imply a more severe disease and a higher risk of death.
- Sequential Organ Failure Assessment (SOFA) score at baseline; this score is a validated and commonly used score to track a patient's status during the stay in an ICU. The SOFA score is a scoring system to determine the extent of a person's organ function or rate of failure (27-31). The score is based upon six different scores, one each for the respiratory system (*i.e.*, PaO2/FiO2 ratio), the cardiovascular system (*i.e.*, mean arterial pressure and vasopressor requirement), the hepatic system (*i.e.*, bilirubin level), the coagulation system (*i.e.*, platelet count), the renal system (*i.e.*, creatinine level or urine output), and the neurological system (*i.e.*, Glasgow Coma Score). For each of these systems, a maximum of four points can be attributed. SOFA scores are determined on a daily basis during ICU admission.

Treatment-related variables:

- Medication use
- Interventions performed (*i.e.*, type and number of interventions)
- Sequential Organ Failure Assessment (SOFA) score on day 1 to 4 (or until ICU discharge or death).
- Length of stay in the ICU
- Mortality during ICU stay and during hospital stay

Sample size calculation

In order to reliably calculate correlation coefficients for the association between IAP, I-FABP and Claudin-3 levels, at least 75 patients with IAH are needed. Malbrain *et al.* showed in a multicenter study that in a general ICU population, the prevalence of IAH (*i.e.*, IAP > 12 mmHg) and ACS (*i.e.*, IAP > 20 mmHg with concomitant new organ dysfunction) was 32%, and 4%, respectively (23). Since we will only follow-up on patients with a minimum of two IAH/ACS risk factors, the percentage of enrolled patients that will develop IAH or ACS will be higher, and is likely to exceed 40% (unpublished data). Therefore, enrolling a total population of 200 patients will be sufficient to ascertain availability of 80 patients with IAH.

This will also be sufficient to compare I-FABP levels in patients with physiologic IAP levels with patients that developed IAH with adequate statistical power. Based upon data provided by Kanda *et al*. we expect that mean I-FABP levels will be 20.0 ± 10.0 ng/mL (range 0–100 ng/mL) in patients without IAH (32). In patients with IAH, the I-FABP levels will be higher (≥20 ng/mL). An overall population of 200 patients (consisting of 120 controls and 80 patients with IAH) will be sufficient to detect a 0.5 SD increase to 30.0 ± 12.5 ng/mL in I-FABP level in patients with IAH (two-sided test with an α level of 0.05) with >90% statistical power.

Recruitment and consent

Upon identification of two IAH risk factors, treatment should be initiated in compliance with international guidelines of the WSACS. This implies that the baseline IAP measurement and the first urine sample may have been collected prior to obtaining informed consent from the patient or his/her legal representative. Eligible persons admitted to the ICU who are at risk for developing IAH will be informed about the trial and asked for consent at the ICU. If patients are unconscious or otherwise not able to sign informed consent, their legal representative will be informed about the trial and asked to sign informed consent on behalf of the patient. Upon recovery the patient will be asked to sign final consent. The patient and their legal representative will receive information and a consent form from the attending physician, the clinical investigator or a research assistant. If a patient or his/her legal representative decides not to sign informed consent, data and samples collected for that patient will be disposed of, and patients will be excluded from analysis.

Study procedures

In patient with ≥2 risk factors for IAH or ACS, the intra-abdominal pressure will be measured using an intra-bladder technique. The modified Kron technique described by Cheatham and Safcsak (33) will be applied for measuring IAP. In the current study, 20 mL of saline will be used in order to comply with the current recommendations of the WSACS. For the IAP measurement, a Foley catheter will be disconnected and a 3-way-valve will be inserted to create a continuous connection to a pressure transducer (DTXPlus™ PRESS PA, reference No 686496; Argon Critical Care Systems, Singapore). For every single measurement the valve connecting the urinary drainage bag is closed and 20 mL of saline is instilled. The mid-axillary line will be used as reference. During the first 72 hours after enrolment, IAP measurement will be repeated every six hours (Table 1). At those time points (including baseline), the following samples will be collected:

Table 1: Schedule of enrolment, interventions, and assessments

	Study period		
	Enrolment *	**Measurement ****	**Close-out**
TIMEPOINT	***<T_0***	***T_0 to T_{72}***	***ICU discharge***
ENROLMENT:			
Eligibility screen	X		
Informed Consent	X		
ASSESSMENTS:			
Baseline variables	X		
Disease-related variables	X		
IAP measurement		X	
Blood sample		X	
Urine sample		X	
I-FABP measurement		X	
Claudin-3 measurement		X	
Creatinine measurement		X	
Treatment-related variables		X	

SOFA score	X	
Adverse events	X	X
Length of ICU stay	X	X
Mortality during ICU stay	X	X
Secondary interventions	X	X

* Patients are considered eligible as soon as two IAH risk factors are present. This can either be at ICU admission or later on during ICU stay.

**Patients are followed until 72 hours or until discharge from the ICU, whichever comes first. Measurements are performed every six hours.

1) Urine samples for measurement of I-FABP, Claudin-3 and creatinine levels: A single fresh specimen of urine will be collected from the urinary bladder catheter that is already in situ. Samples will be kept on ice and then frozen at −80°C in aliquots within two hours of collection.
2) Blood samples for measurement of serum I-FABP levels (NB: this only applies to patients enrolled at Erasmus MC, Rotterdam, the Netherlands): A single blood sample (10 mL) will be drawn from the arterial line that is already *in situ*. Blood will be collected in pre-chilled vacutainer containing EDTA as anticoagulent (BD Vacutainer, Becton Dickinson Diagnostics, Aalst, Belgium) and kept on ice. Blood will be centrifuged at 4°C, 4000x g for 15 minutes. Serum will be stored in aliquots at −80°C within 2 hours until analysis.

The reason for following up on patients during the first 72 hours after enrollment is based upon our observation (unpublished data) that over 95% of patients that deteriorate clinically due to increased IAP will do so during the 12–24 hours. In order not to miss any patients that may deteriorate somewhat later (*e.g.*, due to leak at the surgical site), we have set the time frame at 72 hours.

In order to assess if levels of I-FABP or Claudine-3 can be used as a prognostic marker for intestinal ischemia-related morbidity it is necessary to also collect clinical data of patients during their entire stay at the ICU. These data will be extracted from the ICU patient data management system (PDMS), where they are stored as part of clinical routine. This will be done using the APACHE II, APACHE IV, SAPS II and SOFA score, which will be collected routinely for any patient admitted to the ICU. Follow-up in the ICU will include a daily physical examination, vital signs monitoring, routine blood tests, and chest radiographs or

other ancillary tests as required. The attending physicians will record complications and events as well as any (secondary) intervention performed such as decompression laparotomy.

Data collection

Most variables will be collected as part of standard of care and are routinely recorded in electronic patients records. The intra-abdominal pressure will be measured by the ward nurse and recorded in the PDMS system and on case record forms (CRF). This CRF contains no patient identifiers. Urine and serum samples will be collected, processed and frozen at −80°C by the researchers or a research nurse. I-FABP and Claudin-3 levels will be measured by the researcher (SGS) and results will be recorded in the CRF. CRFs are stored and secured at the hospital where the patient is included.

Data management

Research data will be stored in a database (SPSS), and will be handled confidentially and anonymously. Research data that can be traced to individual patients can only be viewed by authorized personnel. These persons are the members of the research team, members of the health care inspection, and members of the Medical Ethics Committee Erasmus MC. The handling of personal data will be in compliance with the Dutch Data Protection Act and the privacy regulation of the Erasmus MC.

Research data will be stored under a code number. Only the code number will be used for study documentation, progress reports and publications. The principal investigator and research assistant are the only persons with the information linking individual persons to study code numbers. Patient data and materials will be stored for a maximum of 15 years after the end of the study. Patients need to consent with this, and if not, their materials will be disposed of upon termination of the study.

Statistical analysis

Data will be analyzed at the end of the study using the Statistical Package for the Social Sciences (SPSS) version 21 or higher (SPSS, Chicago, Ill., USA) and will be reported following the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines. No interim analysis will be done. Normality of continuous data will be assessed by the Shapiro Wilk tests and by inspecting the frequency distributions (histograms). Homogeneity of variances will be tested using the Levene's test.

Descriptive analysis will be performed in order to report baseline characteristics (intrinsic variables and disease-related variables) and outcome measures of the entire cohort as well as for the group of patients that develop IAH (IAH group; IAP of 12 mmHg or higher on two separate recordings) versus those that do not (control group). For continuous data mean and SD (parametric data) or medians and percentiles (non-parametric data) will be calculated and reported. For categorical data, numbers and frequencies will be calculated and reported for the entire cohort and for the IAH and the control group separately. Univariate analysis will be performed in order to test the difference in the primary and secondary outcome measures between the IAH group and the control group. Continuous data such as the I-FABP level (primary outcome) of the Claudin-3 level (secondary outcome) will be tested using a Student's T-test (parametric data) or a Mann Whitney U-test (non-parametric data). Chi-squared analysis will be used for statistical testing of categorical data such as the number of secondary interventions. A p-value <0.05 will be taken as threshold of statistical significance. Depending upon the number of patients within the cohort of the study that develop ACS and the mortality rate, similar tests will be used to compare data for those who developed ACS (or those who died) versus those who did not. The patient cohort to be included will be heterogeneous by nature, as IAH and ACS risk factors will differ between patients. If it is possible to identify subgroups of patients (*e.g.*, liver transplant patients) subgroup analyses may be performed. P-values <0.05 will be taken as threshold of statistical significance.

The prognostic role of the I-FABP and Claudin-3 on development of IAH, ACS, (increasing) organ dysfunction (based upon SOFA increase) or mortality will be assessed. This analysis will be performed with Stata software, version 10.0 or higher (StatCorp LP, College Station, TX, USA), using the generalized linear latent and mixed model (GLLAMM) framework. Herein, the binary outcome IAH (or new organ dysfunction or ACS or mortality) will be used as dependent variable, and the level of I-FABP or Claudin-3 will be included in the model as time-dependent variable. Patient ID will be included as clustering variable as up to 13 measurements per patient will be available. Additional covariates such as age, gender, number of IAH risk factors, and BM will be entered into the model in order to evaluate their effect on the relation between biomarker level and outcome. Random intercept and slope will be considered. Results will be expressed as Odds Ratios with their corresponding 95% confidence interval and p-values.

Data monitoring

No data monitoring committee has been established as this study is not an interventional study and all data are either recorded in patient files (*i.e.*, all clinical data including baseline, disease-related and treatment-related variables) as part of standard of care, or are generated electronically (*i.e.,* ELISA results and laboratory tests). A random sample of at least 10% of all data will be double checked by a member of the research team in order to check the quality of the data entry into the database. The only exception to this will be the primary outcome, for which 100% of data will be checked.

Ethical considerations

The study will be conducted according to the principles of the Declaration of Helsinki (64th World Medical Association General Assembly, Fortaleza, October 2013). This study has been given a waiver by the medical research ethics committee (MREC) Erasmus MC, University Medical Center Rotterdam (Rotterdam, The Netherlands; reference number MEC-2011-016) and by the local hospital board in the participating center (Radboud University Medical Center, Nijmegen, The Netherlands). Following review of the protocol (version 1.0, dd December 13, 2010), the MREC concluded that this study is not subject to the Medical Research Involving Human Subjects Act (WMO, in Dutch "Wet Medisch-wetenschappelijk Onderzoek met mensen"). They concluded that the study is a medical/scientific research, but no patients are subjected to procedures or are required to follow rules of behavior. Consequently, the statutory obligation to provide insurance for subjects participating in medical research (article 7, subsection 6 of the WMO and Medical Research (Human Subjects) Compulsory Insurance Decree of 23 June 2003) was also waived. The reason for this dispensation is that participation in this study is without risks. Any important protocol amendments will be submitted to the MREC Erasmus MC before implementation.

Dissemination policy

Research data can be presented or publicized in agreement with the clinical investigator and project leaders only. No research data that can be traced to individual persons will be presented or published.

DISCUSSION

Every year, approximately 80,000 patients are admitted to an ICU in the Netherlands (34). Specific groups of patients such as those who underwent major surgery (*e.g.*, vascular or intestinal surgery) or who sustained severe trauma are at risk of developing morbidity and mortality from postoperative or posttraumatic systemic inflammatory response syndrome, sepsis and multiple organ dysfunction. The development of such potentially lethal complications in relatively healthy surgical or trauma patients is poorly understood. Evidence is accumulating that intra-abdominal hypertension plays a central role in the origin of such postoperative and posttraumatic sequelae. An increased intra-abdominal pressure level is currently the best indicator of intra-abdominal complications. However, the IAP level does not always represent the presence or absence of organ dysfunction, substantial intra-abdominal damage may be present already prior to the development of IAH and ACS. There is a distinctive need for a non-invasive early-onset diagnostic test and biomarkers. The main aim of the current study is to test if urinary I-FABP or Claudine-3 levels can be used as diagnostic tool for identifying patients at risk for IAP-related complications. This marker can then be used in order to take the necessary clinical measures (*e.g.*, decompressive laparotomy) before the IAP has reached the level of irreversible damage to vital organs. This may prevent serious morbidity or even death in a large group patients admitted to the ICU.

LIST OF ABBREVIATIONS

ACS, Abdominal compartment syndrome; APACHE II, Acute physiology and chronic health evaluation II; APACHE IV, Acute physiology and chronic health evaluation IV; ELISA, Enzyme-linked immunoSorbent assay; HRP, Horse-radish peroxidase; IAH, Intra-abdominal hypertension; IAP, Intra-abdominal pressure; ICU, Intensive care unit; I-FABP, Intestinal fatty acid binding protein (I-FABP); METC, Medisch ethische toetsings commissie; MREC, Medical research ethics committee; NTR, Netherlands trial register; PVDF, Polyvinylidene fluoride; SAPS II, Simplified acute physiology score II; SDS-PAGE, Sodium dodecyl sulphate polyacrylamide gel electrophoresis; SOFA, Sequential organ failure assessment; SPSS, Statistical package for the social sciences; STROBE, STrengthening the reporting of OBservational studies in epidemiology; WMO, Wet medisch-wetenschappelijk Onderzoek met mensen; WSACS, World society of the abdominal compartment syndrome (WSACS)

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REFERENCES

1. Vidal MG, Ruiz Weisser J, Gonzalez F, Toro MA, Loudet C, Balasini C, et al. Incidence and clinical effects of intra-abdominal hypertension in critically ill patients. Crit Care Med. 2008;36:1823–31.
2. Khan S, Verma AK, Ahmad SM, Ahmad R. Analyzing intra-abdominal pressures and outcomes in patients undergoing emergency laparotomy. J Emerg Trauma Shock. 2010;3:318–25.
3. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the world society of the abdominal compartment syndrome. Intensive Care Med. 2013;39:1190–206.
4. Fink MP, Delude RL. Epithelial barrier dysfunction: a unifying theme to explain the pathogenesis of multiple organ dysfunction at the cellular level. Crit Care Clin. 2005;21:177–96.
5. Moore FA. The role of the gastrointestinal tract in postinjury multiple organ failure. Am J Surg. 1999;178:449–53.
6. Rotstein OD. Pathogenesis of multiple organ dysfunction syndrome: gut origin, protection, and decontamination. Surg Infect (Larchmt). 2000;1:217–23. discussion 223–215.
7. Derikx JP, Poeze M, van Bijnen AA, Buurman WA, Heineman E. Evidence for intestinal and liver epithelial cell injury in the early phase of sepsis. Shock. 2007;28:544–8.
8. Derikx JP, van Waardenburg DA, Thuijls G, Willigers HM, Koenraads M, van Bijnen AA, et al. New insight in loss of Gut barrier during major non-abdominal surgery. PLoS One. 2008;3:e3954.
9. De Haan JJ, Lubbers T, Derikx JP, Relja B, Henrich D, Greve JW, et al. Rapid development of intestinal cell damage following severe trauma: a prospective observational cohort study. Crit Care. 2009;13:R86.
10. Relja B, Szermutzky M, Henrich D, Maier M, de Haan JJ, Lubbers T, et al. Intestinal-FABP and liver-FABP: Novel markers for severe abdominal injury. Acad Emerg Med. 2010;17:729–35.

11. Ockner RK, Manning JA. Fatty acid-binding protein in small intestine. Identification, isolation, and evidence for its role in cellular fatty acid transport. J Clin Invest. 1974;54:326–38.
12. Pelsers MM, Hermens WT, Glatz JF. Fatty acid-binding proteins as plasma markers of tissue injury. Clin Chim Acta. 2005;352:15–35.
13. Edelson MB, Sonnino RE, Bagwell CE, Lieberman JM, Marks WH, Rozycki HJ. Plasma intestinal fatty acid binding protein in neonates with necrotizing enterocolitis: a pilot study. J Pediatr Surg. 1999;34:1453–7.
14. Gollin G, Marks C, Marks WH. Intestinal fatty acid binding protein in serum and urine reflects early ischemic injury to the small bowel. Surgery. 1993;113:545–51.
15. Gollin G, Marks WH. Elevation of circulating intestinal fatty acid binding protein in a luminal contents-initiated model of NEC. J Pediatr Surg. 1993;28:367–70. discussion 370–371.
16. Suenaert P, Bulteel V, Lemmens L, Noman M, Geypens B, Van Assche G, et al. Anti-tumor necrosis factor treatment restores the gut barrier in Crohn's disease. Am J Gastroenterol. 2002;97:2000–4.
17. Zeissig S, Burgel N, Gunzel D, Richter J, Mankertz J, Wahnschaffe U, et al. Changes in expression and distribution of claudin 2, 5 and 8 lead to discontinuous tight junctions and barrier dysfunction in active Crohn's disease. Gut. 2007;56:61–72.
18. Rahner C, Mitic LL, Anderson JM. Heterogeneity in expression and subcellular localization of claudins 2, 3, 4, and 5 in the rat liver, pancreas, and gut. Gastroenterology. 2001;120:411–22.
19. Turksen K, Troy TC. Barriers built on claudins. J Cell Sci. 2004;117:2435–47.
20. Thuijls G, Derikx JP, de Haan JJ, Grootjans J, de Bruine A, Masclee AA, et al. Urine-based detection of intestinal tight junction loss. J Clin Gastroenterol. 2010;44:e14–9.
21. Biancofiore G, Bindi ML, Romanelli AM, Bisa M, Boldrini A, Consani G, et al. Postoperative intra-abdominal pressure and renal function after liver transplantation. Arch Surg. 2003;138:703–6.

22. Biancofiore G, Bindi ML, Romanelli AM, Boldrini A, Consani G, Bisa M, et al. Intra-abdominal pressure monitoring in liver transplant recipients: a prospective study. Intensive Care Med. 2003;29:30–6.
23. Malbrain ML, Chiumello D, Pelosi P, Bihari D, Innes R, Ranieri VM, et al. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. Crit Care Med. 2005;33:315–22.
24. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13:818–29.
25. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute physiology and chronic health evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med. 2006;34:1297–310.
26. Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. Jama. 1993;270:2957–63.
27. Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European society of intensive care medicine. Crit Care Med. 1998;26:1793–800.
28. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European society of intensive care medicine. Intensive Care Med. 1996;22:707–10.
29. de Mendonca A, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli M, et al. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med. 2000;26:915–21.
30. Moreno R, Vincent JL, Matos R, Mendonca A, Cantraine F, Thijs L, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Working group on sepsis related problems of the ESICM. Intensive Care Med. 1999;25:686–96.

31. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. Jama. 2001;286:1754–8.
32. Kanda T, Fujii H, Tani T, Murakami H, Suda T, Sakai Y, et al. Intestinal fatty acid-binding protein is a useful diagnostic marker for mesenteric infarction in humans. Gastroenterology. 1996;110:339–43.
33. Cheatham ML, Safcsak K. Intraabdominal pressure: a revised method for measurement. J Am Coll Surg. 1998;186:594–5.
34. National intensive care evaluation (NICE) [in Dutch Stichting NICE]. http://www.stichting-nice.nl/. Last accessed on May 15, 2014.

Chapter 8

Intestinal fatty acid binding protein as a predictor for intra-abdominal pressure-related complications in patients admitted to the intensive care unit; a prospective cohort study (I-Fabulous study)

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ABSTRACT

Objective: Critically ill patients are at risk for intra-abdominal hypertension (IAH) and related complications such as organ failure, abdominal compartment syndrome (ACS), and death. This study aimed to determine the value of urinary and serum intestinal fatty acid binding protein (I-FABP) levels as early marker for IAH-associated complications.

Methods: A prospective observational study was conducted in two academic institutional mixed medical-surgical ICUs in the Netherlands. Adult patients admitted to the ICU with two or more risk factors for IAH (198) were included. Urinary and serum I-FABP and intra-abdominal pressure (IAP) were measured every six hours during 72 hours.

Results: Fifteen (8%) patients developed ACS and 74 (37%) developed new organ failure. I-FABP and IAP were positively correlated. Patients who developed ACS had higher median baseline levels of urinary I-FABP (235(P25-P75 85-1747)µg/g creat) than patients with IAH who did not develop ACS (87(P25-P75 33-246)µg/g, p=0.037). With an odds ratio of 1.00, neither urinary nor serum I-FABP indicated increased risk for developing new organ failure or ACS.

Conclusions: While statistical differences between groups were observed, I-FABP levels have no value in the early identification of individual patients at risk for IAH-related complications and should not be used in clinical practice.

INTRODUCTION

Increased pressure in the abdomen, known as intra-abdominal hypertension (IAH), plays an important role in the development of complications in critically ill patients (1). Increased pressure in the abdomen, known as intra-abdominal hypertension (IAH), plays an important role in the development of complications in critically ill patients (2). Untreated, ACS is associated with high morbidity and mortality rates (3). The ultimate treatment of IAH is a decompressive laparotomy.
Risk factors for IAH and subsequent ACS include massive bleeding (e.g. from a ruptured aneurysm of the abdominal aorta or trauma), a severe inflammatory state resulting in edema and ascites (e.g after abdominal surgery, hyper-hydration to treat hypovolemic shock or pancreatitis). These risk factors may apply to a relevant percentage of the patients admitted in the ICU. In case ACS develops, the associated mortality risk may be as high as 80% (4). Early identification of patients at risk for ACS and IAH-related complications might improve outcome. The current gold standard, as put forward by the World Society of the Abdominal Compartment Syndrome (WSACS; www.wsacs.org), requires intra-bladder pressure measurements (2). This is a simple and cheap technique, yielding immediate results. However, the level of IAP alone is neither a reliable indicator for clinical outcome, nor does it indicate when surgical therapy should be considered as clinical decision-making also involves other parameters (5, 6). In this context, intestinal fatty acid binding protein (I-FABP) may be of interest.

In this context, intestinal fatty acid binding protein (I-FABP) may be of interest. I-FABP is a peptide exclusively present in mature enterocytes that is released into the circulation upon enterocyte damage and is rapidly excreted into the urine (7). Elevated levels of I-FABP have been found in urine and serum of patients with intestinal ischemia, celiac disease, systemic inflammatory response syndrome, necrotizing enterocolitis and increasing norepinephrine infusion rate (8-16). This suggests that intestinal ischemia with subsequent enterocyte damage is an early and rapidly developing complication of IAH. Since it is also assumed that early decompression improves outcome, I-FABP is a potential and specific biomarker to identify such patients in a reversible phase. Consequently, I-FABP and other biomarkers are considered promising for the early identification of intra-abdominal pressure related complications, they may even be supportive in determining

the need for, and timing of decompressive measures to relieve the abdominal pressure (17).

The main aim of the current study was to determine the value of serum or urinary levels of I-FABP as early marker for IAH-related complications.

MATERIALS AND METHODS

This prospective, observational study was conducted in two academic hospitals in The Netherlands. The study was approved by the Medical Research Ethics Committee (MREC) in the principal study hospital (reference number MEC-2011-016) and by the local hospital board in the participating center (reference number MEC-2013-076). The study is registered at the Netherlands Trial Register (NTR4638). Signed informed consent by patient or proxy was obtained. The study protocol has been published previously (18).

Patients

Adult patients (18 years or older) admitted to the ICU between April 18, 2011 and March 20, 2015, with at least two risk factors for IAH were eligible (2). Liver transplantation was added as a risk factor, as post-transplantation patients also appear to be at risk for developing IAH (19, 20). Patients were enrolled as soon as possible, maximally within 48 hours after meeting the eligibility criteria. Patients in whom intra-bladder pressure measurement was contra-indicated or unreliable, and patients with inflammatory bowel disease that might affect I-FABP levels were excluded from the study.

Treatment

Treatment was initiated in compliance with international guidelines of the WSACS (2). The IAH/ACS Management Algorithm provides a decision tree for the follow-up of patients related to the IAP level.

Sample collection

During the first 72 hours after enrolment, urine (and blood in a subgroup of 129 patients of one hospital) was sampled every six hours. One hospital was not able to process blood samples for this study. Urine samples were kept on ice and then frozen at −80°C within two hours after collection. Blood was centrifuged at 4°C, 4000g for 15 minutes and stored at −80°C until further analysis.

Data collection

Patient characteristics, ICU admission diagnosis, baseline serum lactate concentrations, urinary creatinine levels at baseline, Simplified Acute Physiology Score (SAPS) II, Sequential Organ Failure Assessment score (SOFA, on day 1 to 4) and Acute Physiology and Chronic Health Evaluation (APACHE) II and IV scores were recorded.

Urinary and serum concentrations of I-FABP were analyzed in duplicate using a highly specific, commercially available enzyme-linked immunosorbent assay (ELISA) that selectively detects human I-FABP (HyCult Biotechnology, Uden, The Netherlands). I-FABP levels in urine were adjusted to urinary creatinine levels in order to correct for renal function. Analysis of claudine-3 levels as was planned for accourding to the protocol, was not feasible due to financial reasons. Intra-abdominal pressure was measured using an intra-bladder technique according to Kron et al. (2) with an instilling volume of 20 mL of sodium chloride 0.9% solution, also every 6 hours during the first 72 hours after enrolment. Complications (New organ failure, ACS and death), as well as any (secondary) intervention performed such as decompression laparotomy, were recorded. The monitoring of occurrence and extent of new organ failure was based upon change in SOFA score. New organ failure was diagnosed if the score in one of six SOFA subdomains increased to ≥3, compared with the day before. Furthermore, mortality during 72 hours of follow-up was registered.

Statistical analysis

A sample size calculation based on previous studies of IAH and I-FABP indicated that an overall population of 200 patients (anticipated to consist of approximately 120 patients without elevated abdominal pressure and 80 patients with IAH) would need to be enrolled in order to detect a 0.5 SD increase in I-FABP level in patients with IAH (two-sided test with an α level of 0.05) with >90% statistical power (21, 22).

Statistical analyses were performed using IBM SPSS statistics 22 (IBM, Armonk, NY, USA). ROC analysis and calculation of the Youden index associated criterions were performed with MedCalc Statistical Software version 17.4 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2017). P-values in plots were calculated with Kruskal-Wallis tests using GraphPad Prism version 5.03 (GraphPad for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com).

Normality of continuous data was assessed by the Shapiro Wilk test. Homogeneity of variances was tested using the Levene's test. Parametric data are presented as mean and standard deviation (SD) and were compared by means of Student t test, non-parametric data were presented by median and quartiles and were compared using Mann-Whitney U-test or Kruskal-Wallis test with Mann-Whitney post-hoc test for pairwise comparisons. Statistical significance was accepted at $p<0.05$.

Linear mixed-effect model was used to determine the correlation between I-FABP levels and IAP. For this later analysis, restricted maximum likelihood method was used, random intercept and slope were considered. Gender, age, BMI, APACHE II at baseline, lactate, mean arterial pressure, and time from baseline measurement were entered as covariates into the model to evaluate their effect on the correlation between I-FABP level and IAP. For determining the predictive value of I-FABP on peak IAP and ACS, repeated measurements of the biomarker were realigned and recoded T=0 for the moment peak IAP or ACS occurred. Median (P25-P75) I-FABP levels were plotted separately for patients with the outcome of interest and control patients. For comparison with the non-ACS control group, the median time point at which ACS occurred in the ACS group was also used as T=0 for the non-ACS patients.

Prognostic role of repeated I-FABP on development of IAH, ACS or new organ failure was assessed using a generalized linear mixed model (GLMM) framework with binomial logit link. The binary outcomes of IAH (IAH versus no IAH; and vice versa for new organ failure or ACS) were used as dependent variable. Patient ID was used as a clustering variable as up to 13 measurements per patient were available. BMI, age, gender, time from baseline measurement, APACHE score, associated mean arterial pressure, and lactate levels were entered as covariate into the model to evaluate their effect on the relation between I-FABP level and outcome. Data points which occurred after the event of interest were left out of this analysis. Random intercept and slope were considered. Results were expressed as odds ratios with corresponding 95% confidence interval and p-values.

Given the low number of new events (IAH, ACS, or mortality), a preliminary confounder model was developed using new organ failure as dependent variable. The variables gender, BMI, baseline serum lactate concentration, Simplified SAPS II, APACHE II, and abdominal status (no IAH/IAH/ACS) were added as covariates. In a final model, the mean and maximum I-FABP level across all measurements as well as the area under the curve of I-FABP level was also added as covariate. The optimal regression model was developed using backstep modelling based on likelihood ratio.

RESULTS

From a total of 200 included patients, two patients were excluded from analysis as informed consent was withdrawn (Figure 1). No patients were lost to follow-up. Clinical baseline characteristics of 198 included patients are shown in Table 1. BMI, SAPS II score, lactate levels, and positive end-expiratory pressure at ICU admission were significantly higher in patients who developed IAH than in patients who did not. Patients had a median number of 4 (P25-P75 3-6) risk factors for IAH. Of 118 patients who developed IAH, 90 (76%) already had IAH at baseline. Fifteen (8%) of the 198 patients were diagnosed with abdominal compartment syndrome of which 12 (80%) already at baseline. The median time-point of development of ACS was T=0 (P25-P75 0-0). Two patients underwent decompressive laparotomy, one of these patients had intestinal ischemia and underwent a colonic resection. Eighteen (9%) patients died in the ICU during the study. Urinary and serum I-FABP levels over time in patients with or without IAH, organ failure, or abdominal compartment syndrome are shown in Figure 2.

Group-based analyses of urinary and serum I-FABP levels related to IAP, IAH, ACS, and organ failure

The baseline levels of urinary and serum I-FABP were not significantly different between patients with or without IAH (Figure 3). Median baseline levels of urinary I-FABP were higher in patients who developed ACS (235 (P25-P75 85-1747) µg/g creat) than in patients with IAH who did not develop ACS (87 (P25-P75 33-246) µg/g, p=0.037, Figure 3A). Also, they were higher than in patients without new organ failure and IAP>20 mmHg;90 (P25-P75 25-202) µg/g creat, p=0.035, Figure 3B). No differences in baseline levels of serum I-FABP were found between patients with and without IAH, neither in patients with ACS and patients with new organ failure without IAP>20 mmHg (Figures 3C and D).
Multi-level correlation over the complete follow-up period showed that urinary I-FABP levels and IAP were positively and linearly correlated in unadjusted and adjusted models (Table 2). Serum I-FABP levels did not correlate with IAP.

Patient-based analyses of urinary and serum I-FABP levels related to IAP, IAH, ACS, and organ failure

Intra-abdominal hypertension:

No significant peaks in serum or urinary I-FABP levels prior to the peak value of IAP could be demonstrated (Figure 4). Only median urinary I-FABP levels were significantly, but not clinically relevantly, higher in the patients with IAH vs. patients without IAH, only at T-12 (84.5 µg/g creat vs. 41.2 µg/g creat respectively, p=0.04).

Abdominal compartment syndrome:

Median serum I-FABP levels were 3432 (P25 – P75 189-6839) ng/L in patients with ACS at time of ACS occurrence (T0), compared with 602 (P25 – P75174-1631) in patients that did not develop ACS (p=0.2; Figure 5). I-FABP measurements before ACS developed, were only available in 2 patients. The calculation of receiver operator characteristics (ROC) was performed on I-FABP values from the moment ACS had already emerged (Table 3). I-FABP showed no discriminatory ability on the development of ACS. The area under the ROC curve (AUC) of urinary I-FABP was 0.62 (95% CI 0.55–0.69, p = 0.13) with a sensitivity of 64.3% (95% CI 35.1- 87.2%) and a specificity of 59.3% (95% CI 51.7-66.6%). Serum I-FABP AUC was 0.75 (95% CI 0.67-0.83) with a sensitivity of 66.7% (95% CI 22.3-95.7%) and specificity of 92.5% (95% CI 86.2-96.5%). Since no predictive value on ACS was found, determination of the predictive value on organ failure was obsolete and not performed.

Analyses of repeated urinary and serum I-FABP levels related to IAP, IAH, ACS, and organ failure

Unadjusted generalized linear mixed model analysis demonstrated no statistically significant predictive value of repeated I-FABP measurements on the development of IAH, new organ failure or ACS on a patient level (Table 4). The odds ratio of urinary I-FABP in predicting ACS was 1.00 (95% CI 1.00-1.00, p=0.07), and 1.00 (95% CI 1.00-1.00, P=0.69) for serum I-FABP. Adjusting for covariates did not improve any of the prediction models in this study. Both the preliminary and final logistic regression models did not demonstrate a significant value of I-FABP measurement on the onset of new organ failure on a patient level (data not shown). Both in the unadjusted and adjusted analyses, the p-value for the mean I-FABP level, maximum I-FABP level, and area under the I-FABP curve were larger than 0.05.

DISCUSSION

The present study represents the largest cohort on I-FABP related to abdominal pressure and complications in ICU patients. Although I -FABP levels are statistically different between the groups of patients with IAH/ACS and those without, urinary and serum I-FABP levels have no relevant value in the early identification of patients at risk for IAH-related complications on an individual patient level. Intestinal ischemia or mucosal disruption (as measured by I-FABP) are no early signs of IAH-related complications.

These findings are in contrast with the limited available literature on this subject. Diagnostic values of urinary and serum I-FABP levels have been investigated previously in specific subgroups of patients. Several studies suggest that I-FABP may be useful as marker for the diagnosis of intestinal ischemia in patients with acute abdominal pain or after aortic surgery (23-25). A meta-analysis of 1,246 patients confirmed that I-FABP may be useful in diagnosing intestinal ischemia (26). However, included studies were small and heterogeneous, group differences were not corrected for, and in some studies no histo-pathological examination was performed. This could have led to overestimation of the diagnostic value of I-FABP in the detection of intestinal ischemia. Indeed, experimental models showed that intestinal ischemia could only be detected in pigs with abdominal pressures above 20-25 mmHg and became more apparent at 30-40 mmHg (27, 28). Translation to human circumstances is difficult, but this may suggest that intestinal ischemia only occurs when ACS already occurred. Data from the current study cannot confirm this. An animal study exposing animals to increasing IAP and evaluating both I-FABP levels and ischemia would be needed. I-FABP was measured in critically ill ICU patients with risk factors for IAH. Increased I-FABP levels were found in the small group of patients with ACS. A larger group of patients is needed for confirmation and to provide a meaning for this finding. I-FABP levels were not only elevated in patients with IAH, ACS, or new organ failure, but also in patients without these conditions. Among these patients, peak serum I-FABP levels were even four to nine fold higher than in control groups of other studies that used the same ELISA kit (24, 25). The control groups in previous studies consisted of healthy controls, patients with acute abdominal pain due to other conditions such as bowel obstruction, appendicitis, coprostasis or diverticulitis, or patients with an uncomplicated course after aortic surgery (23-25). Our control group of ICU patients likely

suffer from more severe conditions that already increase I-FABP. Nevertheless, from a clinical point of view, ICU patients with risk factors for IAH represent the correct control group.

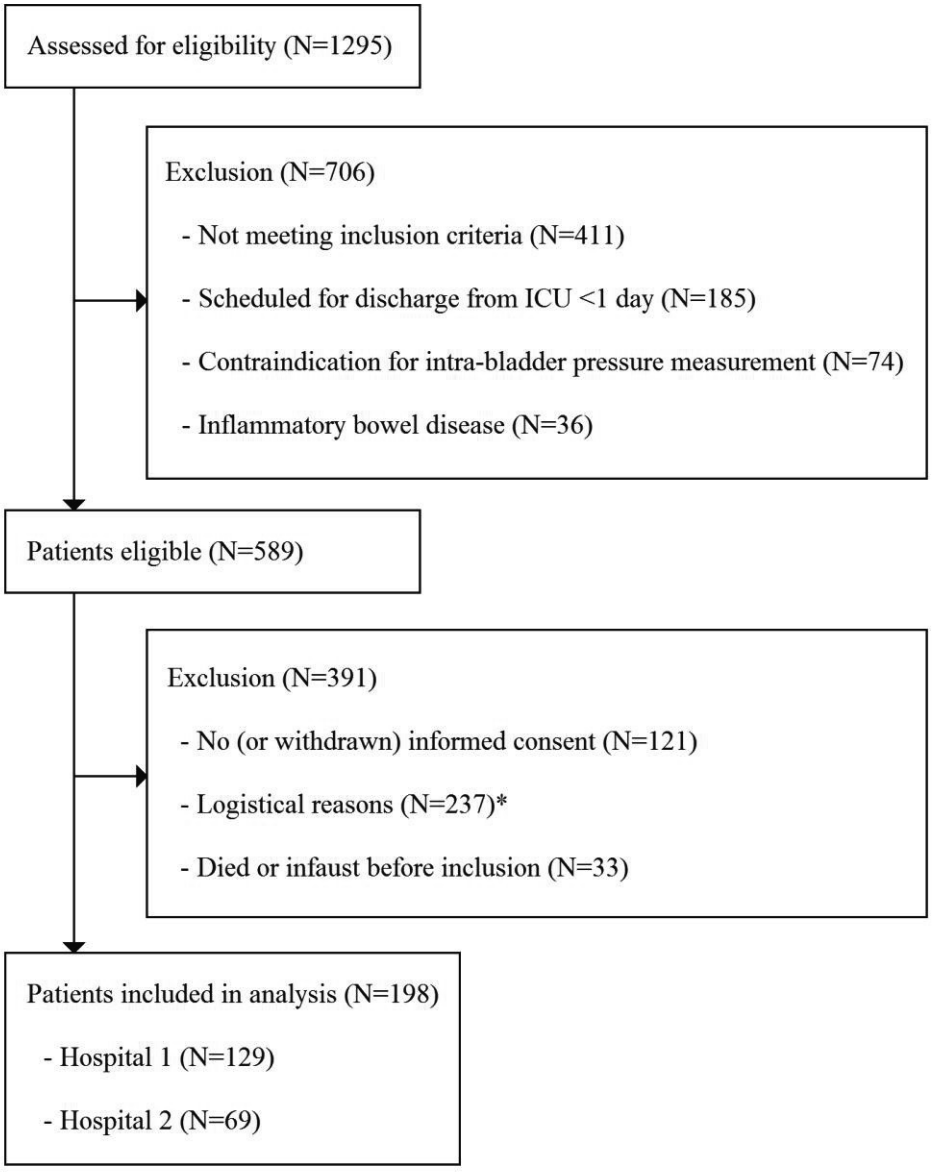
This study has several limitations. First, 237 patients were excluded for logistical reasons, it's unclear (but ulnlikely) whether this has lead to a selection bias. Second, the rate of ACS in the present study in patients with risk factors for IAH was 8%. This is not completely in line with recently reported rates of ACS of 3-6% among general population of adult ICU patients not selected for the presence of risk factors (6, 29). Aggressive medical and minimally invasive therapies to avoid sustained IAH or ACS in our patient cohort may account for this relatively low rate of ACS. Since few patients developed ACS and 80% (12 out of 15) of patients had already developed ACS at baseline measurement, it was not possible to demonstrate a peak in I-FABP values prior to development of ACS. The latter also applied for the 76% of patients that had already developed IAH at baseline. In general, the relatively low number of patients with newly developed IAH or ACS during follow-up has limited the statistical analysis and made the study underpowered for analysis of newly developed ACS. Third, our study illustrates that IAH and ACS develop very rapidly. As a consequence, many patients had already developed IAH or ACS before informed consent was obtained. As a result, many relevant patho-physiologic changes prior to the actual onset of IAH or ACS, were missed. Given the short half-life of I-FABP, an increase in I-FABP prior to onset of IAH or ACS may also have been mist. Fourth, it was difficult to assess the endpoint 'new organ failure'. WSACS defined ACS as an IAP >20 mmHg that is associated with new organ failure (2). The most applied and objective assessment for the presence of organ failure is the SOFA score. This score is calculated only once a day, all other time varying outcomes where measured 4 times a day. Therefore, it was impossible to accurately determine at what time organ failure actually occurred, related to the other measurements. This affected the moment ACS was diagnosed in the present study. Moreover, inherent to the observational nature of our study, it remains unclear to what extent and how new organ failure can be attributed to IAP. Fifth, a study design with repeated measurements every six hours (i.e. with an overnight measurement) resulted in missing measurements. Given the rapid development of IAH and ACS, a peak in abdominal pressure or I-FABP levels can easily be missed in the case of a missed measurement. Nevertheless, the consequences of these limitations were

minimized by mixed model analysis. As a last limitation, blood could only be collected at one hospital. Since the case-mix was similar in both hospitals, this has unlike influenced the results.

CONCLUSION

A relevant diagnostic value of I-FABP levels for identifying individual patients at risk for intra-abdominal pressure related complications could not be demonstrated. Therefore, I-FABP should be re-analysed in a study that includes patients in who IAP has not exceeded 20 mmHg yet. Until then, it should not be used for early detection of IAH related complications in daily clinical practice.

Figure 1: Flowchart



* Logistical reasons included unavailability of proxy to provide consent within the acceptable time window or insufficient staff to perform measurements.

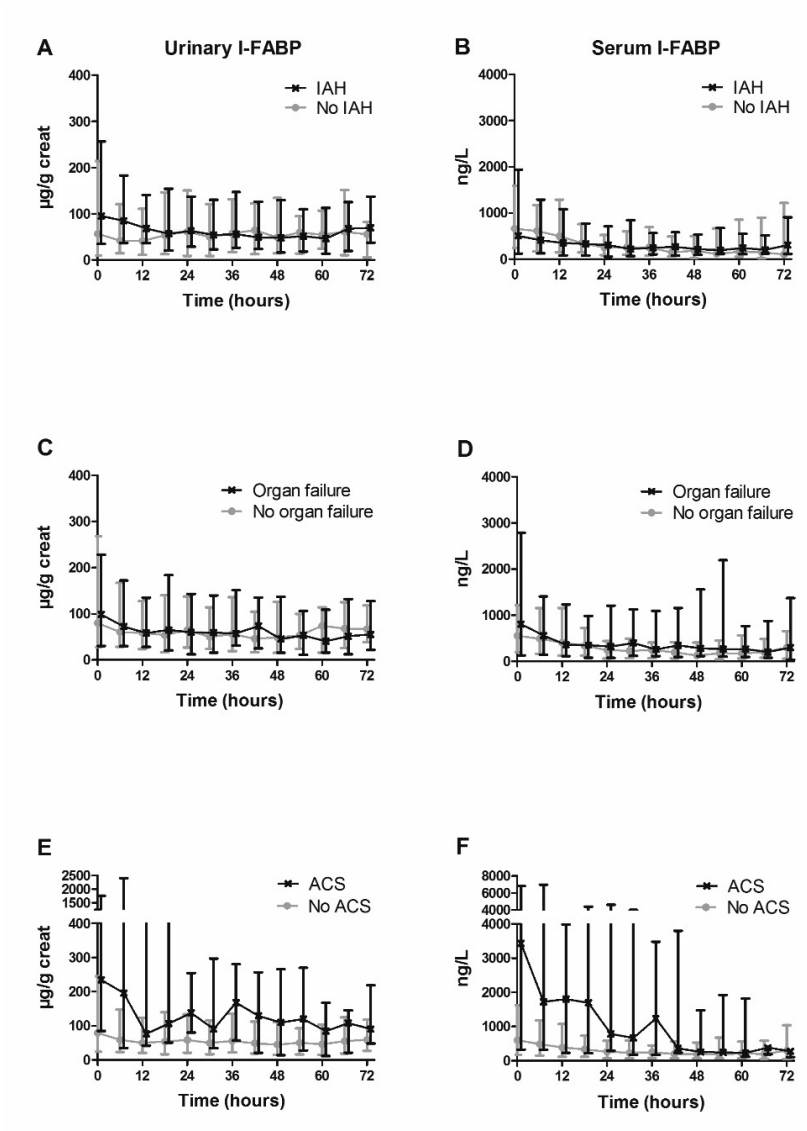
Table 1: Baseline characteristics and overview of risk factors at enrolment for patients with versus without intra-abdominal hypertension

	All N=198	IAH N=118	No IAH N=80	P-value
Age (years)	62 (51 - 70)	64 (53 - 71)	60 (49 - 69)	0.145
BMI (kg/m^2)	25 (23 - 29)	27 (24 - 31)	24 (22 - 28)	0.001
APACHE II score	21 (17 - 25)	22 (17 - 27)	21 (16 - 24)	0.105
SAPS II score	44 (30 - 57)	50 (37 - 61)	35 (24 - 50)	<0.001
SOFA score	8 (6 - 11)	9 (6 - 12)	8 (5 - 11)	0.158
Mean arterial pressure (mmHg)	80 (72 - 90)	81 (72 - 95)	80 (73 - 87)	0.406
IAP (mmHg)	11 (7 - 15)	14 (12 - 17)	6 (4 - 8)	<0.001
Mechanical ventilation (intubated)	138 (69.7%)	94 (79.7%)	44 (55.0%)	<0.001
PEEP (mmHg)	8 (6 - 10)	10 (8 - 12)	6 (5 - 10)	<0.001
Lactate at admission (mmol/L)	1.9 (1.3 - 3.3)	2.2 (1.5 - 3.4)	1.6 (1.2 - 2.3)	0.020
Risk factors, n	4 (3 - 6)	5 (4 - 6)	4 (3 - 5)	0.086
PEEP (any level)	149 (75.3%)	94 (79.7%)	55 (68.8%)	0.094
Coagulopathy	131 (66.2%)	76 (64.4%)	55 (68.8%)	0.545
Abdominal surgery	127 (64.1%)	71 (60.2%)	56 (70.0%)	0.176
Sepsis	67 (33.8%)	50 (42.4%)	17 (21.3%)	0.002
Massive resuscitation (>5L)	66 (33.3%)	39 (33.1%)	27 (33.8%)	1.000
Oliguria	62 (31.3%)	44 (37.3%)	18 (22.5%)	0.030
Cirrhosis	45 (22.7%)	17 (14.4%)	28 (35.0%)	0.001
BMI>30	40 (20.2%)	30 (25.4%)	10 (12.5%)	0.031
Massive transfusion(protocol started)	35 (17.7%)	19 (16.4%)	16 (20.0%)	0.571
Pancreatitis or peritonitis	35 (17.7%)	26 (22.0%)	9 (11.3%)	0.059
Hemo/pneumoperitoneum	27 (13.6%)	20 (16.9%)	7 (8.8%)	0.139
Liver transplantation	26 (13.1%)	7 (5.9%)	19 (23.8%)	<0.001
Acidosis pH<7.35)	24 (12.1%)	18 (15.3%)	6 (7.5%)	0.123
Trauma	20 (10.1%)	13 (11.0%)	7 (8.8%)	0.641
Damage control surgery	20 (10.1%)	13 (11.0%)	7 (8.8%)	0.641
Ileus	19 (9.6%)	16 (13.6%)	3 (3.8%)	0.026
Abdominal wall reconstruction	5 (2.5%)	4 (3.4%)	1 (1.3%)	0.650
Prone position	4 (2.0%)	4 (3.4%)	0 (0.0%)	0.149
Hypothermia (T<35°C)	0 (0.0%)	0 (0.0%)	0 (0.0%)	N.D.

Data are presented as number with corresponding percentage (%) or median (P_{25} - P_{75}). P-values were calculated using a Mann Whitney U-test or Fisher exact test. None of the patients had burn injuries. APACHE, Acute Physiology and Chronic Health Evaluation; BMI,

body mass index; IAH, intra-abdominal hypertension; IAP, intra-abdominal pressure; N.D., not determined; PEEP, positive end expiratory pressure; SAPS, Simplified Acute Physiology Score; SOFA, sequential organ failure assessment.

Figure 2: Change in urinary (A, C, E) and serum (B, D, F) I-FABP levels over time in patients with or without intra-abdominal hypertension (A, B), organ failure (C, D), or abdominal compartment sydrome (E, F)



Data are represented as median with P_{25}-P_{75}.

ACS, abdominal compartment syndrome; creat, creatinine; IAH, intra-abdominal hypertension; I-FABP, intestinal fatty acid binding protein.

Table 2: Univariate and multivariable analysis of correlation between I-FABP and intra-abdominal pressure

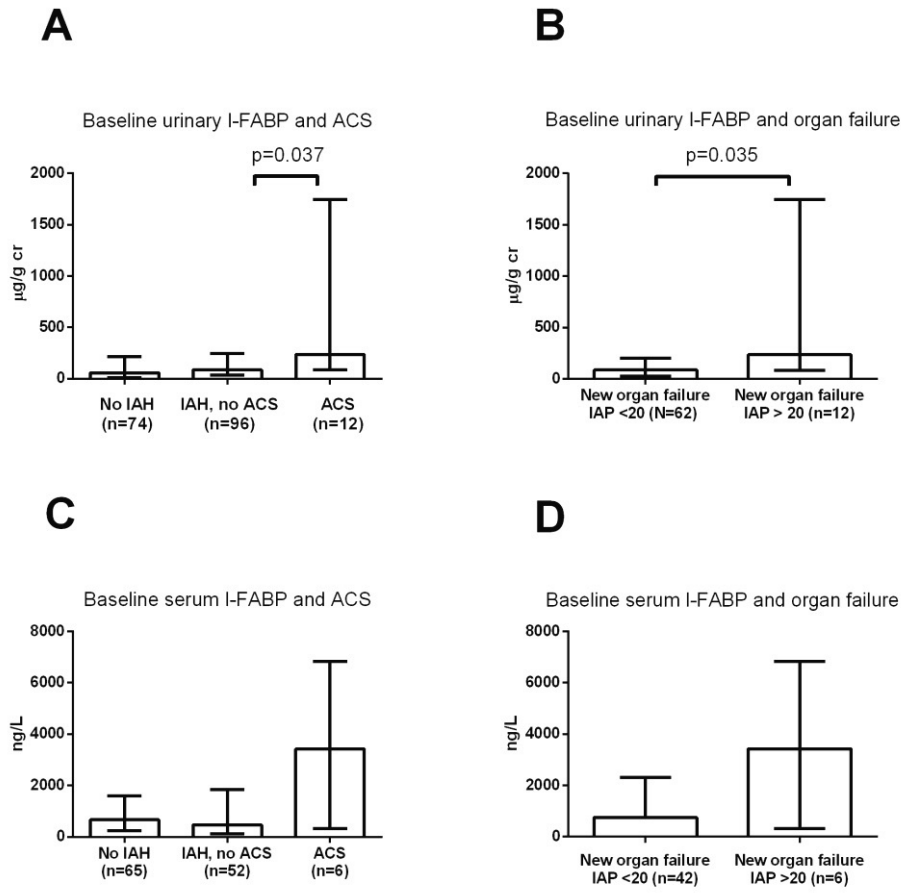
	Urinary I-FABP (µg/g creat)			Serum I-FABP (ng/L)		
Unadjusted linear mixed model	**N***	**Estimate (95% CI)**	**P**	**N**	Estimate (95% CI)	**P**
All patients	1,641	28 (5-51)	0.017	1121	82 (-11-176)	0.084
Patients with IAH	1,06	37 (3-71)	0.034	608	77 (-21-175)	0.124
Adjusted linear mixed model**	**N**	**Estimate**	**P**	**N**	**Estimate**	**P**
All patients	1,123	31 (5-57)	0.019	988	59 (-40-158)	0.243
Patients with IAH	211	42 (3-81)	0.035	211	58 (-47-164)	0.278

The coefficient estimates for the linear mixed models are shown with 95% confidence interval between brackets.

CI, confidence interval; creat, creatinine; IAH, intra-abdominal hypertension; I-FABP, intestinal fatty acid binding protein; N*, number of samples used for this analysis, i.e. this number includes multiple observations of same patients.

* Analysis was adjusted for lactate and MAP.

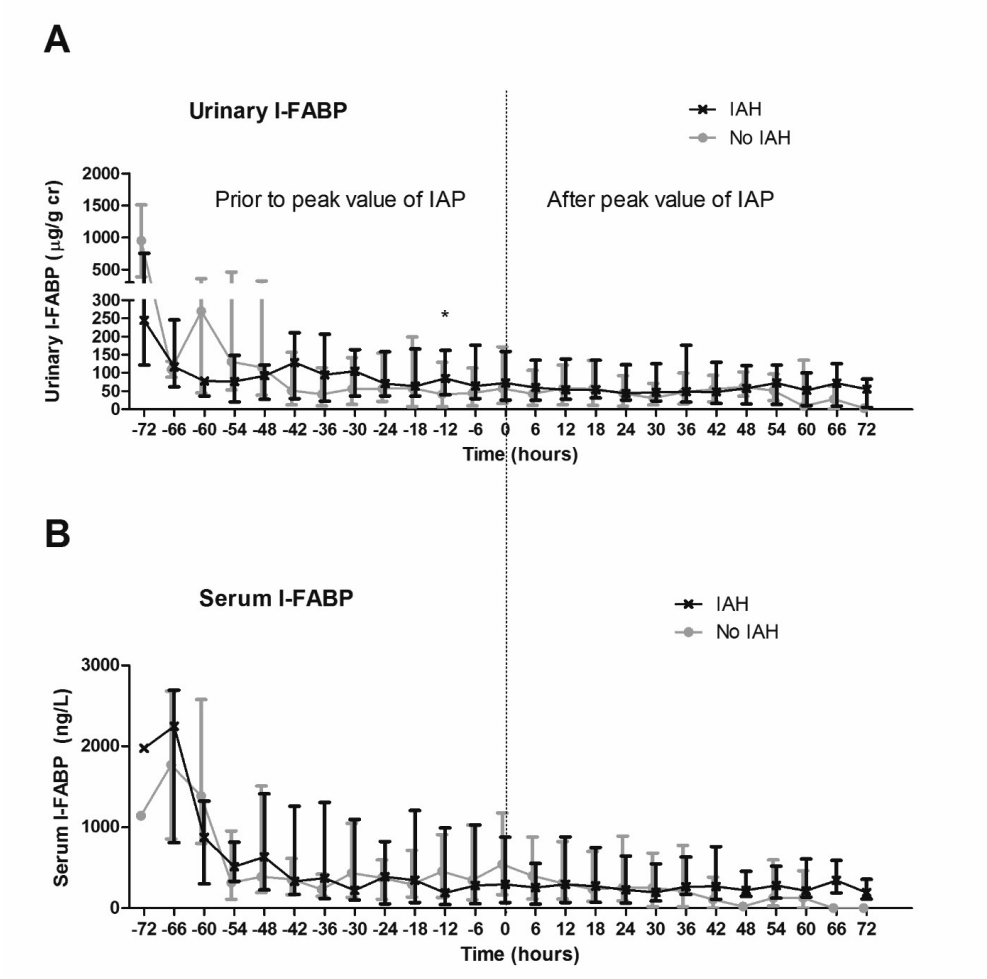
Figure 3: I-FABP levels at baseline in patients admitted to the ICU with at least 2 risk factors for intra-abdominal hypertension.



Data are represented as median with P_{25}-P_{75}.

ACS, abdominal compartment syndrome; creat, creatinine; IAH, intra-abdominal hypertension; I-FABP, intestinal fatty acid binding protein.

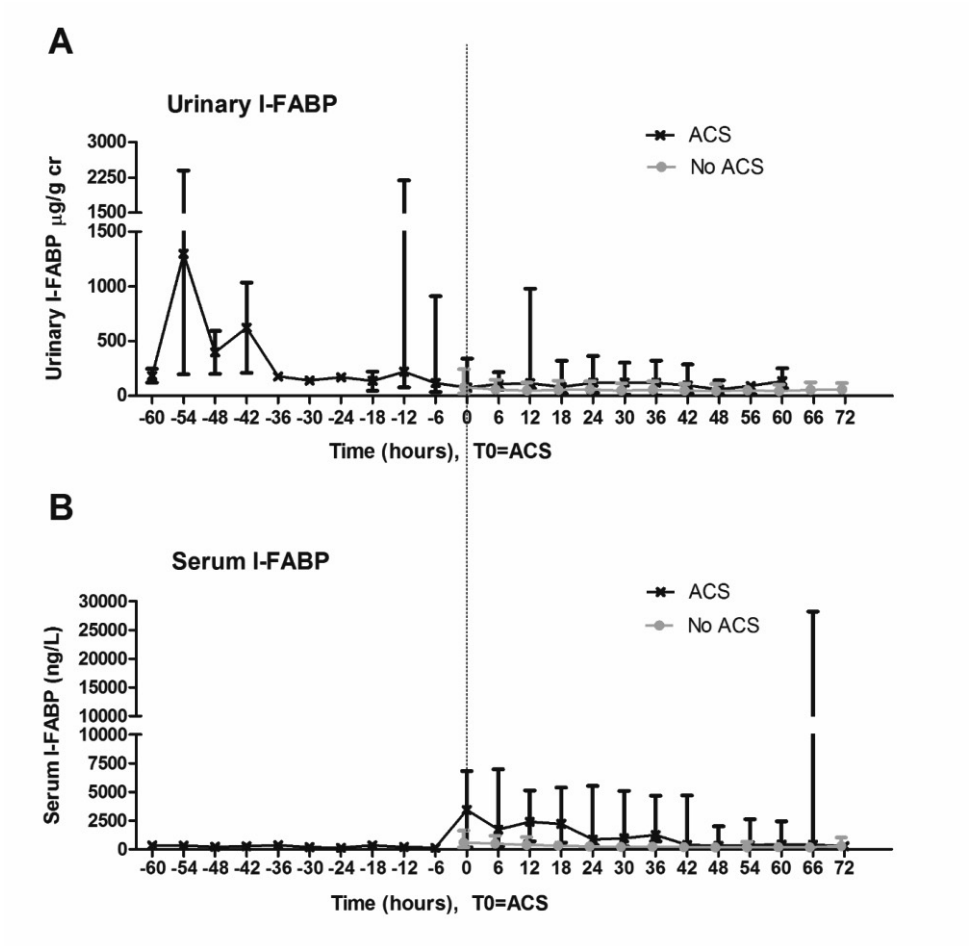
Figure 4: Time course of median (P_{25}-P_{75}) levels of I-FABP before and after peak values of IAP. 0 Denotes the peak value of IAP. (A) Urinary I-FABP levels. (B) Serum I-FABP levels.



Data are represented as median with P_{25}-P_{75}. * Indicates statistically significant difference, tested using Kruskal-Wallis tests.

IAH, intra-abdominal hypertension; IAP, intra-abdominal pressure; I-FABP, intestinal fatty acid binding protein.

Figure 5: Time course of median levels of I-FABP before and after ACS. 0 denotes the moment of ACS. (A) Urinary I-FABP. (B) Serum I-FABP.



Data are represented as median with P_{25}-P_{75}. No statistically significant differences were found, using Kruskal-Wallis tests.

ACS, abdominal compartment syndrome; I-FABP, intestinal fatty acid binding protein.

Table 3: Diagnostic performance of multiple urinary and serum I-FABP levels for intra-abdominal hypertension, organ failure, and

All patients	**Event**	**N**	**AUC (95% CI)**	**P**	**Cut-off value (95% CI)**	**Sensitivity (%) (95% CI)**	**Specificity (%) (95% CI)**
Urinary I-FABP (µg/g creat)	IAH	191	0.57 (0.50-0.64)	0.085	44 (34-604)	91.2 (84.3-95.7)	26.9 (17.5-38.2)
	High-grade IAH	113	0.57 (0.48-0.67)	0.311	214 (84-5,644)	63.2 (38.4-83.7)	56.4 (45.8-66.6)
	Organ failure	181	0.61 (0.54-0.68)	0.009	586 (108-2,186)	33.3 (22.7-45.4)	87.2 (79.4-92.8)
	ACS	191	0.62 (0.55-0.69)	0.127	222 (41-1,994)	64.3 (35.1-87.2)	59.3 (51.7-66.6)
Urinary I-FABP (µg/g creat; AUC*)	IAH	186	0.57 (0.50-0.64)	0.096	30.3 (9.2-191)	79.6 (70.8-86.8)	35.9 (25.3-47.6)
	High-grade IAH	108	0.61 (0.51-0.70)	0.227	159 (38-229)	56.2 (29.9-80.2)	77.2 (67.2-85.3)
	Organ failure	176	0.60 (0.52-0.67)	0.026	301 (300-765)	22.5 (13.5-34.0)	96.2 (90.5-99.0)
	ACS	186	0.67 (0.60-0.74)	0.066	126 (38-812)	66.7 (34.9-90.1)	77.0 (70.0-83.0)
Serum I-FABP (ng/L)	IAH	126	0.50 (0.41-0.59)	0.947	4,588 (4,525-4,588)	78.3 (65.8-87.9)	4.6 (0.9-12.7)
	High-grade IAH	60	0.64 (0.51-0.76)	0.278	5,957 (5,297-50,158)	55.6 (21.2-86.3)	90.2 (78.6-96.7)
	Organ failure	121	0.60 (0.51-0.69)	0.073	2,869 (2,684-6,002)	44.7 (30.2-59.9)	87.8 (78.2-94.3)
	ACS	126	0.75 (0.67-0.83)	0.042	5,956 (5,297-29,894)	66.7 (22.3-95.7)	92.5 (86.2-96.5)
Serum I-FABP (ng/L; AUC*)	IAH	126	0.54 (0.45-0.63)	0.417	292 (104-1,394)	53.3 (40.0-66.3)	68.2 (55.6-79.1)
	High-grade IAH	60	0.62 (0.49-0.75)	0.298	1355 (107-5,764)	44.1 (13.7-78.8)	84.3 (71.4-93.0)
	Organ failure	121	0.60 (0.50-0.68)	0.092	968 (752-1,702)	46.8 (32.1-61.9)	83.8 (73.4-91.3)
	ACS	126	0.71 (0.62-0.79)	0.063	955 (211-4,164)	66.7 (22.3-95.7)	72.5 (63.6-80.3)
Patients with IAH							
Urinary I-FABP (µg/g creat)	Organ failure	108	0.63 (0.53-0.72)	0.018	487 (77-906)	41.7 (27.6-56.8)	85.0 (73.4-92.9)
	ACS	113	0.60 (0.50-0.69)	0.268	1,775 (390-10,584)	28.6 (8.4-58.1)	93.9 (87.3-97.7)

Urinary I-FABP (µg/g creat; AUC*)	Organ failure	103	0.63 (0.52-0.72)	0.027	150 (117-387)	46.8 (32.1-61.9)	82.4 (69.6-91.1)
	ACS	108	0.65 (0.56-0.74)	0.123	158 (24-229)	66.7 (34.9-90.1)	77.1 (67.4-85.0)
Serum I-FABP (ng/L)	Organ failure	57	0.62 (0.48-0.75)	0.116	2,869 (2,210-50,158)	48.2 (28.7-68.1)	86.7 (69.3-96.2)
	ACS	60	0.75 (0.62-0.85)	0.316	5,956 (5,297-27,769)	66.7 (22.3-95.7)	88.9 (77.4-95.8)
Serum I-FABP (ng/L; AUC*)	Organ failure	57	0.62 (0.48-0.74)	0.127	968 (128-1,525)	44.4 (25.5-64.7)	83.3 (65.3-94.4)
	ACS	60	0.72 (0.59-0.83)	0.023	211 (139-871)	100.0 (54.1-100.0)	40.7 (27.6-55.0)

Data were analyzed using ROC analysis. Sensitivity and specificity are shown as percentage. AUC, cut-off value, sensitivity, and specificity are shown with 95% confidence interval within brackets.

*AUC is calculated as the area under the curve divided by the number of measurements (displaying mean excretion per time point). Missing data were linearly imputed.

ACS, abdominal compartment syndrome; AUC, area under the receiver operating characteristics curve; CI, confidence interval; creat, creatinine; IAH, intra-abdominal hypertension; IAP, intra-abdominal pressure; I-FABP, intestinal fatty acid binding protein; N.A., not applicable; ROC, receiver operating characteristic.

Table 4 – Prognostic role of urinary and serum I-FABP levels on development of intra-abdominal hypertension, abdominal compartment syndrome and organ failure

	Event		Unadjusted analysis	
All patients		**N**	**OR (95% CI)**	**P**
Urinary I-FABP (μg/g creat)	IAH	818	1.000 (1.000-1.001)	0.266
	ACS	710	1.000 (1.000-1.001)	0.066
	Organ failure	694	1.000 (1.000-1.001)	0.178
Serum I-FABP (ng/L)	IAH	652	1.000 (1.000-1.000)	0.339
	ACS	568	1.000 (1.000-1.000)	0.686
	Organ failure	561	1.000 (1.000-1.000)	0.576
Patients with IAH				
Urinary I-FABP (μg/g creat)	ACS	218	1.000 (1.000-1.001)	0.115
	Organ failure	212	1.000 (1.000-1.001)	0.359
Serum I-FABP (ng/L)	ACS	123	1.000 (1.000-1.000)	0.733
	Organ failure	120	1.000 (1.000-1.000)	0.705

Data were analyzed using a generalized linear mixed model. The OR is shown with 95% confidence interval within brackets.

Adjusting for covariates did not significantly improve any of the models; therefore, adjusted analysis is not shown.

ACS, abdominal compartment syndrome; CI, confidence interval; creat, creatinine; IAH, intra-abdominal hypertension; I-FABP, intestinal fatty acid binding protein; OR, odds ratio.

REFERENCES

1. Moore FA. The role of the gastrointestinal tract in postinjury multiple organ failure. Am J Surg. 1999;178(6):449-53.
2. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, et al. IAH and the ACS: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med. 2013;39(7):1190-206.
3. Balogh ZJ, Lumsdaine W, Moore EE, Moore FA: Postinjury abdominal compartment syndrome: from recognition to prevention. Lancet 2014, 384(9952):1466-1475.
4. Vidal MG, Ruiz Weisser J, Gonzalez F, Toro MA, Loudet C, Balasini C, et al. Incidence and clinical effects of intra-abdominal hypertension in critically ill patients. Crit Care Med. 2008;36(6):1823-31.
5. Eddy V, Nunn C, Morris JA, Jr. Abdominal compartment syndrome. The Nashville experience. Surg Clin North Am. 1997;77(4):801-12.
6. Reintam Blaser A, Regli A, De Keulenaer B, Kimball EJ, Starkopf L, Davis WA, et al. Incidence, Risk Factors, and Outcomes of Intra-Abdominal Hypertension in Critically Ill Patients-A Prospective Multicenter Study (IROI Study). Crit Care Med. 2019.
7. Lieberman JM, Sacchettini J, Marks C, Marks WH. Human intestinal fatty acid binding protein: report of an assay with studies in normal volunteers and intestinal ischemia. Surgery. 1997;121(3):335-42.
8. de Haan JJ, Lubbers T, Derikx JP, Relja B, Henrich D, Greve JW, et al. Rapid development of intestinal cell damage following severe trauma: a prospective observational cohort study. Crit Care. 2009;13(3):R86.
9. Derikx JP, van Waardenburg DA, Thuijls G, Willigers HM, Koenraads M, van Bijnen AA, et al. New Insight in Loss of Gut Barrier during Major Non-Abdominal Surgery. PLoS One. 2008;3(12):e3954.
10. Edelson MB, Sonnino RE, Bagwell CE, Lieberman JM, Marks WH, Rozycki HJ. Plasma intestinal fatty acid binding protein in neonates with necrotizing enterocolitis: a pilot study. J Pediatr Surg. 1999;34(10):1453-7.

11. Gollin G, Marks C, Marks WH. Intestinal fatty acid binding protein in serum and urine reflects early ischemic injury to the small bowel. Surgery. 1993;113(5):545-51.
12. Gollin G, Marks WH. Elevation of circulating intestinal fatty acid binding protein in a luminal contents-initiated model of NEC. J Pediatr Surg. 1993;28(3):367-70; discussion 70-1.
13. Ockner RK, Manning JA. Fatty acid-binding protein in small intestine. Identification, isolation, and evidence for its role in cellular fatty acid transport. J Clin Invest. 1974;54(2):326-38.
14. Pelsers MM, Hermens WT, Glatz JF. Fatty acid-binding proteins as plasma markers of tissue injury. Clin Chim Acta. 2005;352(1-2):15-35.
15. Relja B, Szermutzky M, Henrich D, Maier M, de Haan JJ, Lubbers T, et al. Intestinal-FABP and liver-FABP: Novel markers for severe abdominal injury. Acad Emerg Med. 2010;17(7):729-35.
16. Habes QLM, van Ede L, Gerretsen J, Kox M, Pickkers P. Norepinephrine Contributes to Enterocyte Damage in Septic Shock Patients: A Prospective Cohort Study. Shock. 2018;49(2):137-43.
17. Hecker A, Hecker B, Hecker M, Riedel JG, Weigand MA, Padberg W. Acute abdominal compartment syndrome: current diagnostic and therapeutic options. Langenbecks Arch Surg. 2016;401(1):15-24.
18. Strang SG, Van Waes OJ, Van der Hoven B, Ali S, Verhofstad MH, Pickkers P, et al. Intestinal fatty acid binding protein as a marker for intra-abdominal pressure-related complications in patients admitted to the intensive care unit; study protocol for a prospective cohort study (I-Fabulous study). Scand J Trauma Resusc Emerg Med. 2015;23:6.
19. Biancofiore G, Bindi ML, Romanelli AM, Bisa M, Boldrini A, Consani G, et al. Postoperative intra-abdominal pressure and renal function after liver transplantation. Arch Surg. 2003;138(7):703-6.
20. Biancofiore G, Bindi ML, Romanelli AM, Boldrini A, Consani G, Bisa M, et al. Intra-abdominal pressure monitoring in liver transplant recipients: a prospective study. Intensive Care Med. 2003;29(1):30-6.

21. Malbrain ML, Chiumello D, Pelosi P, Bihari D, Innes R, Ranieri VM, et al. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. Crit Care Med. 2005;33(2):315-22.
22. Kanda T, Fujii H, Tani T, Murakami H, Suda T, Sakai Y, et al. Intestinal fatty acid-binding protein is a useful diagnostic marker for mesenteric infarction in humans. Gastroenterology. 1996;110(2):339-43.
23. Kanda T, Tsukahara A, Ueki K, Sakai Y, Tani T, Nishimura A, et al. Diagnosis of ischemic small bowel disease by measurement of serum intestinal fatty acid-binding protein in patients with acute abdomen: a multicenter, observer-blinded validation study. J Gastroenterol. 2011;46(4):492-500.
24. Thuijls G, van Wijck K, Grootjans J, Derikx JP, van Bijnen AA, Heineman E, et al. Early diagnosis of intestinal ischemia using urinary and plasma fatty acid binding proteins. Ann Surg. 2011;253(2):303-8.
25. Vermeulen Windsant IC, Hellenthal FA, Derikx JP, Prins MH, Buurman WA, Jacobs MJ, et al. Circulating intestinal fatty acid-binding protein as an early marker of intestinal necrosis after aortic surgery: a prospective observational cohort study. Ann Surg. 2012;255(4):796-803.
26. Sun DL, Cen YY, Li SM, Li WM, Lu QP, Xu PY. Accuracy of the serum intestinal fatty-acid-binding protein for diagnosis of acute intestinal ischemia: a meta-analysis. Sci Rep. 2016;6:34371.
27. Nielsen C, Kirkegard J, Erlandsen EJ, Lindholt JS, Mortensen FV. D-lactate is a valid biomarker of intestinal ischemia induced by abdominal compartment syndrome. J Surg Res. 2015;194(2):400-4.
28. Diebel LN, Dulchavsky SA, Wilson RF. Effect of increased intra-abdominal pressure on mesenteric arterial and intestinal mucosal blood flow. J Trauma. 1992;33(1):45-8; discussion 8-9.
29. Murphy PB, Parry NG, Sela N, Leslie K, Vogt K, Ball I. Intra-Abdominal Hypertension Is More Common Than Previously Thought: A Prospective Study in a Mixed Medical-Surgical ICU. Crit Care Med. 2018;46(6):958-64.

Chapter 9

Relation between intra-abdominal pressure and early intestinal ischemia in rats

SUBMITTED

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ABSTRACT

Background: Timing of abdominal decompression in patients at risk for abdominal compartment syndrome (ACS) is challenging. Little is known on early irreversible effects of transient or subclinical increase of intra-abdominal pressure (IAP) to 20 mmHg. The aim of this study was to determine the relation between IAP and respiratory parameters, hemodynamic parameters, and the development of early intestinal ischemia in rats.

Methods: Twenty-five anesthetized and ventilated male adult Sprague-Dawley rats were randomly assigned to five groups and exposed to IAPs of 0, 5, 10, 15, or 20 mmHg for three hours. Respiratory parameters, hemodynamic parameters and serum samples were collected at baseline, 90, and 180 minutes. Serum albumin-cobalt binding (ACB) capacity was determined as measure for systemic ischemia. Intestines were processed for histopathologic examination for ischemia. Spearman rank correlation was used to test the association between IAP and individual variables.

Results: IAP was negatively associated with mean arterial pressure at 90 (Spearman correlation coefficient; Rs= -0.446, p=0.025) and 180 minutes (Rs= -0.466, p=0.019), oxygen saturation and partial oxygen pressure (pO2) at 90 minutes (Rs= -0.673, p<0.001; Rs= -0.561, p=0.004) and 180 minutes (Rs= -0.882, p<0.001; Rs= -0.752, p<0.001), pH-value at 90 (Rs= -0.819, p<0.001) and 180 minutes (Rs= -0.934, p<0.001). IAP was positively associated with central venous pressure (Rs= 0.581, p=0.002) at 180 minutes. There were no associations between IAP and lactate level or ACB capacity. No signs for intestinal ischemia were found.

Conclusion: Although increasing IAP was associated with respiratory and hemodynamic difficulties, no early intestinal ischemia was found.

INTRODODUCTION

Intra-abdominal pressure (IAP) is the pressure concealed within the abdominal cavity. A substantial increase in IAP ≥12 mmHg is termed intra-abdominal hypertension (IAH). If IAH exceeds 20 mmHg, reduced intra-abdominal arterial perfusion pressure will result in organ dysfunction which is termed abdominal compartment syndrome (ACS). This condition is related to high morbidity and mortality (1, 2). Risk factors and treatment options for ACS have been listed by the Abdominal Compartment Society (WSACS) in the 'Consensus definitions and clinical practice guidelines' (3). According to these guidelines, a decompression laparotomy should be performed if non-invasive measures failed.

An IAP of 20 to 25 mmHg for a period of only 60 minutes may already reduce mucosal blood flow of the intestines of rats and deteriorate intestinal-barrier function (4). Moreover, IAH may cause irreversible intestinal ischemia before alterations in cardiac output or mean arterial pressure (MAP) become noticeable (5, 6). Therefore, *early* surgical decompression before the development of ACS is becoming increasingly common (7). Since this treatment is related to high morbidity, the surgeon must be sure whether organ dysfunction is caused by IAH (8).

The detrimental effects of ACS and persistent high IAP are well known (9). However, the early irreversible effects of subclinical or transient IAH with intra-abdominal pressures up to 20 mmHg are unknown. Knowledge of such effects may help surgeons in decision-making on early surgical abdominal decompression. As it is hardly feasible to study this in humans, an animal model should be used. The aim of this study was to determine the relation between early increased IAP and respiratory parameters, hemodynamic parameters, and the development of intestinal ischemia in rats.

METHODS

All animal experiments were performed in accordance with the recommendations of the Guide for the Care and Use of Laboratory Animals, and under the regulation and permission of the local Animal Care Committee. Adult (8-10 weeks old) male Sprague-Dawley rats (300-350 g, specific pathogen-free, Harlan Laboratories, Boxmeer, The Netherlands) were supplied with standard laboratory rat chow and water ad libitum, housed per two/three in individually ventilated cages, maintained on a 12:12-h light-dark cycle and acclimated for at least one week before the experiment. This manuscript was reported in line with the ARRIVE statement (10).

Experimental model and IAH induction

Twenty-five anesthetized and ventilated rats were randomly assigned to five groups and exposed in random order to an IAP of 0, 5, 10, 15, or 20 mmHg for three hours. From a pilot study it was known that exposing rats to higher levels of IAP or for a prolonged period of time was not feasible in this model. This was due to the detrimental effects on hemodynamic and respiratory parameters. Rats were anesthetized with intra-peritoneal ketamine hydrochloride (50 µg/g), ventilated following tracheostomy and kept warm by a warming pad and tin foil. A capnograph and pulse oxymeter (both Siemens SC9000 XL monitor, Siemens Medical Systems, EM-PCS, Danvers, U.S.A.) were installed to measure end-tidal CO2 concentrations in expired air (EtCO2) and oxygen saturation. The carotid artery and internal jugular vein were cannulated (PE-50) for blood draw access and monitoring; the arterial blood pressures (systolic, diastolic and mean), heart rate (HR), and central venous pressure (CVP). The tail vein was cannulated for anesthetic and fluid infusion (10 µl per gram body weight of KMA-mix, consisting of 0.72 ml 100 mg/ml ketamine, 0.08 ml 1mg/ml medetomidine, and 0.3 ml 0.5 mg/ml atropine, in 20 ml normal saline). Administration of antibiotics was considered as non-contributing since the experiment lasted only 3 hours. An intra-peritoneal catheter (12 Ch Redon drain) was placed for fluid instillation and IAP monitoring by a midline laparotomy. The abdomen was closed with a running suture, including all layers of the abdominal wall.

The model used in this study has been described in detail previously (11). All animals were allowed to stabilize for 30 min before baseline measurements of MAP, CVP, heart rate (HR), end tidal CO_2 ($EtCO_2$), and saturation. Direct continuous measurement of IAP was

performed via the intra-peritoneal catheter. After baseline analysis, the IAP was increased by instillation of warmed (40 °C) Gelafundin® (Gelafundingelatine polysuccinate 4%; B. Braun Medical B.V., Oss, The Netherlands) and placing the fluid bag on specific level. A plaster cuff was applied to the abdomen of rats in order to reduce the required volume of Gelafundin (not in original model). The IAP and positive end expiratory pressure (PEEP) were kept at the same level during the experiment. Ventilatory and hemodynamic adaptations were made to compensate for deterioration during IAH. The respiratory rate and peak inspiratory pressure were increased to maintain EtCO2 between 4.5 and 6.0 kPa. MAP was kept between 70 and 110 mmHg by Voluven® administering (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride, Fresenius Kabi B.V. Zeist, The Netherlands). After completion of the experiment, all animals were sacrificed by exsanguination.

Blood sampling

Blood samples (with a capillary) were drawn at baseline, at 90 and 180 minutes for analyzing blood gases and serum lactate (ABL800 FLEX analyzer, Radiometer, Copenhagen, Denmark). All analyses were done once. At the same time points, single blood samples (0.6 mL) were drawn for duplicate determination of albumin-cobalt binding (ACB) capacity according to Bar-Or *et al,* as measure of systemic ischemia (12). This biomarker is a highly sensitive and rapid marker for ischemia, but it is nonspecific for tissue type and therefore a marker for systemic ischemia. The ACB test is a low-cost test which is easy to perform and well available. Also, the assay showed promising results for the detection of ischemia in an animal model of ACS. (13). The ACB test indicates systemic ischemia when its absorbance reaches above 0.4 absorbance units (ABSU), measured using a microplate reader (Wallac 1420 Victor2, Perkin Elmer, Groningen, the Netherlands).

Histological examination

For each rat, five cross-sectional samples were taken at random locations of the intestine. If macroscopic damage was visible, samples were taken there as well. Samples were fixed with 10% formalin, embedded in paraffin and sliced in 4–5 µm sections, stained with routine hematoxylin and eosin (H-E) and examined under a light microscope by a pathologist (KM) and clinical researcher (SGS), discrepancy was discussed. Histopathology was graded according to the Parks and Chiu/Park scoring systems for intestinal mucosal

injury (Parks score for inflammation and necrosis and Park/Chiu score for mucosal lifting) (14-16). All samples were scored at the most extensively affected areas. Mean scores of the five samples were calculated.

Statistical methods

The sample size calculation was based on an expected correlation coefficient between IAP and Parks/Chiu score of 0.95. With an alpha error of 0.05 (two-tailed) and a beta of 0.2, five animals per group were needed. Data for all animals were analyzed using SPSS statistical software, version 21.0 (SPSS Inc., Chicago, IL). All data were non-parametric and are displayed as median with corresponding quartiles (P_{25}-P_{75}). Kruskal-Wallis Test was used in order to test differences in body weight between groups. Spearman rank correlation tests was used in order to test the association between IAP and the individual variables.

RESULTS

Basic characteristics

The median body weight of the rats was 377 g (P_{25}-P_{75}, 368-392 g), there was no association between body weight and the IAP-group the rats were assigned to (p= 0.767). The median body temperature decreased statistically significantly to 36.0 ˚C at 90 minutes (Figure 1A). At that time point, temperature was negatively correlated with IAP (Spearman rank correlation coefficient; Rs= -0.444, p= 0.026). At 180 minutes, body temperature had normalized again. A decrease in the median MAP was noted in all groups (Figure 1B). MAP was negatively correlated with IAP, both at 90 minutes (from MAP 108 mmHg in the control group to 97 mmHg in the highest IAP group; Rs= -0.446, p= 0.025) and at 180 minutes (from MAP 119 mmHg to 95 mmHg, respectively; Rs= -0.466, p=0.019). CVP remained fairly constant across time in all groups (Figure 1C). At 180 minutes, the median CVP ranged from -2 mmHg in the control group to 2 mmHg in the highest IAP group (positive correlation with IAP, Rs= 0.581, p= 0.002). All animals completed the experiment and were used in the analyses.

Respiratory characteristics

IAP was positively correlated with median EtCO2 at 180 minutes (from 4.5 kPa in the control group to 5.4 kPa in the highest IAP group; Rs= 0.639, p= 0.001). Respiratory deterioration was reflected in all individual parameters of arterial blood gas analysis by a dose-dependent correlation with IAP and time (Figure 2). Most notably, a decrease was seen in median pH (ranging from 7.27 in the control group to 6.86 in the highest IAP group; Figure 2A) and median pO2 (ranging from 503 mmHg to 192 mmHg; Figure 2B) at 180 minutes. pH and pCO2 values were negatively correlated with IAP at that time point (Rs= -0.934, p< 0 .001 and Rs= -0.752, p< 0.001 respectively). Bicarbonate levels and oxygen saturation also decreased, and demonstrated a negatively correlation with IAP (Figure 2D and 2F). Positive correlations were seen between IAP and pCO2 (Rs= 0.882, p< 0.001; Figure 2C) and base deficit (Rs= 0.862, p< 0.001; Figure 2E) at 180 minutes. Median pCO2 increased over time with a range from 44.2 mmHg in the control group to 99.6 mmHg in the highest IAP group, and median base deficit increased with a range from 5.3 to 11.9 for the same groups at 180 minutes.

Outcome characteristics

During the last phase of this experiment, serum lactate levels increased. No significant correlation was found between this and IAP (Rs= 0.178, p=0.417; Figure 3A). Although a decrease was seen in ACB capacity (demonstrated by an increase of ABSU), group medians did not reach the threshold of 0.4 ABSU for systemic ischemia. No correlation between ACB capacity and IAP was observed (Figure 3B). This finding was confirmed by histopathological examination, no evident signs for ischemic damage were found in the H-E stained sections (Figure 4). The Parks score was comparable in all groups: no inflammation or necrosis was found in any of the specimens. The Park/Chiu score for mucosal lifting ranged from 0 to 4, no significant correlation between Park/Chiu score and IAP was found (Rs -0.141, p= 0.501).

DISCUSSION

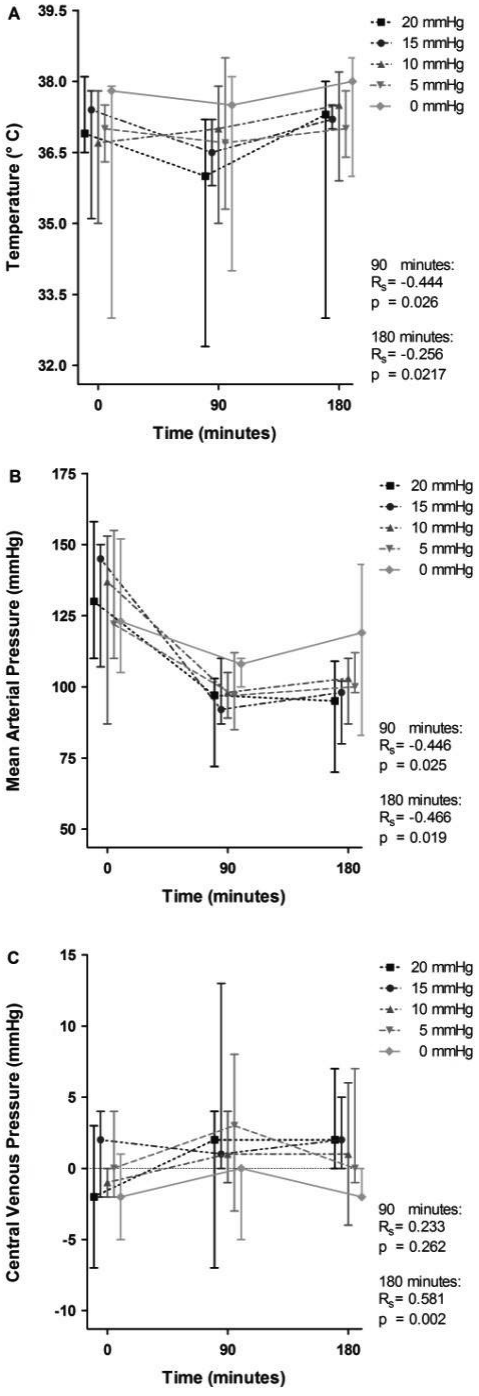
In this model of IAH, an increase in IAP did not result in significant ischemic complications within the first three hours. Even though a relation was seen between increasing IAP and hemodynamic deterioration, no histopathologic signs of irreversible damage to the intestines were found; nor were there any signs of systemic ischemia throughout the experiment as tested using the ACB assay. This is in contrast with the results of the only other similar study in rabbits. In this study, rabbits were exposed to an IAP of 25 mmHg for 1 hour. During this period, histopathology and the ACB assay demonstrated a statistically significant increase in intestinal ischemia (13).

The findings of this study may indicate that in the earliest phase of increasing IAP, physicians have some time to focus on adequate respiratory and hemodynamic support, before preventive open abdomen decompression is applied. In the first phase of IAH, respiratory deterioration may already be very profound without causing irreversible damage to the intestines. During this period, the possible effects of less-invasive measures can be awaited with no further harm being done. This supports the theory that effects of percutaneous catheter decompression (PCD) can be awaited for a period of four hours; if PCD was not effective, urgent open abdomen decompression should be initiated (7).
The respiratory and hemodynamic deterioration observed in this study demonstrated the suitability of the model used. Apart from the metabolic acidosis in the 0 mmHg group, outcomes seem to be an adequate reflection of IAH in humans (17, 18). The metabolic acidosis in the 0 mmHg group was unexpected, a finding possibly due to the rats being relatively hypo-volemic. In order to keep rats as normovolemic as possible, rats in the 0 mmHg group only received resuscitation fluids for compensation of blood collection. As confirmed by the negative CVPs, this minimal support seems to have been insufficient.
All animals were sacrificed at 180 minutes for histopathological evaluation, reperfusion following decompression was not awaited. Theoretically, during reperfusion, free radicals may cause significant oxidative damage (19). The oxidative damage might even be more extensive than the damage induced by IAH itself. Demonstrating this however, was not the aim of this study.

Possible limitations of this study were the relatively small sample size and the small size of the animals used in this experiment. It is known that the abdominal wall elasticity of small animals significantly differs from the elasticity in humans (20). Even though a plaster cuff was placed around the abdomen of the rats, this may have influenced the results of the present study. Moreover, the pathophysiology of ACS in critically ill humans is likely different from ACS in the otherwise healthy rats used in the current model. Translation of this IAH model to the human situation should therefore be done with caution.
The period of 180 minutes was relatively short compared with patients who are observed and conservatively managed after bowel obstruction or non-operatively managed blunt abdominal trauma. This is inherent to the selected rat model (from a pilot study it was known that exposing the rats to IAP levels of 25 or 30 mmHg resulted in death within one hour). During the experiment of the rats that were exposed to 20 mmHg IAP, the hemodynamic and respiratory parameters progressed to lethal levels. This made it impossible to keep the animals alive longer than 180 minutes. At that time point, arterial blood gas values reached morbid levels in the highest IAP group. In one case, the rat died instantaneously when the intra-abdominal pressure was relieved. Nevertheless, this experiment was suitable for demonstrating a principle. The outcomes of this study require confirmation in larger study groups or larger animals.

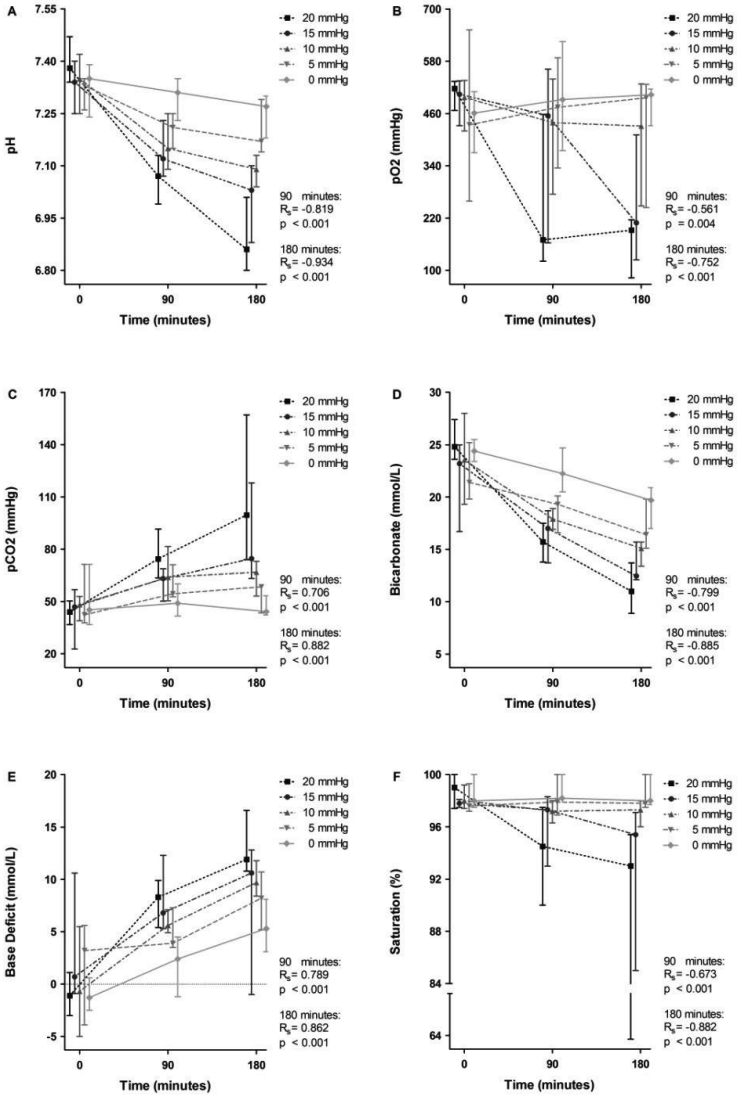
In conclusion, during this experimental study of increased IAP, no signs of early irreversible ischemic damage were found, while profound deterioration of respiratory and hemodynamic parameters were already present. These findings may indicate that in the early phase of increasing IAP, physicians have some time to focus on adequate respiratory and hemodynamic support, before preventive open abdomen decompression is applied. Non-invasive measures such as relaxation and striving for negative fluid balances which prevent a further increase of IAP, seem preferable.

Figure 1: Effect of IAP increase on temperature, MAP and CVP at 0, 90 and 180 minutes



Temperature (A), mean arterial pressure (B) and central venous pressures (C) at 0, 90, and 180 minutes are demonstrated for the individual IAP groups and displayed as median with upper and lower limit. The Spearman correlation coefficient (Rs) and p-value (p) represent correlation between IAP and the individual variables with corresponding statistical significance, at 90 and 180 minutes.

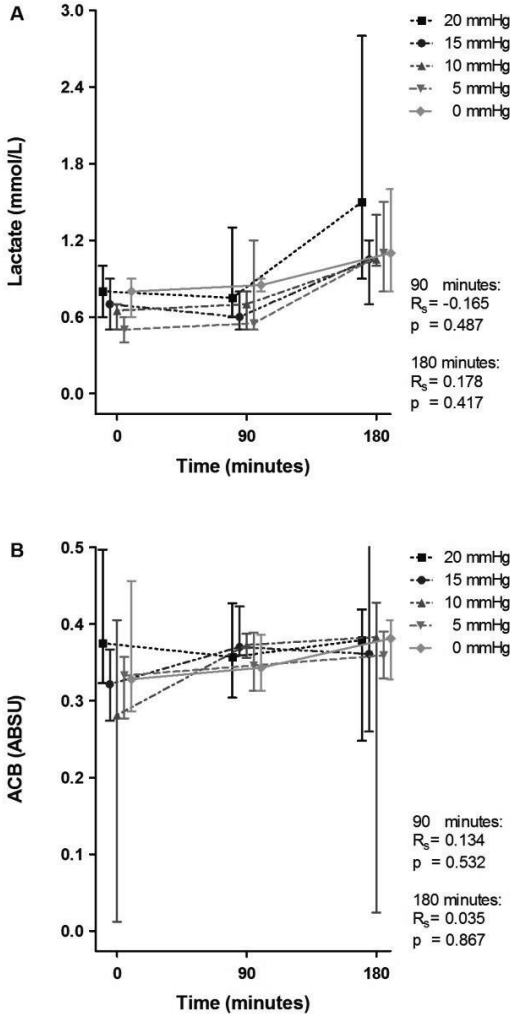
Figure 2: Effect of IAP increase on arterial blood gas values at 0, 90 and 180 minutes



The pH (A), pO2 (B), pCO2 (C), bicarbonate (D), base deficit (E) and saturation (F) at 0, 90, and 180 minutes are demonstrated for the individual IAP groups and displayed as median with upper and lower limit.

The Spearman correlation coefficient (R_s) and p-value (p) represent correlation between IAP and the individual variables with corresponding statistical significance, at 90 and 180 minutes.

Figure 3: Effect of IAP increase on serum lactate and albumin-cobalt binding at 0, 90 and 180 minutes

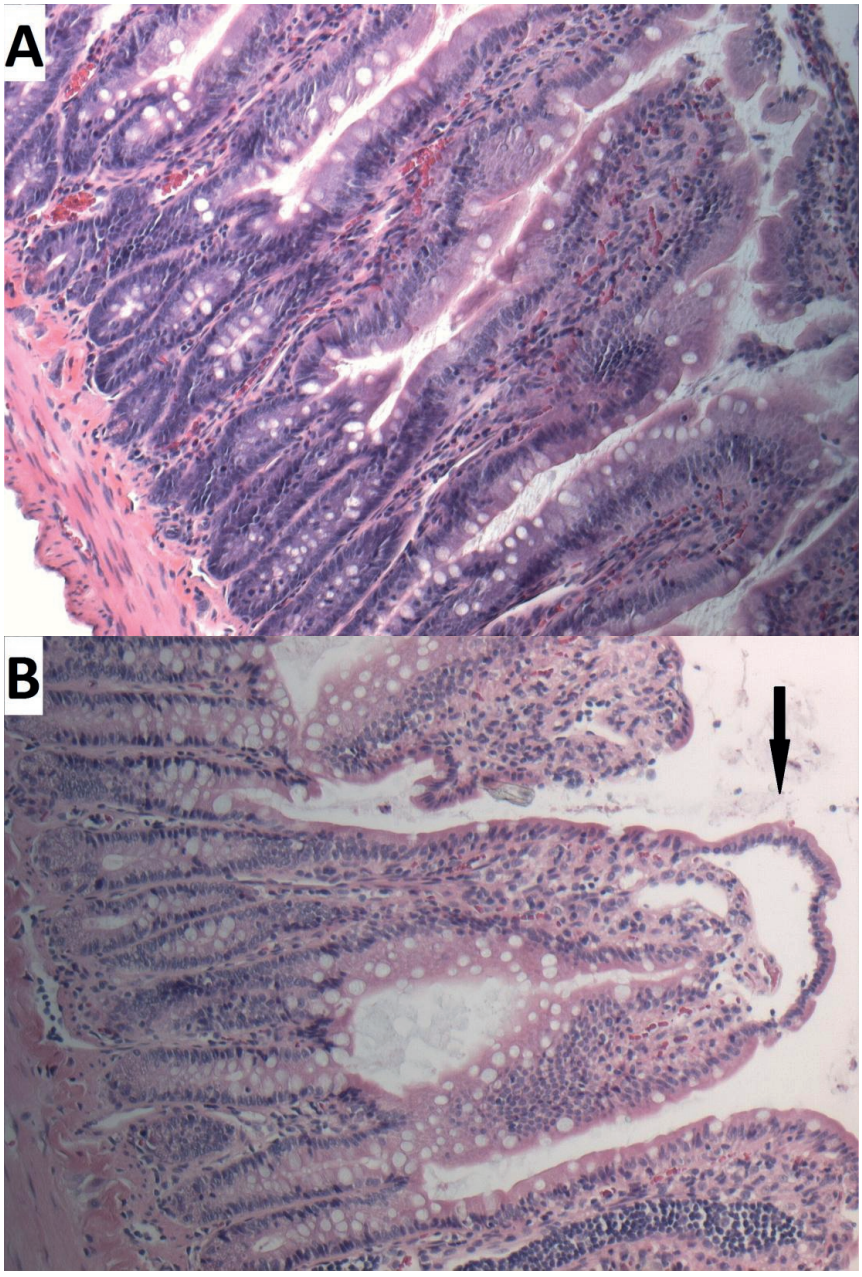


ABSU, absorbance units; ACB, albumin-cobalt binding capacity

Lactate (A) and albumin-cobalt binding (B) at 0, 90 and 180 minutes are demonstrated for the individual groups and displayed as median with upper and lower limit.

The Spearman correlation coefficient (Rs) and p-value (p) represent correlation between IAP and the individual variables with corresponding statistical significance, at 90 and 180 minutes.

Figure 4: H&E sections of the least and most extensively damaged mucosa



In most sections of rats in all groups, no lesions were found in the small intestine (A). Grade 3 Parks/Chiu lesions of ischemia (*i.e.,* mucosal lifting down sides of the villi; see arrow) were seen sporadically (B).

REFERENCES

1. Malbrain ML, Chiumello D, Pelosi P, et al. (2005) Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. Crit Care Med. 33:315-22.
2. Ejike JC, Humbert S, Bahjri K, et al. (2007) Outcomes of children with abdominal compartment syndrome. Acta Clin Belg Suppl.141-8.
3. Kirkpatrick AW, Roberts DJ, De Waele J, et al. (2013) Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med. 39:1190-206.
4. Diebel LN, Dulchavsky SA, Brown WJ. (1997) Splanchnic ischemia and bacterial translocation in the abdominal compartment syndrome. J Trauma. 43:852-5.
5. Diebel LN, Wilson RF, Dulchavsky SA, et al. (1992) Effect of increased intra-abdominal pressure on hepatic arterial, portal venous, and hepatic microcirculatory blood flow. J Trauma. 33:279-82; discussion 82-3.
6. Diebel LN, Dulchavsky SA, Wilson RF. (1992) Effect of increased intra-abdominal pressure on mesenteric arterial and intestinal mucosal blood flow. J Trauma. 33:45-8; discussion 8-9.
7. Cheatham ML, Safcsak K. (2011) Percutaneous catheter decompression in the treatment of elevated intraabdominal pressure. Chest. 140:1428-35.
8. Mayberry JC, Burgess EA, Goldman RK, et al. (2004) Enterocutaneous fistula and ventral hernia after absorbable mesh prosthesis closure for trauma: the plain truth. J Trauma. 57:157-62; discussion 63-3.
9. Uysal E, Kirdak T, Korun N. (2015) Alterations in Thyroid Hormones Due to Increased Intraabdominal Pressure in Rats. Journal of investigative surgery : the official journal of the Academy of Surgical Research. 28:317-22.
10. Kilkenny C, Browne W, Cuthill IC, et al. (2010) Animal research: reporting in vivo experiments: the ARRIVE guidelines. The journal of gene medicine. 12:561-3.
11. Meier C, Schramm R, Holstein JH, et al. (2006) Measurement of compartment pressure of the rectus sheath during intra-abdominal hypertension in rats. Intensive Care Med. 32:1644-8.

12. Bar-Or D, Lau E, Winkler JV. (2000) A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia-a preliminary report. J Emerg Med. 19:311-5.
13. Unluer EE, Kilic TY, Akgol E, et al. (2010) The role of cobalt-albumin binding analysis in the diagnosis of experimental abdominal compartment syndrome in rabbits. Ulus Travma Acil Cerrahi Derg. 16:491-6.
14. Parks DA, Bulkley GB, Granger DN, et al. (1982) Ischemic injury in the cat small intestine: role of superoxide radicals. Gastroenterology. 82:9-15.
15. Chiu CJ, McArdle AH, Brown R, et al. (1970) Intestinal mucosal lesion in low-flow states. I. A morphological, hemodynamic, and metabolic reappraisal. Arch Surg. 101:478-83.
16. Park PO, Haglund U, Bulkley GB, et al. (1990) The sequence of development of intestinal tissue injury after strangulation ischemia and reperfusion. Surgery. 107:574-80.
17. Lozen Y. (1999) Intraabdominal hypertension and abdominal compartment syndrome in trauma: pathophysiology and interventions. AACN Clin Issues. 10:104-12; quiz 35-7.
18. Cullen DJ, Coyle JP, Teplick R, et al. (1989) Cardiovascular, pulmonary, and renal effects of massively increased intra-abdominal pressure in critically ill patients. Crit Care Med. 17:118-21.
19. Saracoglu KT, Saracoglu A, Umuroglu T, et al. (2013) The preventive effect of dopamine infusion in rats with abdominal compartment syndrome. Journal of investigative surgery : the official journal of the Academy of Surgical Research. 26:334-9.
20. Yoshino O, Quail A, Oldmeadow C, et al. (2012) The interpretation of intra-abdominal pressures from animal models: the rabbit to human example. Injury. 43:169-73.

PART IV - DISCUSSION

PART IV - Discussion

Chapter 10

General discussion and future perspectives

GENERAL DISCUSSION

In this chapter, the results of the studies described in this thesis are discussed and put into perspective, and it elaborates how results fit in the already existing knowledge on the topic. Finally, implications of the current study findings are outlined and suggestions for future research are made.

Although up to date WSACS guidelines regarding management of IAH and ACS were not uniformly known and implemented in Dutch surgical practices **(Chapter 2)**, they were considerably better used than the global average (1). This is possibly due to the structure of Dutch surgical training and the international scientific orientation of Dutch clinicians. The well available knowledge may have resulted in a more aggressive ACS treatment and more frequent use of surgical abdominal decompression in the Netherlands when compared with responses of previous surveys carried out elsewhere (2). However, Dutch surgeons seemed to favour mesh assisted techniques for temporary abdominal closure (TAC) following decompressive laparotomy while vacuum assisted techniques are advocated by the recently published WSES guidelines for open abdomen treatment (3, 4). Open abdomens were relatively frequent used in the Netherlands, despite that earlier literature showed that the disadvantages of that treatment outweigh the benefits among some patient categories (5). Today however, it is more widely accepted that the long term outcomes of open abdomen treatment are not that debilitating and life altering as thought before (6).

Epidemiology

A direct relation between acidosis, hypothermia, resuscitation fluid volume and IAH **(Chapter 3)** has been described before (7-9). However, the demonstrated association between coagulopathy and high grade IAH was not. Also, a previously presumed benefit for colloid resuscitation (including hydroxyethyl starches; HES) over crystalloid resuscitation was not supported by the data from this study and is now not longer advocated in recent literature (10-12). The study also showed that an open abdomen does not necessarily prevent ACS from re-occurring. Although not many cases were described before in literature, recurrent ACS was recognized before (13). The presented study was the first to identify risk factors for that condition: age, ISS and a blunt mechanism of

abdominal injury. These identified characteristics of patients who developed recurrent ACS might help clinicians to prevent, recognize and treat this syndrome timely.

The study presented in **Chapter 4** did not confirm a decrease in ACS prevalence and related mortality among trauma patients after introduction of WSACS guidelines. This is unexpected, but should be put in perspective. The methodology of a systematic review is the best available tool for determining long term trends in these epidemiologic features, but it is still far from ideal. Different study designs of included studies (*i.e.*, RCT, longitudinal cohort study, or case series), heterogeneous populations, different definitions of ACS used and a possible reporting bias obviously influenced the results of this study. A long term uniform data registry would be more suitable for that aim. Such a data registry which includes IAP or IAH and ACS occurrence is not available to our knowledge. The data presented in the chapter did however emphasize that ACS prevalence was highest in patients who had undergone a trauma laparotomy. This finding is in line with the previously noted increase in ACS prevalence after introduction of damage control surgery. Until now it remained unclear whether this increase is influenced by a parallel increase in survival of patients that would otherwise have died before ACS would become imminent (14). Despite the methodological shortcomings, the study showed that the supposed elimination of post-injury ACS by Balogh *et al.*, has not yet become reality.

Chapter 5 showed that prevalence of IAH and ACS among severe burn patients was very high with 64.7-74.5% and 4.1-16.6%, respectively. The demonstrated mortality rate of patients with ACS (74.8%) was even more striking. These numbers indicate that there is still much room for improvement of care for such patients. As an obvious first step, we would recommend that the definitions for IAH and ACS as set by WSACS are used uniformly in studies and publications. It was remarkable however that even in more recent literature, this was not the case.

The described study furthermore provided an overview of the best available literature regarding prevalence, treatment and outcome of IAH and ACS in severe burn patients. This could be seen as a starting point for further research. Most importantly, it concluded that tools for early recognition of IAH related adverse outcomes were probably more

important than the measurement of IAP or APP itself. These tools however were not available yet (15, 16).

A prospective multicenter study among severe burn patients as presented in **Chapter 6** showed a lower IAH prevalence (53%) than demonstrated in the previous chapter. However, this was consistent with a recent African study reporting an IAH-prevalence of 58% among severe burn patients (17). The absence of ACS cases in this chapter contrasted literature. A reduction in prevalence of IAH and ACS was confirmed in other studies and was mainly attributed to modern restrained resuscitation regimes (18, 19). This explanation seems logically given the secondary ACS etiology of over-resuscitation which is usually seen in severe burn patients (with and without truncal burns influencing abdominal wall compliance).
In an attempt to provide for a marker for IAH related adverse outcomes, this chapter showed that the promising biomarker of urinary I -FABP had no significant diagnostic or predictive value for that aim in this population (20-23).

Markers for adverse outcome

A study that aimed to provide a potent predictor for IAH related adverse outcome in a general ICU population was described in **Chapters7 and 8**. The population studied showed a prevalence of ACS of 8% which was higher than in previous studies (24, 25). This was likely due to the fact that included patients were selected for having at least two risk factors for IAH as other studies did not. The study again showed that promising urinary and serum I-FABP levels had no relevant value in the early identification of patients at risk for IAH-related adverse outcome (20-23). Interestingly, the peak serum I-FABP levels among included patients without IAH were four to nine fold higher than in control groups of these studies (using the same ELISA kit). The control groups in these studies consisted of healthy controls, patients with acute abdominal pain due to other conditions such as bowel obstruction, appendicitis, coprostasis or diverticulitis, or patients with an uncomplicated course after aortic surgery. Since ICU patients in the I-Fabulous Study **(Chapter 8)** likely suffered from more severe conditions that might have already increased I-FABP levels, these false-positive patients (with elevated I-FABP, but no IAH or ACS) might explain why the results of the current study contrast those found in literature. This does not mean however, that other biomarkers are not suitable for the aim. The need for such

a marker remains in a time in which ACS is becoming a rarer diagnosis. Especially when less experienced physicians have to decide whether or not imminent ACS should be surgically decompressed.

As opposed to previous literature, an increase in IAP did not result in significant ischemic complications within the first three hours as measured by serum albumin-cobalt binding (ACB) assay and histopathology in an animal model (**Chapter 9)** (26). These results however may support the WSACS theory that the effects of percutaneous catheter decompression (PCD) can be awaited for a period of three to four hours before decompressive laparotomy is initiated (27). Despite the nature of this pilot study of only 25 rats, it showed that even in relatively low levels of increased IAP (below 20 mmHg) without obvious organ failure, hemodynamic and respiratory failure already occur. Unfortunately, the results of the study were not encouraging enough to perform larger scale studies for the easily performed ACB assay as marker for IAH related adverse outcome.

FUTURE PERSPECTIVES

Although prevalences of IAH, ACS and related adverse outcome have already decreased significantly, outcome could possibly be further improved by better implementation of evidence based treatment algorithms, improved knowledge of the implication of IAH related conditions, novel methods for recognition of IAH and related adverse outcomes and uniform registration. These four points are discussed in more detail below.

Implementation

Although the ACS development after vascular surgery or among patients with pancreatitis is increasingly well understood, further implementation of evidence based treatment algorithms to prevent ACS would most likely also benefit severely injured patients (30). The diversity of acute general surgical conditions with different timeframes and presentations of IAH related adverse outcomes also need additional systematic research (31, 32). For patients with post-operative abdominal sepsis, large abdominal wall surgery such as bilateral Ramirez or transverse abdominis muscle release (TAR) procedures, or non-operatively managed patients with (traumatic) intra-abdominal hemorrhage, it now is unclear whether IAH-related adverse effects play a relevant role in their outcome. Whether IAH is a relevant determinant for these patients or if they benefit from the treatment algorithms does not necessarily need to be studied in prospective research. For that aim IAPs are easily measured and added as a variable in other future surgical and ICU studies.

Clinical implication of IAP

IAH (without organ failure) is common on ICUs, but its clinical significance is unknown. Intra-abdominal hypertension without ACS has no direct clinical implications, but in combination with pre-existing impaired renal or pulmonary function the syndrome is harmful as a result of impaired compensatory reserve. The role of IAH in the outcome of these patients is not well established and should be further studied. Given the very specific patient group, it seems difficult to set up new prospective research for this, certainly considering how little patients would actually be helped with the results of such a study. To study this role it seems more appropriate to combine already collected data

from databases and retrospectively compare the results. Again, uniform handling of internationally accepted (WSACS) definitions is of hallmark importance for this.

Recognition

ACS is not frequently seen in modern time of damage control resuscitation and permissive hypotension. This may well be the result of systematic identification of modifiable risk factors, and subsequent change of management of severely ill and injured patients at the emergency room, theatre and ICU. The recent published prevalence of 0–2% of post-injury ACS is valid only for the highest performing trauma centers (28). In those hospitals, multi-disciplinary state of the art approach with physicians familiar with the risk of ACS is known to be effective (29). The global average prevalence and outcomes of these patients however, are likely to be much worse. The importance of ACS surveillance with IAP monitoring of patients with risk factors for IAH and ACS remains unchanged.

As early recognition is of importance for the outcome of ACS, the need for markers for IAH related adverse outcome remains. In a time in which ACS is becoming a more rare diagnosis, it can help less experienced physicians to decide whether or not imminent ACS should be surgically decompressed. Intestinal fatty acid binding protein and to a lesser extent albumin cobalt binding capacity, proved not to be adequate for that aim.
(1) Similar to the way I-FABP is a marker for intestinal mucosa damage, Claudine-3 is a marker for tight-junction decay of the same epithelium. Since this is a rapid process that occurs with mild ischemia, possibly it is a specific and suitable marker for this purpose (33).
(2) To a lesser extent, D-lactate might be interesting as such a marker. D-lactate is a marker for intestinal ischemia and has also been associated with increasing IAP. Essays for that marker are already in use in many hospitals and therefore are a low-threshold alternative.
(3) More recently, 'mitochondrial Ca2+ uptake 1' (MICU1, the key protein regulating the oxidative process in de gut) has also been proposed to as such a marker (34). Leng *et al*, detected changes in the expression of MICU1 during the development of increased intestinal permeability in rats with IAH. Their results indicated that MICU1-related oxidation/anti-oxidation disequilibrium is strongly involved in IAH-induced damage to

intestinal barriers. This marker could serve as a marker for IAH related adverse outcome, but might also hold promise for preventing the progression of IAH to gut-derived sepsis by MICU1-targeted treatment. However, for this marker it first must be made plausible that it could be cost-effective, because at first sight this appears to be a problem.
Nevertheless, the potential of these three new proposed markers for early recognition of IAH related adverse outcome, deserves further exploration. In a time where IAH related adverse outcomes become more rare, these markers might hold important promise for adequate and timely therapy in case of the rare situation of imminent ACS.

Registration

The progress that has already been made in preventing IAH and ACS and improving the outcome of patients with these syndromes, suggest that it is no longer feasible or necessary to set up large prospective studies for severe burn patients with IAH or ACS as primary endpoint. In the Netherlands the mandatory National Intensive Care Evaluation (NICE) registration is an easier way to collect data on organ failure. This registration includes 80.000 patients annually in all Dutch ICU's and started in 1996. For burn patients, registering the SOFA score is apparently not mandatory. Our proposal would be to do this nationally and internationally. Each ICU study among serious burn patients would then only have to record IAP measurements (in a standardized way, and preferably all from the same percentage of TBSA) as variables. It is not unlikely that organ failure in these patients is more often associated with IAH than assumed. In that case, it would be considerable to use IAP as extra monitoring to prevent over-resuscitation.

REFERENCES

1. Wise R, Roberts DJ, Vandervelden S, Debergh D, De Waele JJ, De Laet I, et al. Awareness and knowledge of intra-abdominal hypertension and abdominal compartment syndrome: results of an international survey. Anaesthesiol Intensive Ther. 2015;47(1):14-29.
2. Otto J, Kaemmer D, Hoer J, Jansen M, Schumpelick V, Strik M, et al. [Importance of abdominal compartment syndrome in Germany: a questionnaire]. Anaesthesist. 2009;58(6):607-10.
3. Ejike JC, Newcombe J, Baerg J, Bahjri K, Mathur M. Understanding of Abdominal Compartment Syndrome among Pediatric Healthcare Providers. Crit Care Res Pract. 2010;2010:876013.
4. Coccolini F, Roberts D, Ansaloni L, Ivatury R, Gamberini E, Kluger Y, et al. The open abdomen in trauma and non-trauma patients: WSES guidelines. World J Emerg Surg. 2018;13:7.
5. Zhou JC, Zhao HC, Pan KH, Xu QP. Current recognition and management of intra-abdominal hypertension and abdominal compartment syndrome among tertiary Chinese intensive care physicians. J Zhejiang Univ Sci B. 2011;12(2):156-62.
6. Cheatham ML, Safcsak K. Longterm impact of abdominal decompression: a prospective comparative analysis. J Am Coll Surg. 2008;207(4):573-9.
7. Madigan MC, Kemp CD, Johnson JC, Cotton BA. Secondary abdominal compartment syndrome after severe extremity injury: are early, aggressive fluid resuscitation strategies to blame? J Trauma. 2008;64(2):280-5.
8. Balogh Z, McKinley BA, Holcomb JB, Miller CC, Cocanour CS, Kozar RA, et al. Both primary and secondary abdominal compartment syndrome can be predicted early and are harbingers of multiple organ failure. J Trauma. 2003;54(5):848-59; discussion 59-61.
9. Malbrain ML, Chiumello D, Pelosi P, Bihari D, Innes R, Ranieri VM, et al. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. Crit Care Med. 2005;33(2):315-22.

10. Annane D, Siami S, Jaber S, Martin C, Elatrous S, Declere AD, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA. 2013;310(17):1809-17.
11. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367(20):1901-11.
12. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367(2):124-34.
13. Duchesne JC, Baucom CC, Rennie KV, Simmons J, McSwain NE, Jr. Recurrent abdominal compartment syndrome: an inciting factor of the second hit phenomenon. Am Surg. 2009;75(12):1193-8.
14. Balogh ZJ, Lumsdaine W, Moore EE, Moore FA. Postinjury abdominal compartment syndrome: from recognition to prevention. Lancet. 2014;384(9952):1466-75.
15. O'Mara MS, Reed N, Palmieri TL, Greenhalgh DG. Immediate and long-term outcomes of decompressive laparotomy for abdominal compartment syndrome in pediatric burn patients. American Burn Association 39th Annual Meeting, March 20-23, 2007, Manchester Grand Hyatt, San Diego, California. J Burn Care Res. 2007;28(2):S137-S.
16. Wilson MD, Dziewulski P. Severe gastrointestinal haemorrhage and ischaemic necrosis of the small bowel in a child with 70% full-thickness burns: a case report. Burns. 2001;27(7):763-6.
17. Mbiine R, Alenyo R, Kobusingye O, Kuteesa J, Nakanwagi C, Lekuya HM, et al. Intra-abdominal hypertension in severe burns: prevalence, incidence and mortality in a sub-Saharan African hospital. Int J Burns Trauma. 2017;7(6):80-7.
18. Ruiz-Castilla M, Barret JP, Sanz D, Aguilera J, Serracanta J, Garcia V, et al. Analysis of intra-abdominal hypertension in severe burned patients: the Vall d'Hebron experience. Burns. 2014;40(4):719-24.
19. Sanchez-Sanchez M, Garcia-de-Lorenzo A, Herrero E, Asensio MJ, Galvan B, Cachafeiro L. Prevalence of intra-abdominal hypertension (IAH) among patients with severe burns. Burns. 2014;40(3):533.

20. Kanda T, Tsukahara A, Ueki K, Sakai Y, Tani T, Nishimura A, et al. Diagnosis of ischemic small bowel disease by measurement of serum intestinal fatty acid-binding protein in patients with acute abdomen: a multicenter, observer-blinded validation study. J Gastroenterol. 2011;46(4):492-500.
21. Sun DL, Cen YY, Li SM, Li WM, Lu QP, Xu PY. Accuracy of the serum intestinal fatty-acid-binding protein for diagnosis of acute intestinal ischemia: a meta-analysis. Sci Rep. 2016;6:34371.
22. Thuijls G, van Wijck K, Grootjans J, Derikx JP, van Bijnen AA, Heineman E, et al. Early diagnosis of intestinal ischemia using urinary and plasma fatty acid binding proteins. Ann Surg. 2011;253(2):303-8.
23. Vermeulen Windsant IC, Hellenthal FA, Derikx JP, Prins MH, Buurman WA, Jacobs MJ, et al. Circulating intestinal fatty acid-binding protein as an early marker of intestinal necrosis after aortic surgery: a prospective observational cohort study. Ann Surg. 2012;255(4):796-803.
24. Reintam Blaser A, Regli A, De Keulenaer B, Kimball EJ, Starkopf L, Davis WA, et al. Incidence, risk factors, and outcomes of intra-abdominal hypertension in critically Ill patients-a prospective multicenter study (IROI Study). Crit Care Med. 2019;47(4):535-42.
25. Murphy PB, Parry NG, Sela N, Leslie K, Vogt K, Ball I. Intra-Abdominal Hypertension Is More Common Than Previously Thought: A Prospective Study in a Mixed Medical-Surgical ICU. Crit Care Med. 2018;46(6):958-64.
26. Unluer EE, Kilic TY, Akgol E, Isguven D, Vardar E, Bayol U, et al. The role of cobalt-albumin binding analysis in the diagnosis of experimental abdominal compartment syndrome in rabbits. Ulus Travma Acil Cerrahi Derg. 2010;16(6):491-6.
27. Cheatham ML, Safcsak K. Percutaneous catheter decompression in the treatment of elevated intraabdominal pressure. Chest. 2011;140(6):1428-35.
28. Balogh ZJ, Martin A, van Wessem KP, King KL, Mackay P, Havill K. Mission to eliminate postinjury abdominal compartment syndrome. Arch Surg. 2011;146(8):938-43.

29. Nguyen J, Noory M, Capano-Wehrle L, Gaughan J, Hazelton JP. Expeditious diagnosis and laparotomy for patients with acute abdominal compartment syndrome may improve survival. Am Surg. 2018;84(11):1836-40.
30. Smidfelt K, Nordanstig J, Wingren U, Bergstrom G, Langenskiold M. Routine open abdomen treatment compared with on-demand open abdomen or direct closure following open repair of ruptured abdominal aortic aneurysms: A propensity score-matched study. SAGE Open Med. 2019;7:2050312119833501.
31. Mentula P, Hienonen P, Kemppainen E, Puolakkainen P, Leppaniemi A. Surgical decompression for abdominal compartment syndrome in severe acute pancreatitis. Arch Surg. 2010;145(8):764-9.
32. Boele van Hensbroek P, Wind J, Dijkgraaf MG, Busch OR, Goslings JC. Temporary closure of the open abdomen: a systematic review on delayed primary fascial closure in patients with an open abdomen. World J Surg. 2009;33(2):199-207.
33. Hecker A, Hecker B, Hecker M, Riedel JG, Weigand MA, Padberg W. Acute abdominal compartment syndrome: current diagnostic and therapeutic options. Langenbecks Arch Surg. 2016;401(1):15-24.
34. Leng Y, Ge Q, Zhao Z, Wang K, Yao G. MICU1 may be a promising intervention target for gut-derived sepsis induced by intra-abdominal hypertension. Cell Death Discov. 2016;2:16080.

PART IV - Discussion

Chapter 11

Summary and conclusions

Chapter 1 is the introduction of this thesis. It gives an overview of definitions, epidemiology, etiology, risk factors, physiology, clinical presentation, diagnostics, management, and outcome of intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS). Furthermore, a number of knowledge gaps in the literature are identified with regard to epidemiology, risk factors and diagnostic opportunities. Lastly, it's indicated for each chapter how conducted studies contributed to closing these gaps.

Chapter 2 aims to determine the current state of awareness, knowledge, and use of evidence-based medicine with regard to IAH and ACS among Dutch surgeons. A literature-based and expert consensus study was developed for this and completed by 60 respondents. Intra-abdominal pressure (IAP) was measured by 59 (98%) respondents using intra-vesical methods. Diuretics (38 respondents, 63%) and laparotomy (33 respondents, 55%) were considered as useful treatments for IAH as prevention of ACS by the majority. Only 16 (27%) respondents used the evidence-based guideline (from the WSACS - Abdominal Compartment Society) in daily practice, yet another 37 (62%) were willing to do so. Mesh assisted techniques for temporary abdominal closure (TAC) following decompressive laparotomy was preferred by Dutch surgeons, while literature previously showed that vacuum assisted techniques should be favored. Fifty-nine (98%) respondents believed that open abdominal treatment improved the outcome of patients with (imminent) ACS, while 46 (77%) were aware of the high risk of complications from this treatment.

Conclusions:

- Definitions of the WSACS guidelines were well known among respondents, the guidelines themselves however were implemented poorly in Dutch hospitals.
- Mesh assisted techniques for temporary abdominal closure (TAC) following decompressive laparotomy was preferred by Dutch surgeons.
- Respondents supported open abdomen treatment following decompressive laparotomy, even though they were aware of the high associated morbidity and mortality.

Chapter 3 compares the characteristics of patients who developed high-grade intra-abdominal hypertension (IAH) after trauma laparotomy (*i.e.*, grade III of IV IAH; IAP> 20 mmHg) with those of patients who developed low-grade IAH (grade I or II; IAP ≤20 mmHg). The retrospective study was performed among 567 consecutive trauma patients admitted to a level 1 trauma center (specialized hospital for severely injured patients) in Australia. Of the included patients, 10.2% developed high-grade IAH of which 52% (30/58) developed ACS. Open abdomen did not necessarily prevent ACS from re-occurring. Patients with high-grade IAH were older ($p<0.001$), had a higher Injury Severity Score (ISS, $p<0.001$), larger base deficit ($p<0.001$), and lower body temperature at admission ($p=0.011$). In the first 24 hours of admission, patients with high-grade IAH received larger volumes of crystalloid resuscitation fluids ($p<0.001$), larger volumes of colloid resuscitation fluids ($p<0.001$), and more units of packed red blood cells ($p<0.001$). Following surgery, prolonged prothrombin time (PT, $p<0.001$) and activated partial thromboplastin times (aPTT, $p<0.001$) were seen. Patients with high-grade IAH had higher mortality rates than patients without high-grade IAH (25.9% vs. 12.2% respectively, $p=0.012$).

Conclusions:

- Development of high-grade IAH is associated with acidosis, coagulopathy, and hypothermia (also known as the triad of death).
- Patients with high-grade IAH after a trauma laparotomy received significantly larger volumes of crystalloid and colloid resuscitation fluids.

- Open abdomen treatment does not necessarily prevent ACS from re-occurring (recurrent ACS).

Chapter 4 aims to determine the prevalence and mortality of ACS among severely injured patients, and to compare these before and after January 1, 2005, the date of introduction of WSACS guidelines. This was done by means of a systematic literature review and meta-analysis. After pooling data of the 81 included publications, the study demonstrated a prevalence of ACS among trauma patients ranged from 0.0% to 36.4% (N=33,455 patients) with a weighted average prevalence of 5.2% and 3.7% before and after January, 2005, respectively. ACS prevalence was 1.1% in seriously injured patients admitted to the ICU, 2.8% in patients with visceral injuries, and 5.0% in patients who had undergone trauma laparotomy. The mortality rate varied from 0.0% to 100.0% with a weighted average of 47.1% before January 1, 2005 and 53.1% after that date. These values should be interpreted with caution due to the high statistical and clinical heterogeneity across the included studies. Therefore, a causal relationship could not be concluded with improved trauma care or the introduction of the WSACS guidelines.

Conclusions:

- The prevalence of ACS among trauma patients ranges from 0.0% to 36.4% with a pooled average of 4.5%.
- Mortality of trauma patients with ACS ranges from ranges from 0.0% to 100.0% with a pooled average of 48.3%.
- No decrease of ACS prevalence and mortality after introduction of the WSACS guidelines could be demonstrated.
- The supposed elimination of ACS (among severely injured patients) has not yet become a reality.
- Uniform handling of internationally used definitions and cut-off points is crucial for the researching the relatively rare syndromes of IAH and ACS.

Chapter 5 provides an overview of literature regarding IAH and ACS in severe burn patients with a focus on epidemiology and management strategies. A systematic literature review yielded 50 publications, reporting 1616 patients. The prevalence of ACS and IAH in

severe burn patients was 4.1-16.6 % and 64.7-74.5%, respectively. The mean mortality rate of burn patients with ACS was 74.8%. The use of plasma and hypertonic lactated resuscitation fluids could prevent IAH or ACS. Despite that the use of colloid fluids decreased the total needed volume of resuscitation fluids, no benefit of this in preventing IAH was proven. Escharotomy, peritoneal catheter drainage, and decompression laparotomy demonstrated to be effective IAP diminishing treatments in burn patients. Lastly, it showed that markers for IAP-related organ damage or organ failure might be superior to IAP measurements itself.

Conclusions:

- A systematic literature search demonstrated prevalence of ACS and IAH in severe burn patients to be 4.1-16.6 % and 64.7-74.5%, respectively.
- The mean mortality rate of ACS in severe burn patients is estimated as high as 74.8% based on available literature.
- IAH or ACS can be prevented by decreasing resuscitation volume.
- Truncal burns in patients with ACS require immediate escharotomy and should be followed by increasingly invasive decompression measures if no pressure relieve is achieved.
- Diagnostic tools for early recognition of IAH-related adverse outcomes might be more important than the measurement of IAP or APP.

Chapter 6 is a prospective study that focused primarily on determining the prevalence of IAH among severe burn patients. Secondarily, it aimed to determine the value of urinary intestinal fatty acid binding protein (I-FABP) as early marker for IAH-associated complications. I-FABP is a protein that occurs exclusively in the small intestine, an organ in the abdomen that is sensitive to ischemia (oxygen deficiency). With slight ischemic changes in the small intestine, elevated concentrations of this protein can already be measured in blood and urine. The theory is that ischemia of the small intestine is one of the first adverse effects of IAH and may play a central role in the development of inflammation in the rest of the body.
The patients included for this study (N=58, prospectively included in two Dutch burn centers) had a median burn size of 29% of total body surface area (TBSA). Thirty-one (53%)

patients developed IAH, 17 (29%) patients developed new organ failure, but none of the patients developed ACS. Maximal urinary I-FABP levels per patient had a fair discriminatory ability for distinguishing patients with IAH from patients without IAH. Despite this result, no predictive value of urinary I-FABP levels on IAH or new organ failure could be demonstrated.

Conclusions:

- In a population of 58 severe burn patients, IAH was very common, but no cases of ACS were seen.
- Urinary I-FABP levels showed to have no significant diagnostic or predictive value for IAH and related organ failure in a patient population with severe burns.

Chapters 7 and 8 describe the design and outcomes of the I-Fabulous study. This study is the largest prospective cohort study of ICU patients with two or more risk factors for IAH up to date. This study determined the value of urinary and serum intestinal fatty acid binding protein (I-FABP) levels as early marker for IAH-associated complications. Of 198 included patients, 74 (37%) developed new organ failure and 15 (8%) developed ACS. I-FABP and IAP were positively correlated. Patients who developed ACS had higher median baseline levels of urinary I-FABP (235 µg/g creat, corrected for renal function) than patients who only developed IAH but not ACS (87 µg/g, p=0.037). I-FABP had no discriminatory ability between patients with and without ACS as the area under the receiver operating characteristic curve (AUC) was 0.53 for urinary I-FABP and 0.65 for serum I-FABP. An AUC value of 1.0 would be the perfect test, and a value of 0.5 is comparable to tossing a coin). With an odds ratio of 1.00, neither urinary nor serum I-FABP indicated clinically relevant increased risk for developing new organ failure or ACS.

Conclusions:

- The results of this study showed a prevalence of ACS among patients admitted in the ICU with two or more risk factors for IAH of 8%.
- The results of Chapter 8 (and Chapter 6) unequivocally show that intestinal ischemia or mucosal disruption (as measured by I-FABP) are no early signs of IAH-related organ failure or ACS.

- I-FABP has no value for prediction or early detection of IAH-related adverse outcomes in daily clinical practice.

Chapter 9 determines the relation between IAP (at subclinical levels of IAP under 20 mmHg) on one hand, and respiratory parameters, hemodynamic parameters, and the development of early (intestinal) ischemia on the other hand in an experimental model. Although the relevance of subclinical levels of IAP below 20 mmHg with no evidence of organ failure is unclear in the literature, this study demonstrated that these intra-abdominal pressure levels are inversely associated with mean arterial pressure (Spearman correlation coefficient; Rs= -0.466, p=0.019), oxygen saturation (Rs= -0.882, p<0.001), partial oxygen pressure (pO2) (Rs= -0.752, p<0.001), and pH-value (Rs= -0.934, p<0.001). In addition, IAP was positively associated with central venous pressure (Rs= 0.581, p=0.002). No associations were found between IAP and lactate level or albumin-cobalt binding (ACB) capacity, an experimental marker for systemic ischemia. Histological signs for intestinal ischemia were not found.

Conclusions:

- Subclinical levels of intra-abdominal pressure (up to 20 mmHg) were correlated with increasing respiratory and hemodynamic problems in an experimental rat model.
- In the first three hours after onset, abdominal pressures up to levels of 20 mmHg were not associated with significant ischemic complications in rats.
- The results of this first research into the performance of the albumin-cobalt binding (ACB) assay, as easily determined marker for IAH-related adverse outcome, were not encouraging to perform larger scale studies.

Chapter 10 is the general discussion of this thesis and provides future perspectives regarding further improvement of IAH and ACS recognition and management.

PART IV - Discussion

Chapter 12

Nederlandse samenvatting en conclusies

Hoofdstuk 1 is de introductie van dit proefschrift. Het geeft een overzicht van definities, epidemiologie, etiologie, risicofactoren, fysiologie, klinische presentatie, diagnostiek, management en uitkomst of van intra-abdominale hypertensie (IAH) en abdominaal compartimentsyndroom (ACS). Verder werden enkele in de literatuur bestaande kennislacunes geïdentificeerd met betrekking tot epidemiologie, risicofactoren en diagnostische mogelijkheden voor IAH en ACS. Tot slot werd er voor elk hoofdstuk van dit proefschrift aangegeven hoe de uitgevoerde studies bijdroegen om deze lacunes te dichten.

Hoofdstuk 2 heeft als doel om de huidige bewustwording, kennis en gebruik van evidence-based medicine met betrekking tot IAH en ACS bij Nederlandse chirurgen te bepalen. Daarvoor is een op literatuur gebaseerd en expertconsensus vragenlijst ontwikkeld, welke werd ingevuld door 60 respondenten. Intra-abdominale druk (IAP) werd door 59 (98%) respondenten gemeten met behulp van intra-vesicale methoden. Diuretica (38 respondenten, 63%) en laparotomie (33 respondenten, 55%) werden door de meerderheid beschouwd als nuttige behandelingen voor IAH ter preventie van ACS. Mesh-geassisteerde technieken voor tijdelijke abdominale sluiting (TAC) na decompressieve laparotomie hadden de voorkeur van de Nederlandse chirurgen, terwijl uit literatuur een voorkeur voor vacuümondersteunde technieken blijkt. Slechts 16 (27%) respondenten gebruikten de evidence-based richtlijn van de WSACS (The Abdominal Compartment Society) in de dagelijkse praktijk en nog eens 37 (62%) waren bereid om dit alsnog te doen. Negenenvijftig (98%) respondenten geloofden dat open buikbehandeling de uitkomsten van de patiënt met (dreigend) ACS verbetert, terwijl 46 (77%) zich bewust waren van het hoge risico op complicaties van deze behandeling.

Conclusies:

- Definities uit de WSACS richtlijn waren goed bekend onder de respondenten, de richtlijn zelf was echter slecht geïmplementeerd in Nederlandse ziekenhuizen.
- Mesh-geassisteerde technieken voor tijdelijke abdominale sluiting (TAC) na decompressieve laparotomie hadden de voorkeur van de Nederlandse chirurgen.

- Respondenten ondersteunden een open buikbehandeling na een decompressie laparotomie, ook al waren ze zich bewust van de hoge gerelateerde morbiditeit en mortaliteit.

Hoofdstuk 3 vergelijkt de kenmerken van patiënten die na een traumalaparotomie hooggradige intra-abdominale hypertensie (IAH) ontwikkelden (d.w.z. graad III of IV IAH, IAP > 20 mmHg) met die van patiënten waarbij dat niet gebeurde (graad I of II, IAP ≤ 20 mmHg). De retrospectieve studie uit dit hoofdstuk, werd uitgevoerd onder 567 opeenvolgende traumapatiënten die werden opgenomen in een level 1 traumacentrum (gespecialiseerd ziekenhuis voor de ernstig gewonde patiënten) in Australië. Van de geïncludeerde patiënten ontwikkelde 10,2% hooggradige IAH, waarvan 52% (30/58) ACS ontwikkelde. Een aanatl patiënten ontwikkelde ACS zelfs nadat er een open buikbehandeling was gestart. Patiënten met hooggradige IAH waren ouder ($p < 0,001$), hadden een hogere ISS (score voor ernst van letsel, $p < 0,001$), groter base tekort of 'base deficit' ($p < 0,001$) en lagere lichaamstemperatuur bij opname ($p = 0,011$). In de eerste 24 uur na opname ontvingen patiënten met hooggradige IAH een hoger volume cristalloïde resuscitatievloeistoffen ($p <0,001$), grotere volumes colloïde resuscitatievloeistoffen ($p < 0,001$) en meer eenheden van rode bloedcellen ($p <0,001$)). Na de operatie werden een verlengde PT (protrombine tijd, $p <0,001$) en aPTT (geactiveerde partiële thromboplastine tijd, $p <0,001$) waargenomen. Patiënten met hooggradige IAH hadden een hoger risico op overlijden dan degenen die geen hooggradige IAH ontwikkelden (respectievelijk 25,9% vs. 12,2%, $p = 0,012$).

Conclusies:

- Ontwikkeling van hooggradige IAH is geassocieerd met acidose, coagulopathie en hypothermie (ook bekend als de "triad of death").
- Patiënten met hooggradige IAH na een traumalaparotomie ontvingen significant grotere volumes van cristalloïde en colloïde resuscitatievloeistoffen.
- Open buikbehandeling voorkomt niet noodzakelijkerwijs dat ACS nogmaals optreedt ("recurrent ACS").

Hoofdstuk 4 heeft als doel om vast te stellen wat de prevalentie en mortaliteit is van ACS onder ernstig gewonde patiënten en deze te vergelijken voor en na 1 januari 2005 (introductie van WSACS richtlijn). Dit werd gedaan met behulp van een systematisch literatuuronderzoek en meta-analyse. Na pooling van de data van de 81 geïncludeerde publicaties, toonde de studie een ACS prevalentie onder traumapatiënten van 0,0% tot 36,4% (N = 33.455 patiënten), met een gewogen gemiddelde van 5,2% en 3,7% vóór en na januari 2005 respectievelijk. Bij ernstig gewonde IC patiënten was dit 1,1%, 2,8% onder patiënten met visceraal letsel en 5,0% bij patiënten die een traumalaparotomie hadden ondergaan. De mortaliteit varieerde van 0,0% tot 100,0% met een gewogen gemiddelde van 47,1% vóór en 53,1% na 1 januari 2005. Deze waarden moeten met de nodige voorzichtigheid worden geïnterpreteerd gezien de grote statistische en klinische heterogeniteit van de geïncludeerde studies. Daarom kon geen causaal verband worden geconcludeerd met verbeterde traumazorg of de introductie van WSACS richtlijn.

Conclusies:

- De prevalentie van ACS bij traumapatiënten varieert van 0,0% tot 36,4% met een gepoolde prevalentie van 4,5%.
- De mortaliteit van traumapatiënten met ACS varieert van 0,0% tot 100,0% met een gepoolde waarde van 48,3%.
- Geen afname van ACS prevalentie en mortaliteit na introductie van de WSACS richtlijn kon worden aangetoond.
- De veronderstelde eliminatie van ACS (bij ernstig gewonde patiënten) is nog geen realiteit geworden.
- Uniform gebruik van internationaal gebruikte definities en afkappunten is cruciaal voor het onderzoek naar de relatief zeldzame syndromen van IAH en ACS.

Hoofdstuk 5 geeft een overzicht van literatuur met betrekking tot IAH en ACS bij patiënten met ernstige brandwonden met een focus op epidemiologie en managementstrategieën. Er werd systematisch literatuuronderzoek gedaan dat 50 publicaties opleverde welke in totaal 1616 patiënten rapporteerde. De prevalentie van ACS en IAH bij patiënten met ernstige brandwonden was respectievelijk 4,1-16,6% en 64,7-74,5%. De gemiddelde

mortaliteit van brandwonden patiënten met ACS was 74,8%. Het gebruik van plasma en hypertone resuscitatievloeistoffen kan IAH of ACS voorkomen. Ondanks het feit dat het gebruik van colloïde vloeistoffen het totale benodigde volume aan ruscitatie vloeistoffen verminderen, is er niet aangetoond dat dit bijdraagt aan het optreden van IAH. Escharotomie, peritoneale catheter drainage en decompressielaparotomie bleken effectieve IAP verlagende behandelingen te zijn bij patiënten met brandwonden. Ten slotte bleek dat markers voor IAP-gerelateerde orgaanschade of orgaanfalen mogelijk superieur zijn aan de IAP metingen zelf.

Conclusies:

- Systematisch literatuuronderzoek toonde aan dat de prevalentie van ACS en IAH bij patiënten met ernstige brandwonden respectievelijk 4,1-16,6% en 64,7-74,5% was.
- De gemiddelde mortaliteit van ACS bij patiënten met ernstige brandwonden wordt geschat op 74,8% op basis van beschikbare literatuur.
- IAH of ACS kunnen worden voorkomen door het resuscitatievolume te verminderen.
- Brandwonden van de romp bij patiënten met ACS vereisen onmiddellijke escharotomie en moeten worden opgevolgd door toenemend invasieve decompressiemaatregelen als geen drukverlaging wordt bereikt.
- Diagnostische middelen voor vroege herkenning van aan IAH gerelateerde nadelige uitkomsten kunnen belangrijker zijn dan de meting van IAP of APP.

Hoofdstuk 6 is er primair gericht op het bepalen van de prevalentie van IAH bij patiënten met ernstige brandwonden. Secundair had het als doel om te bepalen wat de waarde van het eiwit intestinal fatty acid binding protein (I-FABP) in urine was als vroege marker voor IAH-geassocieerde complicaties. I-FABP is een eiwit dat exclusief voorkomt in de dunne darm, een orgaan in de buik dat gevoelig is voor ischemie (zuurstof tekort). Bij lichte ischemische veranderingen in de dunne darm kan het eiwit al in verhoogde concentraties van zowel bloed als urine gemeten worden. De theorie is dat ischemie van de dunne darm één van de eerste ongewenste effecten is van IAH en mogelijk een centrale rol speelt in het ontwikkelen van inflammatie in de rest van het lichaam.

De patiënten in deze studie (N=58, geïncludeerd in twee Nederlandse brandwondencentra) hadden een mediaan totaal verbrand lichaamsoppervlak (TVLO) van 29%. Eenendertig (53%) patiënten ontwikkelden IAH, zeventien (29%) patiënten ontwikkelden nieuw orgaanfalen, maar geen enkele patiënt ontwikkelde ACS. De maximale I-FABP waarde in urine per patiënt hadden een redelijk discriminerend vermogen tussen patiënten met en zonder IAH. Helaas bleken de individuele I-FABP waarden in urine geen voorspellende waarde te hebben voor IAH of nieuw orgaanfalen in deze populatie patiënten met ernstige brandwonden.

Conclusies:

- De 58 geïncludeerde patiënten met ernstige brandwonden hadden vaak IAH zeer vaak voor, echter werden bij geen van de patiënten ACS waargenomen.
- I-FABP concentraties in de urine bleken geen significante diagnostische of voorspellende waarde te hebben voor IAH en gerelateerd orgaanfalen in een patiëntenpopulatie met ernstige brandwonden.

Hoofdstukken 7 en 8 beschrijven het ontwerp en de resultaten van de I-Fabulous studie. Deze studie was de grootste prospectieve cohortstudie van IC patiënten met twee of meer risicofactoren voor IAH tot nu toe. Het doel van deze studie was om de waarde te bepalen van intestinal fatty acid binding protein (I-FABP) spiegels in urine en serum als vroege marker voor IAH-geassocieerde complicaties. Van 198 geïnjecteerde patiënten ontwikkelden 15 (8%) ACS en 74 (37%) ontwikkelden nieuw orgaanfalen. I-FABP en IAP waren positief gecorreleerd. Patiënten die ACS ontwikkelden, hadden hogere mediane baseline niveaus van I-FABP in de urine (235 µg/g creat, gecorrigeerd voor nierfunctie) dan patiënten die alleen IAH, maar geen ACS ontwikkelden (87 µg/g, p=0,037). I-FABP had geen discriminerend vermogen voor het al dan niet ontwikkelen van ACS gezien de oppervlakte onder de receiver operating characteristic curve (AUC) 0,53 was voor I-FABP in urine, en 0,65 voor I-FABP in serum. Een AUC van 1,0 zou de perfecte test zijn en een waarde van 0,5 is vergelijkbaar met het opgooien van een muntje). Met een odds ratio van 1,00 duidden noch I-FABP in urine noch in serum op een klinisch relevant verhoogd risico op het ontwikkelen van nieuw orgaanfalen of ACS.

Conclusies:

- De resultaten van deze studie lieten een prevalentie van ACS bij IC patiënten met twee of meer risicofactoren voor IAH zien van 8%.
- De resultaten van de hoofdstukken 6 tot 8 tonen ondubbelzinnig aan dat intestinale ischemie of mucosa beschadiging (zoals gemeten met I-FABP) geen vroege tekenen zijn van IAH gerelateerd orgaanfalen of ACS.
- I-FABP heeft geen waarde bij de voorspelling of vroege detectie van IAH gerelateerde negatieve uitkomsten in de dagelijkse klinische praktijk.

Hoofdstuk 9 bepaalt de relatie tussen IAP (op subklinische niveaus van IAP onder d 20 mmHg) enerzijds, en ademhalingsparameters, hemodynamische parameters en de ontwikkeling van ischemie in de vroege darm anderzijds in een proefdier experiment. Hoewel in de literatuur de klinische relevantie van subklinische niveaus van IAP onder de 20 mmHg zonder tekenen van orgaanfalen onduidelijk is, toonde deze studie aan dat dit soort intra-abdominale drukken wél negatief geassocieerd zijn met gemiddelde arteriële druk (Spearman correlatiecoëfficiënt; Rs = -0,466, p = 0,019), zuurstofverzadiging (Rs = -0,882, p <0,001), partiële zuurstofdruk (pO2) (Rs = -0,752, p <0,001) en pH-waarde (Rs = -0,934, p <0,001). Daarnaast was IAP positief geassocieerd met centrale veneuze druk (Rs = 0,581, p = 0,002). Intra-abdominale druk was niet geassocieerd met lactaatniveau of “albumine-cobalt bindingscapaciteit” (ACB), een experimentele marker voor systemische ischemie. Er werden geen histologische tekenen voor intestinale ischemie gevonden.

Conclusies:

- Subklinische niveaus van IAP (tot de 20 mmHg) waren gecorreleerd met toenemende ademhalings- en hemodynamische problemen in een experimenteel rattenmodel.
- In de eerste drie uur na ontstaan, zijn buikdrukken tot en met een niveau van 20 mmHg niet geassocieerd met significante ischemische complicaties bij ratten.
- De resultaten van dit eerste onderzoek naar de prestaties van de albumine-cobalt binding (ACB) test als gemakkelijk te bepalen marker voor IAH-gerelateerde negatieve uitkomsten, waren niet bemoedigend om grootschaliger studies uit te voeren.

Hoofdstuk 10 is de algemene discussie van dit proefschrift en biedt toekomstperspectieven met betrekking tot verdere verbetering van IAH en ACS herkenning en behandelingen.

Appendices

List of publications

Contributing authors

Dankwoord

PhD Portfolio

Curriculum vitae

LIST OF PUBLICATIONS

Recognition and management of intra-abdominal hypertension and abdominal compartment syndrome; a survey among Dutch surgeons
Strang SG, Van Lieshout EMM, Verhoeven RA, Van Waes OJF, Verhofstad MHJ; IAH-ACS Study Group.
Eur J Trauma Emerg Surg. 2017 Feb;43(1):85-98.

Identifying patients at risk for high-grade intra-abdominal hypertension following trauma laparotomy
Strang SG, Van Imhoff DL, Van Lieshout EMM, D'Amours SK, Van Waes OJF.
Injury. 2015 May;46(5):843-8.

Prevalence and mortality of abdominal compartment syndrome in severely injured patient; A systematic review
Strang SG, Van Lieshout EMM, Van Waes OJF, Verhofstad MHJ.
J Trauma Acute Care Surg. 2016 Sep;81(3):585-92.

A systematic review on intra-abdominal pressure in severely burned patients
Strang SG, Van Lieshout EMM, Breederveld RS, Van Waes OJF.
Burns. 2014 Feb;40(1):9-16.

Prevalence of intra-abdominal hypertension and markers for associated complications among severe burn patients; a multicenter prospective cohort study (BURNIAH study)
Strang SG, Breederveld RS, Cleffken BI, Verhofstad MHJ, Van Waes OJF, Van Lieshout EMM
Submitted

Intestinal fatty acid binding protein as a marker for intra-abdominal pressure-related complications in patients admitted to the intensive care unit; study protocol for a prospective cohort study (I-Fabulous study)

Strang SG, Van Waes OJF, Van der Hoven B, Ali S, Verhofstad MHJ, Pickkers P, Van Lieshout EMM.

Scand J Trauma Resusc Emerg Med. 2015 Jan 16;23:6.

Intestinal fatty acid binding protein as a predictor for intra-abdominal pressure-related complications in patients admitted to the intensive care unit; a prospective cohort study (I-Fabulous study)

Strang SG, Habes QLM, Van der Hoven B, Tuinebreijer WE, Verhofstad MHJ, Pickkers P, Van Lieshout EMM, Van Waes OJF

J Crit Care. 2020 Sep 10;S0883-9441(20)30669-9. doi: 10.1016/j.jcrc.2020.08.023. Online ahead of print.

Relation between intra-abdominal pressure and early intestinal ischemia in rats

Strang SG, Van der Hoven B, Monkhorst K, Ali S, Van Lieshout EMM, Van Waes OJF, Verhofstad MHJ

Submitted

PUBLICATION NOT IN THIS THESIS

Postoperatieve wondinfecties na kophalsprotheseplaatsing; effecten van surveillance en registratie

Strang SG, Heeres M, Diepersloot RJA, Clevers GJ, Verleisdonk EJMM

Ned T v Traumachir. 2015 Jun 23(3):46-51

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PhD PORTFOLIO

Summary of PhD training and teaching

Name PhD student:	Steven G. Strang
Erasmus MC Department:	Trauma Research Unit, Department of Surgery
PhD period:	May 2012 – December 2020
Promotor:	Prof. Dr. M.H.J. Verhofstad
Supervisors:	Dr. E.M.M. van Lieshout and Dr. O.J.F. van Waes

1. PhD training

	Year	Workload (ECTS)
General academic skills		
- BROK (Basiscursus Regelgeving en Organisatie van Klinisch trials (GCP course)	2013	0.3
- Research Integrity	2014	2.0
- Biomedical English Writing and Communication	2015	2.0
- Chirurgendagen	2012-2019	4.0
- Traumadagen	2012-2019	4.0
Research skills		
- Laboratory animal science (DEC Course)	2012	2.0
- Biostatistical Methods I	2014	2.0
Presentations on conferences		
- Wetenschapsdag Heelkunde	2012	1.0
- World Congress on Abdominal Compartment Syndrome (WCACS Cartagena)	2013	1.0
- Chirurgendagen	2013	1.0
- Assistentensymposium Traumachirurgie	2014	1.0
- Chirurgendagen	2014	1.0
- Wetenschapsdag Heelkunde	2014	1.0

- European Congress of Trauma and Emergency Surgery (ECTES)	2015	1.0
- World Congress on Abdominal Compartment Syndrome (WCACS Gent)	2015 2018	1.0 1.0
- World Society for Emergency Surgery (WSES) Congress		
- Traumaplatform	2019	1.0
Seminars and workshops		
- Najaarsdag NVvH	2012-2019	2.0

2. Teaching

	Year	**Workload**
Lecturing		
- Vital Functions Course for Ambulances Nurses	2018	1.0
- Surgical Techniques Course for Obstetricians	2018	1.0
Supervising practicals and excursions		
- Examination of BLS of Medical Students	2012-2015	1.0
Supervising Master's theses		
- Youri van Boxtel	2012	2.0
- Allard Vossen	2012	2.0
- Leon Persoon	2012	2.0
- Steven Visser	2012	2.0
- Jordi Goijvaerts	2013	2.0
- Djazz van der Heijden	2013	2.0
- Robert Logger	2013	2.0
- Melvin Voeten	2013	2.0
- Eva de Groot	2014	2.0
- Anne Verhagen-van Brakel	2014	2.0
- Michiel van Buren	2014	2.0
- Roelof Verhoeven	2015	2.0
Total		**55.3**

CURRICULUM VITAE

Steven Gertjan Strang was born on December 15, 1983 in Beusichem, The Netherlands. After graduating from Koningin Wilhelmina College in Culemborg in 2002, he started to study Aerospace Engineering for a year at Delft University of Technology, The Netherlands. In 2013 he started studying Pharmacy and one year later he also started studying Medicine at Utrecht University. He combined these studies for two years. In this period, experiences during internships in Paramaribo (Surinam) and Igogwe (Tanzania) aroused his interest for trauma surgery. In October 2010 he obtained his medical degree and started working at the Diakonessenhuis Hospital in Utrecht, the Netherlands as a surgical resident not in training. In 2012 he had the opportunity to start a PhD research at the Trauma Research Unit of the Department of Surgery at Erasmus MC, Rotterdam, the Netherlands. The research work he did here during three years, led to this thesis. After this period, Steven returned to work as a surgical resident not in training at the Reinier de Graaf Hospital in Delft the Netherlands. On 1 January 2016 he started surgical training at Canisius Wilhelmina Hospital (Drs. F. Polat) and Radboudumc (Dr. B. Verhoeven), Nijmegen, the Netherlands. He lives together with Tessa and is a proud father of three beautiful children (Faye, Philou and Vik).