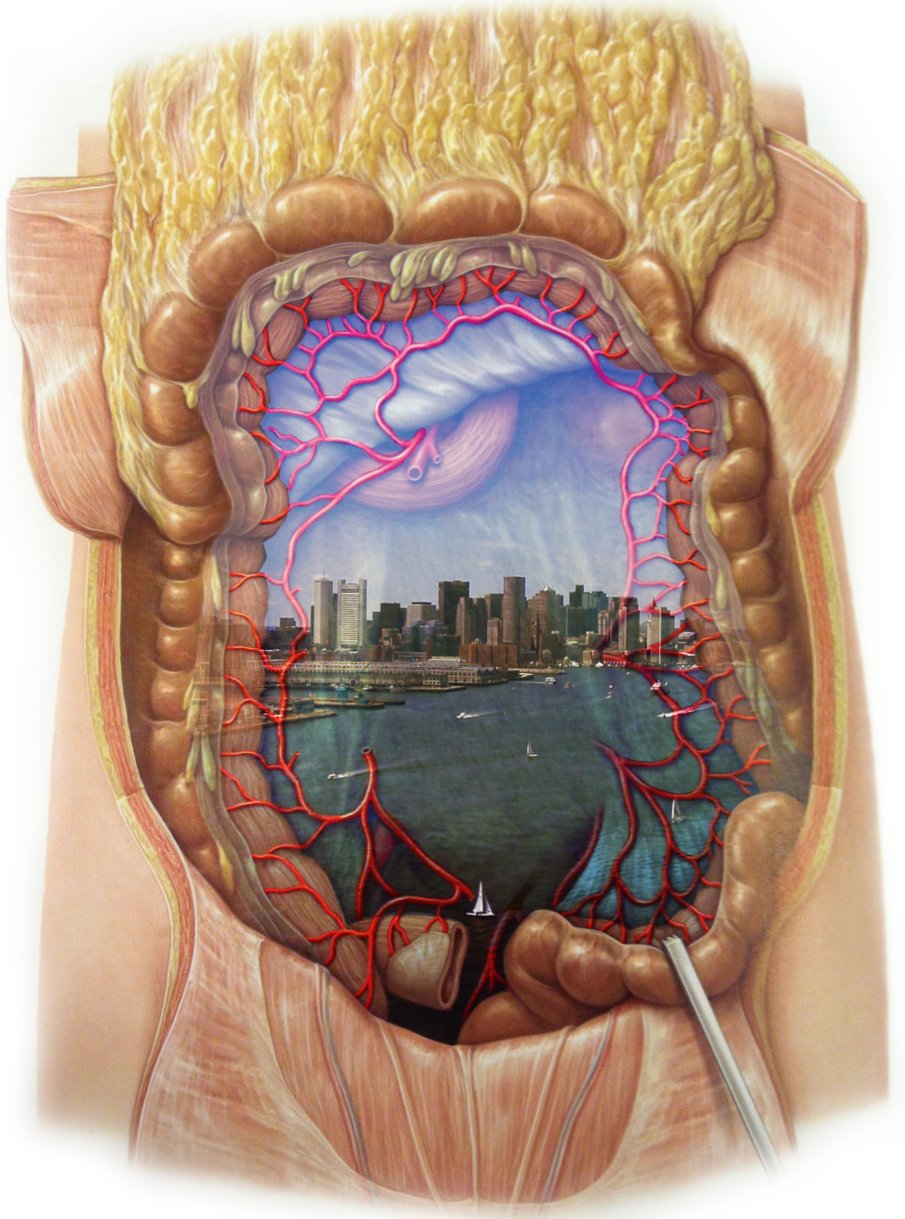
THE VALUE OF SURGICAL TREATMENT IN ABDOMINAL EMERGENCIES

Fulminant *Clostridium difficile* colitis and severe abdominal trauma



Gwendolyn M. van der Wilden

THE VALUE OF SURGICAL TREATMENT IN ABDOMINAL EMERGENCIES

FULMINANT *CLOSTRIDIUM DIFFICILE* COLITIS AND SEVERE ABDOMINAL TRAUMA

Gwendolyn M. van der Wilden

This thesis was prepared at the Department of Surgery, Division of Trauma, Emergency Surgery & Surgical Critical Care, Massachusetts General Hospital & Harvard Medical School, Boston, MA, United States of America and the Department of Trauma Surgery, Leiden University Medical Center & Leiden University, Leiden, the Netherlands.

Author	Gwendolyn M. van der Wilden
Coverphoto	Gwendolyn M. van der Wilden
Cover design	Optima Grafische Communicatie, Rotterdam The Netherlands
Printed by	Optima Grafische Communicatie, Rotterdam The Netherlands

I would gratefully acknowledge the research support I received from the VSB Fonds, Minerva Scholarship Fund, Jo Keur Fonds, and the Bontius Stichting.

This thesis has been sponsored by the Leiden University Fund/Melvin David Olin

ISBN: 978-94-6169-449-2

THE VALUE OF SURGICAL TREATMENT IN ABDOMINAL EMERGENCIES

FULMINANT *CLOSTRIDIUM DIFFICILE* COLITIS AND SEVERE ABDOMINAL TRAUMA

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op woensdag 15 januari 2014
klokke 15.00 uur

door

Gwendolyn Mariëtta van der Wilden
geboren te Rotterdam in 1988

PROMOTIECOMMISSIE

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Medicine is a science of uncertainty and an art of probability
(Sir William Osler, 1849-1919)

Aan Opi en Omi Methorst
Voor mijn ouders, Valerie en Julie

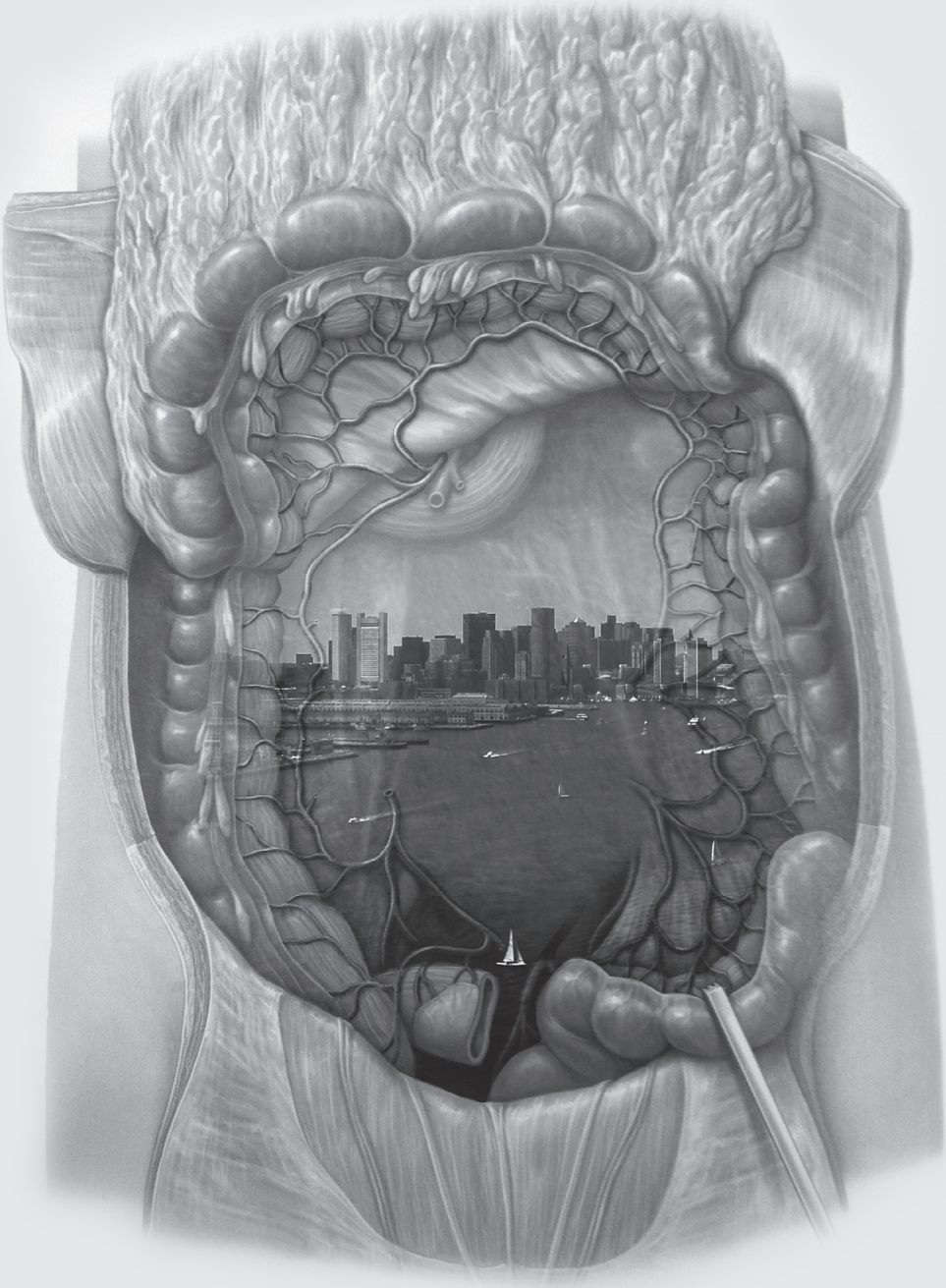
LIST OF ABBREVIATIONS

25(OH)D	25-hydroxyvitamin D
25(OH)D2	ergocalciferol
25(OH)D3	cholecalciferol
AAST	American Association for the Surgery of Trauma
ACS	American College of Surgeons
AIS	abbreviated injury score
aOR	adjusted odds ratio
APACHE II	acute physiology and chronic health evaluation II
BDI	blunt duodenal injury
BLI	blunt liver injuries
BPI	blunt pancreatic injury
BRI	blunt renal injuries
CCI	Charlson Comorbidity Index
CDC	*Clostridium difficile* colitis
CDI	*Clostridium difficile* infection
CDT	*Clostridium difficile* transferase
CI	confidence interval
CT	computed tomography
EBL	estimated blood loss
ED	emergency department
EIA	enzyme immunoassay
ERCP	endoscopic retrograde cholangiopancreatography
FAST	focused assessment with sonography for trauma
fCDC	fulminant *Clostridium difficile* colitis
FFP	fresh frozen plasma
f-NOM	failed non-operative management
GCS	Glascow Coma Scale
GDH	glutamate dehydrogenase
GU	genitourinary
HCO3-	bicarbonate
HGB	hemoglobin
HLOS	hospital length of stay
HR	heart rate
ICD-9	international classification of diseases, 9th revision
ICU	intensive care unit
IMT	intestinal microbiota transplantation
IO	immediate operation

IQ	interquartiles
IQR	interquartile range
ISS	injury severity score
IV	intravenous
LOS	length of stay
MODS	multiple organ dysfunction syndrome
NL	the Netherlands
NOM	non-operative management
NTDB	National Trauma Data Bank
OIS	organ injury scale
OR	odds ratio
PCR	polymerase chain reaction
PDT	pancreatoduodenectomy for trauma
PO	per oral
PR	per rectum
RBC	red blood cells
ReCONECT	Research COnsortium of New England Centers for Trauma
SBP	systolic blood pressure
SD	standard deviation
SIRS	systemic inflammatory response syndrome
s-NOM	successful non-operative management
SSI	surgical site infection
TAC	total abdominal colectomy
TFB	total fluid balance
U.S.	United States of America
VDR	vitamin D receptor
WBC	white blood cells

CONTENTS

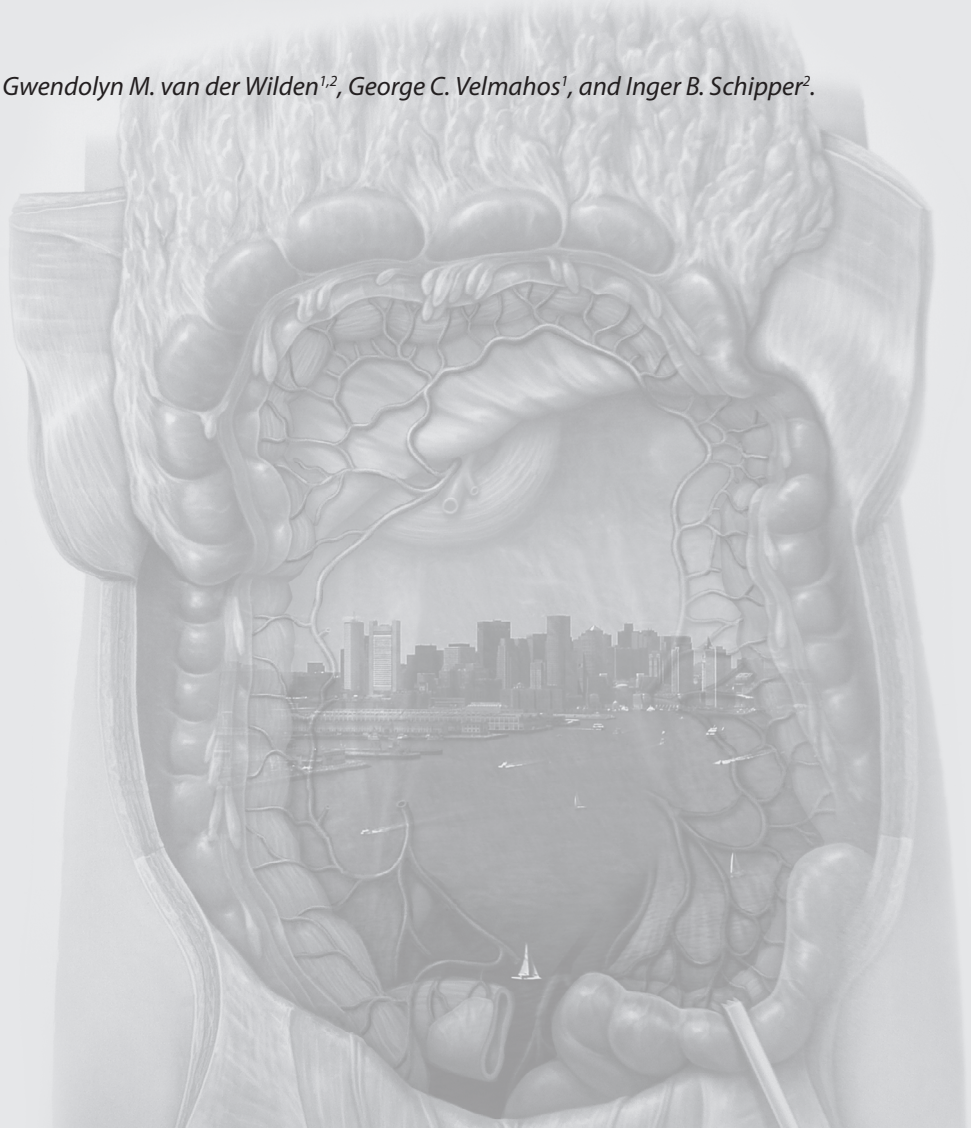
Introduction



Chapter 1

General introduction and outline of the thesis

Gwendolyn M. van der Wilden[1,2], George C. Velmahos[1], and Inger B. Schipper[2].



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Partially published in The MGH Review of Critical Care Medicine, 2013

GENERAL INTRODUCTION

I. Abdominal challenges

The abdominal cavity is enclosed by abdominal muscles, ventrally and laterally, and by the vertebral column dorsally. Situated in between thorax and pelvis, it contains many structures and a number of organs, most of them belonging to the gastrointestinal tract and urinary system. This thesis focuses on emergencies of the abdomen, including those of traumatic as well as non-traumatic etiology.

One of these 'abdominal challenges' is instigated by the intestinal pathogen *Clostridium difficile*. The resulting *C. difficile* infection (CDI) is an emerging disease and the leading cause of nosocomial diarrhea in both North America and Europe. With 3 million new cases every year, and affecting up to 10% of all hospitalized patients in the United States, it is an infection of pandemic proportions.[1-3] The colitis that can follow the colonization by *C. difficile* varies in severity. The most severe is, the fulminant version of *C. difficile* colitis (fCDC), a disease that often constitutes a surgical emergency.

While *C. difficile* colitis (CDC) is especially targeting the older population; traumatic abdominal emergencies primarily affect the younger population. Trauma is the leading cause of death worldwide for people under 45 years of age.[4] In the United States 32.3 million people are treated in the Emergency Department for traumatic injuries each year, of whom 2.5 million are being hospitalized. Annually, the injury-related death rate is around 180.000, and medical costs are estimated to be close to $465 billion.[4-7] Trauma to the abdomen occurs in about 13% of trauma patients and can result in devastating injuries that carry high morbidity and mortality.[6]

Although one could argue that fCDC and abdominal trauma are two distinct diseases, we would suggest that there are major similarities in the host response and possible results. In both entities acute phase response proteins (cytokines) are immediately secreted, leading to a typically exaggerated Systemic Inflammatory Response Syndrome (SIRS).[8, 9] The common final pathway in patients who receive inadequate or delayed treatment or in those who – despite appropriate treatment – cannot tolerate the insult, is Multiple Organ Dysfunction Syndrome (MODS). Mortality rates range from 30% to over 90%. Whether an infection is present or not, the patients' systemic response to this amount of abdominal insult is very similar.[10-15] In other words, these two very different entities (a traumatic injury vs. an intestinal infection) do actually overlap in the systemic response they provoke (Figure 1).[11, 12, 14] Subsequently, treatment strategies may be overlapping as well.[16] Therefore, the overall focus of this thesis will be on the initial treatment of two types of insults causing injury to the abdomen and its tissues; the Clostridium difficile infection and different types of blunt abdominal trauma.

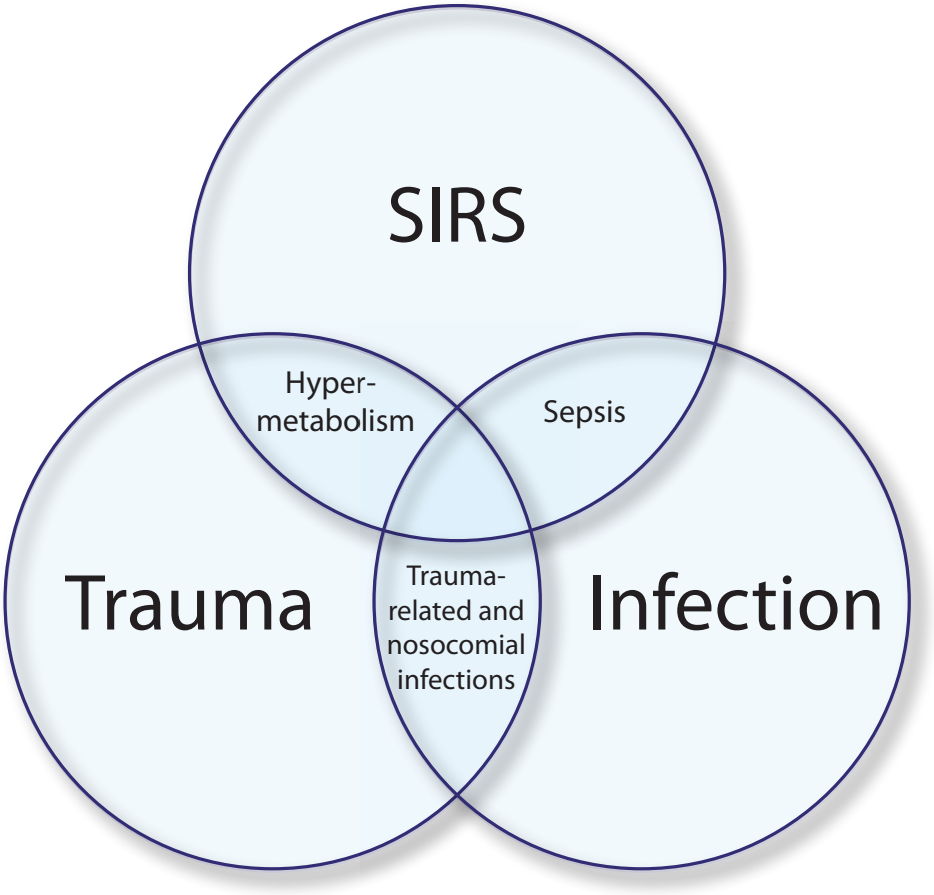

Figure 1. The relationship between *Clostridium difficile* infections and severe abdominal trauma

II. *Clostridium difficile* colitis

(will be partially published in the MGH Board Review of Critical Care Medicine)

a. *Clostridium difficile*

A *Clostridium difficile* infection (CDI) is defined by the following: (1) the presence of related symptoms (most often diarrhea, defined as 3 or more unformed stools in 24 or fewer consecutive hours); (2) either a positive enzyme immunoassay (EIA), detecting the glutamate dehydrogenase (GDH) antigen (an essential enzyme produced by all *C. difficile i*solates) and toxins A and B, or colonoscopic / histopathologic findings confirming pseudomembranous colitis.[17]

Epidemiology

The incidence of *C. difficile* infections in the U.S. increased significantly over the past 10 years, from 5.6 per 1000 discharges in 2001 to 12.8 per 1000 in 2012.[1, 2] Additionally, annual healthcare expenditures attributable to nosocomial CDIs range from $1-3 billion, and the average hospital length of stay is prolonged by 3-6 days.[18-21] It was shown that of all hospital stays with CDI in U.S. hospitals, the overall mortality rate was 9.1% (3.7% when CDI was the principal diagnosis, and 11.7% when it was a secondary diagnosis), compared to 1.9% for all other stays. [1-3] The mortality rate in patients with the most severe version of CDI, fCDC, ranges from 30-80%.[3, 22, 23] The most important risk factors for developing CDI are: an advanced age (higher age-adjusted rate of CDI among persons older than 65 years), previous exposure to antibiotics (frequently clindamycin, fluoroquinolones, penicillins, and cephalosporins), and hospitalization (cumulative daily risk of exposure to *C. difficile* spores in the healthcare setting).[17, 24-28] Other risk factors, although some remain controversial, are: severe underlying disease, chemotherapy, immunosuppression, gastrointestinal surgery (manipulation of the gastrointestinal tract), and the use of acid-suppressing medications (histamine-2-blockers and proton pump inhibitors).[17]

Pathogenesis

C. difficile is an anaerobic gram-positive, spore-forming, toxin-producing bacillus that is transmitted via person-to person spread through the fecal-oral route. It can exist in both spore and vegetative forms. When living outside the colon, it survives in spore form (spores are resistant to heat, acid and antibiotics), and may convert to a fully functional vegetative, toxin-producing form when present in the colon. In this form *C. difficile* becomes susceptible to antimicrobial agents. So there are patients (about 20% of all hospitalized adults) that are carriers of *C. difficile*, but are asymptomatic. They carry the bacillus with them and can contaminate other people.[29-31]

Once a *C. difficile* strain starts releasing exotoxins, it becomes pathogenic. Two potent exotoxins that mediate colitis and diarrhea are toxin A (enterotoxin) and toxin B (cytotoxin). Toxin A is a chemo-attractant for neutrophils and causes inflammation as well as fluid secretion of the colonic mucosa, while both toxins A (TcdA) and B (TcdB) activate inflammatory cytokine release from monocytes.[25, 32-34] Toxin B is essential for the virulence of *C. difficile*, and is approximately ten times more potent than toxin A on a molar basis for mediating colonic mucosal damage. Both toxins adhere to receptors on the human colonocyte brush border and cause necrosis and shedding of these cells into the lumen. The *C. difficile* toxins target Rho family proteins, a group of low molecular weight GTP-binding proteins that regulate actin filaments in all cells. Once Rho proteins are inactivated *by C. difficile* toxins, actin filaments disintegrate and the damaged cell cannot function anymore. This condition ultimately leads to increased capillary perme-

ability and peristalsis. The inflammation may result in toxic megacolon and perforation in fulminant cases.[33] Systemic symptoms are often caused by toxin-induced inflammatory mediators released into the colon (tumor necrosis factor a, interleukin-8, macrophage inflammatory protein-2, and substance P).[35]

Since the beginning of this century there have been many *C. difficile* outbreaks, of which the majority was caused by a newly discovered, hypervirulent strain, NAP1/BI/027. This strain is resistant to fluoroquinolones, has hypersporulation capacity, and produces an additional 'binary' toxin (CDT).[24, 36-38] This binary actin-ADP-ribosylating toxin CDT (*C. difficile* transferase) is not present in other strains, and seems to be associated with more severe disease and community-acquired CDI.[35, 39]

Clinical findings and diagnosis

Clinical findings almost always include diarrhea (typically with characteristic odor), and possibly but less common: fever, nausea, malaise, dehydration, leukocytosis with left shift, as well as abdominal distention and diffuse abdominal tenderness on physical exam.[25, 28, 34]

For years the type of diagnostic test that was used to detect the CDI, was the toxin A/B enzyme immunoassay. Although fast and inexpensive, the sensitivity was debatable and the standard was changed in 2012. The currently used test is a membrane EIA that detects the glutamate dehydrogenase (GDH) antigen (an essential enzyme produced by all *C. difficile* isolates) and toxins A and B. In specimens with discordant GDH antigen and toxin results, an additional polymerase chain reaction (PCR) test for toxigenic *C. difficile* is performed.[17, 26, 27, 40]

An abdominal CT scan may be used to differentiate between CDC and other causes of colitis, and to determine the extent of the disease.[41] However, to diagnose regular CDI, e.g. when awaiting the results of the EIA, an abdominal CT has poor sensitivity (52%), and should not be used for this purpose.[28, 42, 43]

Sometimes endoscopy is used to diagnose patients with CDC, but due to a risk for colonic perforation, it is recommended to only use it in patients with presumably severe CDC in which emergent therapeutic interventions are warranted, and results of regular diagnostic test are taking too long.[28, 44] The most important finding (only in patients with fCDC) will be the presence of pseudomembranes. *C. difficile* toxins are causing a disruption of the cytoskeleton, resulting in ulcerations of the intestinal mucosa. Because of this ulcer formation, a mix of mucus, inflammatory cells and serum proteins are released; this results in yellow/white plaques on the mucosal surface, the so called 'pseudomembranes'. Other possible findings include inflammation, bowel wall edema, erythema, and friability.[17, 41]

Treatment

The treatment of *C. difficile* is most often completely medical. However, when CDI progresses to a severe colitis, there are surgical options that can be considered. First of all there are some general principles that need to be followed, including ending any usage of antimicrobial agents as soon as possible, since this enables the infection to exist. Infection control policies such as contact precautions and increased hand hygiene should be implemented, and the use of anti-peristaltic agents should be avoided. Anti-peristaltic agents (such as narcotics or anti-cholinergics) are a risk factor since they decrease the peristalsis, which is reducing the bacterial clearance and causes colonic dilation.[17, 25, 26]

Metronidazole is the most important antibiotic in the initial phase of CDI. In an initial episode of a mild-to-moderate CDI, metronidazole is being prescribed, while vancomycin could be used as an alternative. For an initial episode of a severe CDI or severe, complicated CDI (progressing towards fCDC), vancomycin is the preferred drug.[45] A recurrence is managed the same as an initial episode, although it needs to be mentioned that metronidazole can cause cumulative neurotoxicity, and should not be used beyond the first recurrence of CDI or for long-term chronic therapy.[17, 46, 47] Fidaxomicin is a new drug that was approved by the FDA in 2011. It has been shown to be as effective as vancomycin but it is more expensive.[48, 49]

Another option in CDI treatment, and especially in recurrences, is fecal bacteriotherapy (intestinal microbiota transplantation; IMT). With IMT, intestinal microorganisms of healthy donor stool are being infused into the intestine of a sick patient to restore their microbiota.[50,51]

In patients that progress towards fCDC, as will be described below, and that fail medical therapy, the current surgical standard of care is a total abdominal colectomy (TAC). During this procedure the entire colon (except from the rectum) is being removed and an ileostomy is created.

b. Fulminant *Clostridium difficile* colitis

Fulminant *Clostridium difficile* colitis (fCDC) is defined as CDC with significant systemic toxic effects and shock, resulting in: the need for ICU admission, requirement of a colectomy, or death.[23] Around 3-5% of patients will progress to the fulminant disease.[3, 52-54] The clinical picture includes symptoms such as diarrhea (either severe or diminished due to ileus and colonic dilation), severe abdominal pain, fever, hypotension (need for vasopressors), tachycardia, severe leukocytosis with left shift, evidence of shock (decreased mental status, new organ failure, lactic acidosis), and an acute abdomen on physical exam. In the most severe cases a toxic megacolon (colonic dilation combined with severe systemic toxicity) and colonic perforation can be seen.[23, 33, 55] As mentioned before, next to antibiotic therapy and supportive care, some of these patients will need

surgery, especially when their clinical status fails to improve and toxic megacolon or colonic perforation is being suspected.[17, 26, 54]

III. Abdominal trauma

Abdominal trauma and intra-abdominal injuries can be caused by either a blunt or penetrating mechanism. About 80% of abdominal trauma is caused by a blunt mechanism (rapid deceleration), such as a motor vehicle collision or fall, while the remaining 20% of patients sustain a penetrating injury (direct trauma), such as a gunshot wound or stab wound. [56, 57]

Injuries to each of the organs are comprehensively graded by severity in the organ injury scales (OIS) of the American Association for the Surgery of Trauma (AAST), and are all based on the magnitude of anatomic disruption.[58] Many studies have been published on the management of intra-abdominal injuries, which can be both operative and non-operative (NOM). The focus of treatment is gradually shifting though, from operative management to a more conservative, sometimes completely non-operative, treatment in certain types of injuries. Non-operative management is considered to have many advantages such as lower hospital costs, a shorter hospital length of stay, avoidance of nontherapeutic celiotomies (with their associated cost and morbidity), consequently fewer intra-abdominal complications, and reduced transfusion rates.[59] A significant gap in the literature needs to be filled though, before conservative management can be adopted in all types and grades of injuries, since data on those patients that are severely injured are missing; previous studies mainly focused on low-grade injuries, which have a high incidence. The chapters on abdominal trauma in this dissertation focus on the specifics around non-operative management in patients with high-grade blunt kidney- and liver injuries, as well as different types of management in severe injuries, both blunt and penetrating, to the pancreatoduodenal complex.

a. The kidneys

Injuries to the genitourinary (GU) system occur in 10% of patients suffering traumatic injuries that require hospital admission. Renal trauma is the most common injury within the GU tract, with an incidence of 1-5% of all traumas, in 80% due to a blunt mechanism.[60, 61] Severity of the injuries is being classified using the kidney OIS (see Table 1).[62] Management ranges from renal exploration with the main indication being continuous hemodynamic instability of renal origin, to non-operative management in stable patients. Conservative management consists of close observation, bed rest, serial abdominal exams and hematocrit checks, hydration, and antibiotics.[61, 63-69] In some cases angiographic embolization will be used.[70, 71] Multiple studies in the literature have proven that NOM is a safe option in low-grade blunt injuries[66, 72, 73], however evidence about the role of NOM in grade IV and V blunt injuries is poor.[74-77] Since grade IV and V injuries to the kidney

also involve the collecting system, the chance that complications occur is increased, and often such complications are significant and require further management.[78, 79] Because the published evidence is lacking appropriate sample size to present valid recommendations regarding both treatment and possible complications of such severe renal injuries, we designed a study that would be able to make those recommendations.

b. The liver

The liver is the most commonly injured abdominal organ in blunt trauma, while it is the second most commonly injured organ in patients with penetrating abdominal trauma.[6, 80] The OIS for liver injuries (Table 2), divides the injuries in low (I, II, and III) and high (IV and V) grades.[81]

In patients with blunt liver trauma a shift from operative to non-operative management occurred over the past three decades; currently more than 80% of cases are being managed without an operation.[80, 82, 83] Reasons that explain the success of conservative management in the liver, foremost in hemodynamically stable patients, are versatile. It is now known that bleeding stops spontaneously after liver injuries in more than 50% of cases, while healing of the liver, even when severely injured, occurs much faster than in other organs. Additionally, there have been huge improvements in imaging, such as CT scanning and FAST exam (Focused Assessment with Sonography for Trauma), as well as advances in critical care monitoring. Conservative management involves monitored care, serial abdominal exams, hemoglobin assessment, and potentially angiographic embolization when vascular extravasation is seen.[84-86] Ongoing transfusion requirements and hemodynamic instability suggest continued bleeding, which is the main indication for

Table 1. Kidney injury scale

Grade*	Type of injury	Description of injury	AIS-90
I	Contusion	Microscopic or gross hematuria, urologic studies normal	2
	Hematoma	Subcapsular, nonexpanding without parenchymal laceration	2
II	Hematoma	Nonexpanding perirenal hematoma confirmed to renal retroperitoneum	2
	Laceration	<1.0 cm parenchymal depth of renal cortex without urinary extravasation	2
III	Laceration	<1.0 cm parenchymal depth of renal cortex without collecting system rupture or urinary extravasation	3
IV	Laceration	Parenchymal laceration extending through renal cortex, medulla, and collecting system	4
	Vascular	Main renal artery or vein injury with contained hemorrhage	4
V	Laceration	Completely shattered kidney	5
	Vascular	Avulsion of renal hilum which devascularizes kidney	5

*Advance one grade for bilateral injuries up to grade III

From Moore et al. [62]

Table 2. Liver injury scale (1994 revision)

Grade*	Type of injury	Description of injury	AIS-90
I	Hematoma	Subcapsular, <10% surface area	2
	Laceration	Capsular tear, <1 cm parenchymal depth	2
II	Hematoma	Subcapsular, 10% to 50% surface area	2
	Laceration	Capsular tear, 1-3 cm parenchymal depth, <10 cm in length	2
III	Hematoma	Subcapsular, >50% surface area of ruptured subcapsular or parenchymal hematoma; intraparenchymal hematoma >10 cm or expanding	3
	Laceration	>3 cm parenchymal depth	3
IV	Laceration	Parenchymal disruption involving 25% to 75% hepatic lobe or 1-3 Couinaud's segments	4
V	Laceration	Parenchymal disruption involving >75% of hepatic lobe or >3 Couinaud's segments within a single lobe	5
	Vascular	Juxtahepatic venous injuries; ie, retrohepatic vena cava/central major hepatic veins	5
VI	Vascular	Hepatic avulsion	6

*Advance one grade for multiple injuries up to grade III
From Moore et al. [81]

operative intervention. When it comes to high grade blunt liver injuries though, limited evidence is available. There is an overwhelming amount of studies showing successful NOM in low grade injuries[80, 82, 83, 87], and even grade IV injuries[88-91], as well as extensive overviews of operative management of high grade injuries[92, 93] However, there are very few papers written focusing on NOM in grade IV and V injuries, which are essentially devastating liver injuries.

c. The pancreatoduodenal complex

In about 3 to 5 per cent of all traumatic abdominal injuries, the pancreas and duodenum are involved, in 75% caused by a penetrating mechanism.[94-96] Combined injuries have a high morbidity and mortality, and due to its retroperitoneal locations in the abdomen, it can be challenging to properly diagnose injuries to the pancreatoduodenal complex, especially with a blunt mechanism.[97-100] Both injuries to the pancreas and duodenum are categorized according to the AAST OIS (Tables 3 and 4), again dividing injuries into low (I,II,III), and high (IV and V) grades.[101] Low grade blunt injuries can be managed without an operation, with gastrointestinal decompression, nutritional support, and careful monitoring and follow-up.[100, 102] However, in high grade blunt injuries, and all penetrating injuries operative intervention is required. Often those are common interventions such as debridement of devitalized tissue, local repair of lacerations, drainage, and for duodenal injuries resection and primary anastomosis.[103-108] The most severe injuries either combined or to the pancreatic head, are managed with resection, namely a pan-

Table 3. Pancreas injury scale

Grade*	Type of injury	Description of injury	AIS-90
I	Hematoma	Minor contusion without duct injury	2
	Laceration	Superficial laceration without duct injury	2
II	Hematoma	Major contusion without duct injury or tissue loss	2
	Laceration	Major laceration without duct injury or tissue loss	3
III	Laceration	Distal transection or parenchymal injury with duct injury	3
IV	Laceration	Proximal transection or parenchymal injury involving ampulla	4
V	Laceration	Massive disruption of pancreatic head	5

*Advance one grade for multiple injuries up to grade III. From Moore et al. [101]

Table 4. Duodenum injury scale

Grade*	Type of injury	Description of injury	AIS-90
I	Hematoma	Involving single portion of duodenum	2
	Laceration	Partial thickness, no perforation	3
II	Hematoma	Involving more than one portion	2
	Laceration	Disruption <50% of circumference	4
III	Laceration	Disruption 50-75% of circumference of D2; Disruption 50-100% of circumference of D1,D3,D4	4 4
IV	Laceration	Disruption >75% of circumference of D2 Involving ampulla or distal common bile duct	5 5
V	Laceration	Massive disruption of duodenopancreatic complex	5
	Vascular	Devascularization of duodenum	5

*Advance one grade for multiple injuries up to grade III. D1-first position of duodenum; D2-second portion of duodenum; D3-third portion of duodenum; D4-fourth portion of duodenum
From Moore et al. [101]

creatoduodenectomy (PDT). This PDT however, is an extremely rare procedure in trauma (performed in 1-5% of all combined injuries) , since the incidence of severe combined injuries is very low.[94, 95, 97, 98, 109] It is not surprising that large series describing this rare and difficult procedure are scarce in the literature, resulting in many questions about specific indications and outcomes that still need to be answered.[110]

OUTLINE OF THE THESIS

This is **chapter 1**, the general introduction and outline of the thesis. As mentioned earlier, this dissertation consists of two parts: trauma and non-trauma challenges in the abdomen. After an elaborate explanation of both trauma related and non-trauma related abdominal emergencies, we continue in the succeeding chapters with **Part 1**,

non-trauma, that consists of studies that offer an extensive, multi-faceted view on the bacterium *Clostridium difficile*, and in particular on fulminant CDC.

In **chapter 2** the search for a clinical prediction rule of fCDC is described. There are certain variables that predict the transition from a 'simple' CDI to fCDC. We hypothesize that if we can identify those variables and design a system with predictive value, we would be able to recognize the patients at risk for fCDC at an earlier moment resulting in an improvement of the associated morbidity and mortality.

Chapter 3 describes a 2-year prospective study on the implementation of a hospital-wide standardized protocol for early surgical consultation in patients with suspected fCDC. Since previous studies have shown that early involvement of the surgical service can improve outcomes, we designed the so-called 'consultation criteria'. The protocol requires referral of patients to the surgical service when they have suspected/confirmed (by toxin assay) CDI and reach the threshold of at least 2 out of 8 criteria. We will compare the 2-year 'post-implementation' cohort to an historic control group of fCDC patients, and hypothesize that outcomes, such as mortality, improve after implementation of this protocol.

The standard of care when patients with fCDC need surgical treatment is a total abdominal colectomy (TAC). In **chapter 4** we look back, in a multicenter study, at a cohort of patients that underwent a TAC and focus on the optimal antibiotic treatment post-operatively. This study aims to determine if there exists a difference in outcomes in those treated with metronidazole alone or with a combination of metronidazole and vancomycin.

The last chapter in part 1, **chapter 5** discusses the influence of vitamin D levels on CDI severity. The hypothesis of this prospective study is that in patients with lower 25-hydroxyvitamin D levels, the CDI will be more severe.

Continuing to **Part 2**; the abdominal challenges of traumatic origin. In **chapter 6** the role of non-operative management in severe blunt renal injuries (BRI) is being discussed. The objectives of this study are to determine the rate and predictors of failure of NOM in patients with grade IV and V BRI. We hypothesize that such high grade injuries can be safely managed without an operation, but that the rate of complications, following operative and non-operative management of BRI, and the need for subsequent interventions is high.

Chapter 7 discusses the rates and predictors of failure of NOM in patients with grade IV and V blunt liver injuries (BLI), with the hypothesis being that such high-grade injuries can be safely managed without needing an operation.

Both studies (**chapter 6 and 7**) are a collaboration between level I and II, verified by the American College of Surgeons (ACS), trauma centers in the northeast of the United States, known as the REsearch COnsortium of New England Centers for Trauma (RECONECT). This collaboration was initiated in 2008 to evaluate injuries of low prevalence

that would be difficult to analyze for each one center alone. So far, five studies have been conducted and this dissertation contains two of them.

Chapter 8 describes the management of severe pancreatoduodenal injuries, and specifically the trauma Whipple (pancreatoduodenectomy for traumatic injuries), using the largest national trauma database in the United States, the NTDB (National Trauma Data Bank).[111] The reasoning behind this study was that this specific procedure, the trauma Whipple, is of such low incidence that there is basically no evidence in the literature that strongly favors or discourages this operation, neither are there strong and accurate indications for performing this rare, and difficult procedure. Our aim was to evaluate the outcomes of patients that undergo a pancreatoduodenectomy for trauma (PDT) in comparison to patients with injuries of similar severity that received alternative operations.

Chapter 9 provides a general discussion, presentation of future perspectives, and a final conclusion. In **chapter 10** the overall summary can be found.

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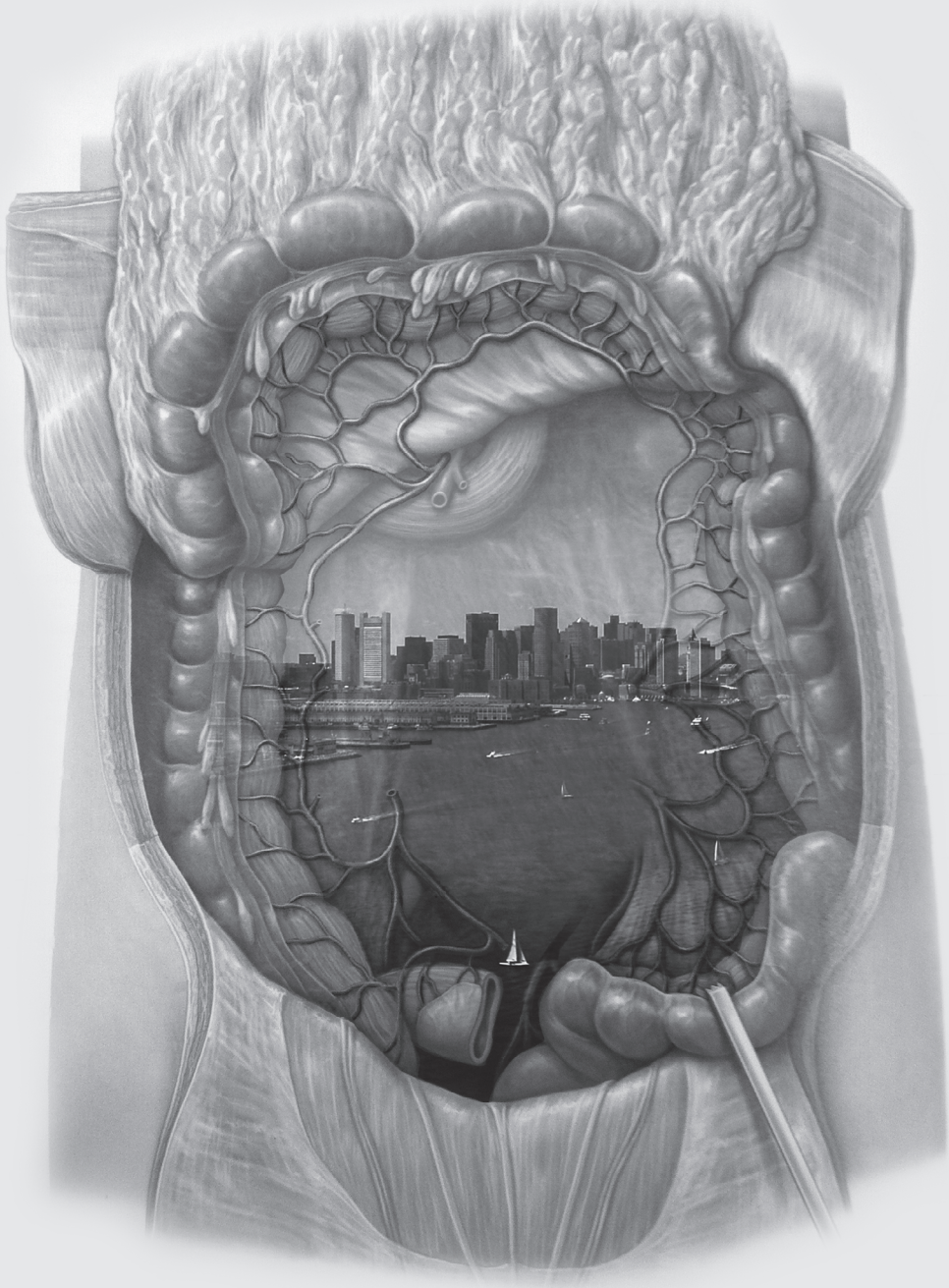
Part I

Fulminant *Clostridium difficile* colitis



Chapter 2

Fulminant *Clostridium Difficile* Colitis: Prospective Development of a Risk Scoring System

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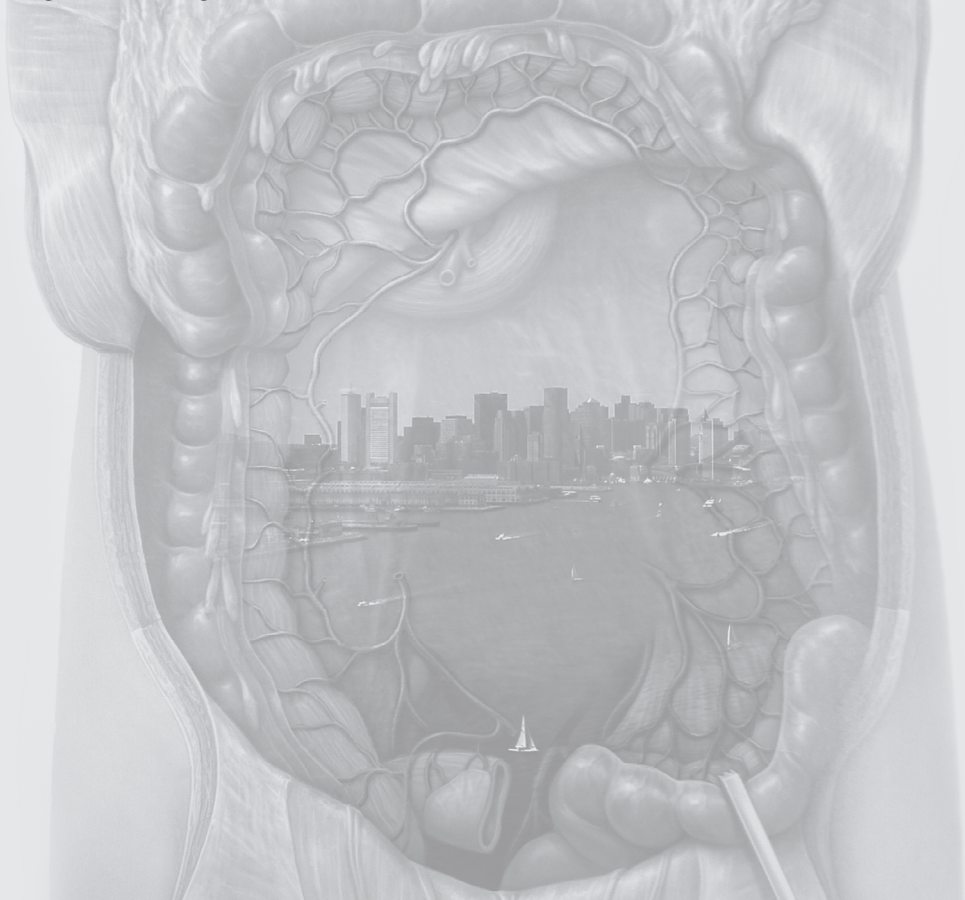

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In press, Journal of Trauma and Acute Care Surgery 2014

ABSTRACT

Background: 2-8% of patients with a *Clostridium difficile* infection will progress to fulminant *C. difficile* colitis (fCDC) which carries high morbidity and mortality. No system exists to rapidly identify patients at risk of developing fCDC and possibly in need of surgical intervention. Our aim was to design a simple and accurate risk scoring system (RSS) for daily clinical practice.

Methods: We prospectively enrolled all patients diagnosed with a *C. difficile* infection and compared patients with and without fCDC. An expert panel, combined with data derived from prior studies, identified four risk factors and a multivariable logistic regression model was performed to determine their effect in predicting fCDC. The RSS was created based on the predictive power of each factor and calibration, discrimination, and test characteristics were subsequently determined. Additionally, the RSS was compared to a previously proposed severity scoring system.

Results: 746 patients diagnosed with C. difficile infection were enrolled between November 2010 and October 2012. Based on the log (odds ratio) of each risk factor, age > 70 years was assigned 2 points, White Blood Cells ≥ 20.000/μL or ≤2.000/μL 1 point, cardiorespiratory failure 7 points, and diffuse abdominal tenderness on physical exam 6 points. Using this system, the discriminatory value of the RSS (c-statistic) was 0.98 (95% confidence interval [CI]: 0.96 – 1).The Hosmer and Lemeshow goodness-of-fit test showed a p-value of 0.78 and the Brier score was 0.019. A value of 6 points was determined to be the threshold for reliably dividing low-risk (<6) from high-risk (≥6) patients.

Conclusions: The RSS is a valid and reliable tool to identify at the bedside patients who are at risk of developing fCDC. External validation is needed before widespread implementation.

INTRODUCTION

Clostridium difficile (*C. difficile*) is the most common cause of hospital-acquired diarrhea, affecting 10% of all hospital admissions, resulting in 3 million new cases in the United States annually.[1-4] Of those cases, 2-8% develop fulminant *C. difficile* colitis (fCDC).[3,5-8] fCDC carries a mortality rate ranging between 13% and 80%.[3,5-23] Many studies on fCDC, including two of our own, have suggested that early surgical involvement in these cases may improve outcomes.[7,9,13,16,22,23] However, it is difficult to expediently identify those patients at risk of developing fCDC, and therefore more likely to require surgical intervention. In 2011 a study by Neal et al from the University of Pittsburgh proposed a scoring system (based on 12 clinical, laboratory, and imaging criteria), to evaluate the severity of *C. difficile* colitis and identify patients at risk for fCDC (Table 1).[24] The complexity of a 12-factor system limits its use in daily clinical practice. Utilization by health care personnel is typically improved when clinical pathways are simple without sacrificing accuracy.[25,26] The aim of this study was to design a simple and accurate risk scoring system (RSS) for patients who are at risk of developing fCDC. We hypothesized that such patients can be reliably identified based on the RSS.

Table 1. Proposed CDAD Severity Scoring System, Neal et al.*

1-3 points "mild-moderate disease," 4-6 points "severe" disease, 7 or more points 'severe complicated' disease	
Criteria	**Points**
Immunosuppression and/or chronic medical condition	1
Abdominal pain and/or distention	1
Hypoalbuminemia (< 3 g/dL)	1
Fever > 38.5°C	1
Intensive care unit admission	1
CT scan with nonspecific findings of pancolitis, ascites, and/or bowel wall thickening	2
White blood cell count > 15,000 or < 1500 and/or band count > 10%	2
Creatinine 1.5 fold > baseline	2
Abdominal peritoneal signs	3
Vasopressors required	5
Mechanical ventilation required attributed to CDAD	5
Disorientation, confusion, or decreased consciousness	5

* This scoring system is for patients with a diagnosis of CDAD and is not yet validated. Neal MD, Alverdy JC, Hall DE, Simmons RL, Zuckerbraun BS. Diverting loop ileostomy and colonic lavage: an alternative to total abdominal colectomy for the treatment of severe, complicated Clostridium difficile associated disease. Ann Surg. 2011 Sep;254(3):423-7; discussion 427-9.

METHODS

Patients

All patients with *C. difficile* colitis admitted to the Massachusetts General Hospital (MGH) between November 1, 2010 and October 31, 2012 were prospectively enrolled in a specific database aiming to collect data on *C. difficile* infections. Until September 1, 2012, the diagnosis was based on the toxin A/B enzyme immunoassay. For the final two months, this was changed to a membrane enzyme immunoassay that detects *C. difficile* glutamate dehydrogenase antigen (an essential enzyme produced by all *C. difficile* isolates) and toxins A/B. In specimens with discordant tests, an additional PCR test for toxigenic *C. difficile* was performed, and the diagnosis was confirmed if the PCR was positive. Per our previous reports[7,13], patients with fCDC were identified by the presence of significant systemic toxic effects and shock, resulting in admission to the intensive care unit (ICU), need for urgent colectomy, or death.

Data

Data were collected through the prospective database and supplemented by the infection control registry and the electronic medical records. We recorded: age, gender, race, ethnicity, admitting service, previous hospitalization (within last 2 months before current admission), previous antibiotic use (within the prior 2 months), use of proton-pump inhibitors, recurrent infection, ICU admission, presence of immunosuppression and/or a chronic medical condition, laboratory values, such as white blood cell count (WBC), bands, serum creatinine levels, serum albumin levels, fever (defined as temperature >101.3 Fahrenheit), abdominal CT scan results (focusing on findings such as pancolitis, ascites, bowel wall thickening, and dilation), the need for mechanical ventilation or vasopressor support, antibiotic use, and mental status change (disorientation, confusion, or decreased consciousness). Physiologic and laboratory parameters, where necessary, were dichotomized at clinically relevant values. Outcome measures such as mortality, surgical intervention (total abdominal colectomy), hospital length of stay (LOS), ICU LOS, and discharge disposition were also collected.

Statistical analyses and development of the severity scoring system

Univariate analysis was performed to compare patients with and without fCDC. Continuous variables were summarized using mean ± standard deviation and compared by Student t-tests for variables with normal distributions or summarized using median with interquartile range (IQR) and compared by Wilcoxon rank sum tests for variables that were not normally distributed. Categorical variables were compared by Fisher's exact test.

Four variables were included in our RSS: Age > 70 years, WBC ≥ 20.000/μL or ≤ 2,000 /μL, cardiorespiratory failure (defined as CDC related vasopressor and/or mechanical ventilation requirement), and diffuse abdominal tenderness on physical exam. These variables were based on consensus among experts and identified as risk factors for a complicated course (development of fCDC or mortality) by various studies.[7,9,11,13,16,18,22,27] The experts consisted of experienced general and acute care surgeons, gastroenterologists, and intensivists, all practicing at the Massachusetts General Hospital. They used a modified Delphi technique to select the most pertinent risk factors among those described in the literature. To determine the effects of these four predictors, we performed a multivariable logistic regression model. Calibration of our system was investigated by the Hosmer-Lemeshow goodness-of-fit test. Discrimination was summarized by the area under the receiver operating curve (AUC) and the Brier score. Each variable in the system was assigned a point, proportional to its parameter estimate from the multivariable logistic regression model.[28] Subsequently, a risk score was calculated by adding up all the points. To compare the RSS to the only previously published scoring system[24], we compared the c statistic from each scoring system. We also compared test characteristics (sensitivity, specificity, positive predictive value, and negative predictive value) based on dichotomized scores. We then divided the risk scores into three risk categories and calculated how many patients were re-classified, as well as how many were correctly re-classified when using the new (MGH) scoring system. Statistical significance was considered at a two-sided $p<0.05$. All statistical analyses were performed using SAS version 9.3 (The SAS Institute, Cary, NC). This study was approved by our Institutional Review Board.

RESULTS

Cohort characteristics

Of 821 patients with confirmed *C. difficile* colitis enrolled in our prospectively collected registry, 75 had incomplete records, were younger than 18 years of age, or were eventually not admitted to the hospital. The remaining 746 patients were included in this study. 48 (6.4%) progressed to fCDC; Table 2 describes those with and without fCDC. Demographics were similar in the two groups. *C. difficile* colitis was more frequently recorded as the primary diagnosis in fCDC patients. As expected, all clinical parameters were worse in the fCDC group. Additionally, fCDC patients were treated more frequently with intravenous metronidazole and vancomycin, while non-fCDC patients more frequently received oral metronidazole. The mortality was significantly higher in the fCDC group, and the ICU LOS was longer; however the hospital stay was similar between the two groups.

Table 2. *Clostridium difficile* infection (CDI) versus fulminant *Clostridium difficile* colitis (fCDC)

Variable	CDI (N=698)	fCDC (N=48)	P value
Demographics			
Age, mean (SD), y	66 ± 17.9	70.6 ± 16.2	0.064
Age ≥ 70 years, No. (%)	323 (46.3)	27 (56.3)	0.18
Male, No. (%)	334 (47.9)	28 (58.3)	0.16
Race, No. (%)			0.84
Caucasian	601 (86.1)	42 (87.5)	
African-American	32 (4.6)	1 (2.1)	
Asian	8 (1.1)	1 (2.1)	
Other	38 (5.4)	2 (4.2)	
Unknown	19 (2.7)	2 (4.2)	
Ethnicity, Hispanic, No. (%)	27 (3.9)	1 (2.1)	0.80
CDI as primary diagnosis, No. (%)	86 (12.3)	23 (47.9)	<0.0001
Admission source, No. (%)			0.60
Home	434 (62.2)	25 (52.1)	
Nursing home	44 (6.3)	5 (10.4)	
OSH	125 (17.9)	11 (22.9)	
Rehab	83 (11.9)	6 (12.5)	
Other	6 (0.9)	1 (2.1)	
Unknown	6 (0.9)	0	
Admitting service, No. (%)			0.006
Surgery	144 (20.6)	20 (41.7)	
Medicine	536 (76.79)	28 (58.33)	
Ob/gyn	7 (1)	0	
Other/unknown	11 (1.6)	0	
Pre-medical history			
Recurrent C. difficile colitis (within last 6 months), No. (%)	143 (20.5)	12 (25)	0.47
Recent hospitalization (within last 2 months), No. (%)	347 (49.7)	27 (56.3)	0.38
Recent antibiotic usage (within last 2 months), No. (%)	533 (76.4)	39 (81.3)	0.44
PPI usage, No. (%)	336 (48.1)	27 (56.3)	0.28
Immunosuppression and/or chronic medical condition, No. (%)	586 (84)	36 (75)	0.25
ICU admission, No. (%)	192 (27.5)	45 (93.8)	<0.0001
Clinical features			
WBC count, median (IQR), /μL	13.2 (9-19.3)	21.4 (15.6-33.8)	<0.0001
WBC >20.000 or <2.000 /μL, No. (%)	162 (23.2)	29 (60.4)	<0.0001
Neutrophil bands, median (IQR), %	8 (3-17)	18 (10.5-26)	<0.0001
Neutrophil bands > 10%, No. (%)	125 (17.9)	30 (62.5)	<0.0001
Albumin, mean (SD), mg/dL	2.8 ± 0.7	2.3 ± 0.6	<0.0001
Albumin < 3g/dL, No. (%)	310 (44.4)	40 (83.3)	<0.0001
Creatinine, median (IQR), mg/dL	1 (0.7-1.7)	1.4 (1.2-2.2)	0.0006

Table 2. (Continued)

Variable	CDI (N=698)	fCDC (N=48)	P value
Creatinine 1.5 fold > baseline, No. (%)	202 (28.9)	22 (45.8)	0.032
Fever, No. (%)	62 (8.9)	9 (18.8)	0.003
Abdominal pain or distention on physical exam, No. (%)	97 (13.9)	47 (97.9)	<0.0001
Peritoneal signs on physical exam, No. (%)	1 (0.1)	31 (64.6)	<0.0001
Diffuse abdominal tenderness on physical exam, No. (%)	80 (11.5)	47 (97.9)	<0.0001
Abnormal abdominal CT scan, No. (%)[a]	161 (23.1)	38 (79.2)	<0.0001
Vasopressors required (CDC related), No. (%)	1 (0.1)	27 (56.3)	<0.0001
Mechanical ventilation required (CDC related), No. (%)	0	19 (39.6)	<0.0001
Cardiorespiratory failure, No. (%)[b]	1 (0.1)	29 (60.4)	<0.0001
Mental status change, No. (%)[c]	107 (15.3)	18 (37.5)	0.0003
Medical treatment			
Metronidazole PO, No. (%)	374 (53.6)	18 (37.5)	0.041
Metronidazole IV, No. (%)	399 (57.2)	46 (95.8)	<0.0001
Vancomycin PO, No. (%)	493 (70.6)	45 (93.8)	0.002
Vancomycin IV, No. (%)	255 (36.5)	28 (58.3)	0.009
Vancomycin PR, No. (%)	29 (4.2)	19 (39.6)	<0.0001
Outcomes			
Mortality, No. (%)	51 (7.3)	13 (27.1)	<0.0001
Total abdominal colectomy, No. (%)	0	19 (39.6)	<0.0001
HLOS, median (IQR), days	11 (6-23)	11.5 (6-20.5)	0.61
ICU admission related to CDC, No. (%)	11 (1.6)	45 (93.8)	<0.0001
ICU LOS, median (IQR), days	0 (0-0)	4 (2-8.5)	<0.0001
Discharge disposition, No. (%)			<0.0001
Home	302 (43.3)	11 (22.9)	
Deceased	51 (7.3)	13 (27.1)	
Nursing home	89 (12.8)	8 (16.7)	
Rehabilitation	226 (32.4)	16 (33.3)	
Other	13 (1.9)	0	
Unknown	17 (2.4)	0	

Abbreviations: CDI, *Clostridium Difficile* Infection; CDC, *Clostridium Difficile* Colitis; PPI, Proton Pump Inhibitors; ICU, Intensive Care Unit; WBC, White Blood Cell count; CT, Computed Tomography; PO, per oral; IV, intravenous; PR, per rectum; HLOS, hospital length of stay; ICU LOS, intensive care unit length of stay.

[a] Abnormal abdominal CT scan: positive for non-specific findings such as: pancolitis, ascites, bowel wall thickening, dilation

[b] Cardiorespiratory failure: the need for mechanical ventilation or vasopressor support

[c] Mental status change: disorientation, confusion, or decreased consciousness

Development of RSS

The 4 risk factors which were included in the multivariable logistic regression model are shown in Table 3. Each risk factor was assigned a number of points, proportional to its parameter estimate obtained from the logistic regression model. Based on the log (odds ratio) of each risk factor, age > 70 years was assigned 2 points, WBC ≥ 20.000/μL or ≤2.000/μL was assigned 1 point, cardiorespiratory failure 7 points, and diffuse abdominal tenderness on physical exam 6 points. Using this system, the discriminatory value of the MGH RSS was high with an area under the curve of the ROC curve (Figure 1) of 0.98 (95% confidence interval [CI]: 0.96 – 1). Additionally, for the RSS, the Hosmer and Lemeshow goodness-of-fit test showed a p-value of 0.78, while the Brier score was 0.019. Table 4 describes the incidence of fCDC in our population according to the RSS. Based on the incidence rate, we used a value of 6 points as the threshold to distinguish low risk (<6) from high risk (>6) patients.

Table 3. Predictors of fulminant *Clostridium difficile* colitis in the RSS development cohort

Variable	Odds Ratio	95% Confidence Interval	Points
Age > 70 years	3.80	1.14 – 13.68	2
WBC ≥ 20.000 or ≤ 2.000 / μL	1.81	0.54 – 6.05	1
Cardiorespiratory failure*	285	24 – 21,491	7
Diffuse abdominal tenderness	189	27 – 8,429	6

Abbreviations: RSS, Risk Scoring System; WBC, White Blood Cell count.
* Cardiorespiratory failure: the need for mechanical ventilation or vasopressor support

Comparison of the RSS and Previously Published Severity Scoring System

We applied the previously published severity scoring system in our population. The area under the curve was 0.96 (95% CI: 0.93 – 0.99). Comparing the C-statistics of the two systems, showed a p-value of 0.22. The previously published system used a value of 4 points as the cut-off for low risk (<4) vs. high risk (≥4). The performance of both scoring systems were tested. This analysis shows a similar sensitivity (97.9%), but a higher specificity (88.4% vs. 46.4%), positive predictive value (36.7% vs. 11.2%), and negative predictive value (99.8% vs. 99.7%) for the RSS. To compare the RSS to the risk categories of the previously published system, we divided the scores into three risk categories as well based on the incidence rate (low risk: 0-5, medium risk: 6, high risk: >7). A total of 382 (50.7%) patients were reclassified by the RSS risk categories, among them, 333 (88.1%) were correctly reclassified by the RSS risk categories as is shown in Table 5.

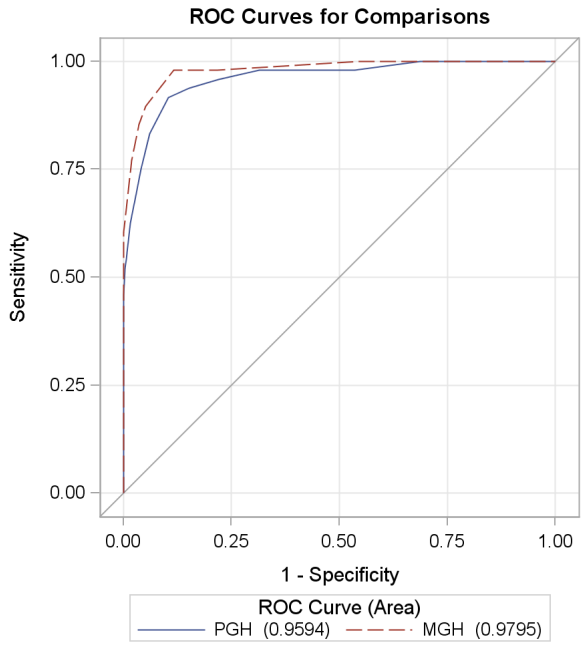

Figure 1. Receiver operating characteristic curves for the risk scoring systems of fulminant CDC (both RSS and Previously Published Severity Scoring System included)
Abbreviations: ROC, receiver operating characteristic curve; CDC, *Clostridium Diffcile* Colitis; MGH, Massachusetts General Hospital Risk Scoring System; PGH, previously published severity scoring system.[29]

Table 4. Risks of fCDC by the Risk Scoring System

	Observed fCDC (development cohort, total n=746)	
Score	**n**	**%**
0	0/249	0
1	0/70	0
2	1/229	0.4
3	0/70	0
6	4/49	8.2
7	2/13	15.4
8	4/16	25
9	8/21	38.1
13	5/5	100
14	10/10	100
15	5/5	100
16	9/9	100

Abbreviation: fCDC, fulminant *Clostridium Difficile* Colitis.
Patients with scores ≥ 6 points were classified as high risk

Table 5. Reclassification table Risk Scoring System vs. Previously Published Severity Scoring System

	MGH score			
PGH score	**Low Risk (0-5)**	**Medium Risk (6)**	**High Risk (≥7)**	**Total**
Low Risk (0-3), N	294	23	8	325
# without fCDC	294	22	8	
# with fCDC	0	1	0	
Medium Risk (4-6), N	184	18	19	221
# without fCDC	184	17	19	
# with fCDC	0	1	0	
High Risk (≥7), N	140	8	52	200
# without fCDC	139	6	9	
# with fCDC	1	2	43	
Total	618	49	79	746

Abbreviations: fCDC, fulminant *Clostridium Diffcile* Colitis; RSS, Risk Scoring System.
Reclassification:
· 184+139+6 patients without fCDC were correctly moved into lower risk categories
· 1 patient with fCDC was correctly moved into a higher risk category
· 1+2 patients with fCDC were incorrectly moved into a lower risk category
· 22+8+19 patients without fCDC were incorrectly moved into higher risk categories

DISCUSSION

In this study we present a severity scoring system for the purpose of detecting patients at risk of developing fCDC. With the goal of using a simplified system that can be easily remembered by clinicians and used at the bedside, we included 4 risk factors selected by an expert panel and based on previous studies.[7,12,29] The RSS successfully discriminates patients with C. difficile infection from those who have fCDC (AUC, 0.98). Calibration was low (Brier score of 0.019), indicating that the possibility of developing fCDC could be estimated accurately. A cut-off of 6 points was used to divide patients at high risk of developing fCDC; this classified 97.9% of patients correctly. In combination with a high specificity (88.4%) and excellent negative predictive value (99.8%) this scoring system proves it has the potential to be used at the bedside in order to safely rule out the possibility of fCDC. The positive predictive value of 36.7% is low, and should be considered against the background of its estimation in a low-prevalence setting (6.4% of total cohort was diagnosed with fCDC).[30]

Since the beginning of the 21st century there have been many *C. difficile* outbreaks; the majority are caused by a newly discovered, hypervirulent strain, NAP1/BI/027.[31,32] This strain is associated with increased severity of the *C. difficile* infection, resulting in a higher likelihood of fCDC (which carries significant morbidity and mortality).[33,34] Prediction rules to detect patients that are at risk for developing CDI, and also predict recurrent CDI, are available.[35-40] Commonly used risk factors, such as age > 65 years, antibiotic usage, and

multiple comorbidities, populate these prediction rules. Although many studies in the fCDC population have been published, describing risk factors of mortality[6,7,10,15,16,18,20,21] and recommending early intervention to prevent unfavorable outcomes[7,9,13,16,22,23], systems to score the severity of fCDC are not common. Only one group has proposed such a system for severe, complicated *C. difficile* colitis.[24] Partially based on recommendations of the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America[1], they designed a system that weighs variables such as cardiorespiratory failure and mental status changes heavily, as well as an additional 10 variables. That system had never been tested or validated until now. The risk factors used in our RSS were based on the literature and derived by expert consensus. In a case-control study by Greenstein and colleagues[12], risk factors for development of fCDC were determined to be: WBC >16.000/mm^3 at therapy start, presence of inflammatory bowel disease, operative therapy in the last 30 days, and history of intravenous immunoglobulin therapy. In a similar, but more recent study by Girotra et al.[29], 'red flags' for developing fCDC were: age > 70 years, abdominal pain, and profound leukocytosis (>18.000/mm^3).

Upon comparison of our 4-factor RSS with the 12-factor Severity Score System[24], we found a non-significant difference in AUC and an equal sensitivity of 97.9%. The two systems are, therefore, similarly effective. However, the RSS has a higher specificity and positive predictive value despite its greater level of simplicity, and is more likely to be adhered to. Additionally, our analysis showed that when the two systems disagreed, 88.1% of the patients were correctly reclassified by our risk categories.

A limitation of our study relates to the low number of patients with fCDC (48 patients, 6.4% of cohort). It is because of this number that we were unable to divide our cohort into a development and validation cohort; external validation is necessary. Furthermore, the RSS was based on 4 predictors, which were chosen by an expert panel and derived from previous data, instead of a statistical model. Again, the low number of cases prevented an exhaustive risk factor analysis by stepwise logistic regression. Even when using only four risk factors, the 95% confidence intervals are particularly wide, attesting to the limited sample size. Although fCDC is becoming more frequent than in the past, its frequency is still low and multicenter studies will be needed to accrue large sample sizes. An additional limitation pertains to the timing of RSS, which was only calculated at one time point. If the WBC or abdominal exam changes, the RSS predictability may change as well. Therefore, a low-probability score should not put the probability of future deterioration completely at rest. It is notable that our score does not include computed tomographic images. For most patients with suspected fCDC a computed tomographic scan will be ordered. However, in our analysis it was found that such images contributed only a very small margin to the accuracy of the RSS (data not shown here) and therefore, it was elected to exclude computed tomographic findings as a risk factor. This buttresses the usual teaching that the physiology rather than the radiology

is important for clinical decision-making, while it has the added benefits that imaging is not required when calculating the risk, thus lowering the threshold of using the RSS, whereas it also saves costs.

In conclusion, we designed a valid and reliable severity scoring system for fCDC that can be used at the bedside to score the severity of disease and identify patients at risk of developing fCDC. The next step will be to externally validate our risk scoring system in order to allow widespread implementation.

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Chapter 3

Reduced mortality in patients with fulminant *Clostridium difficile* colitis due to a new hospital-wide surgical consultation protocol

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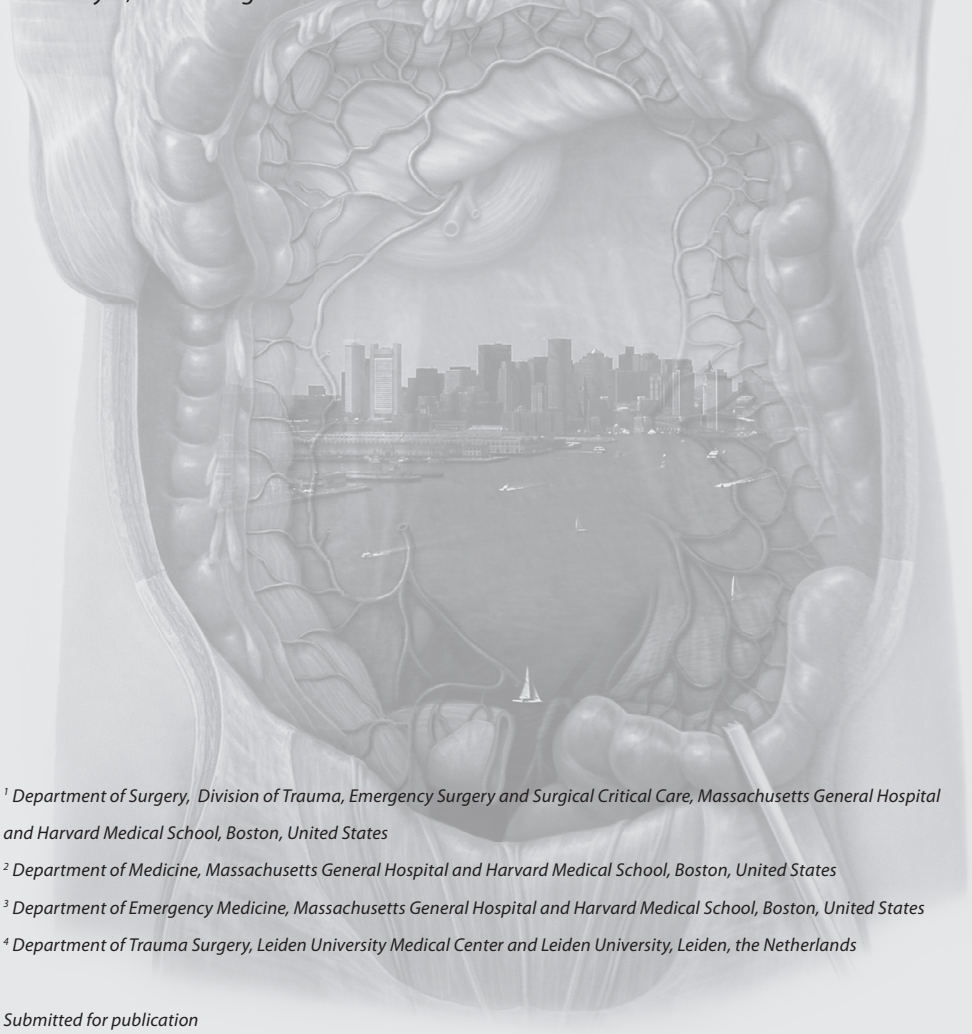

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Submitted for publication

ABSTRACT

Background: Fulminant *Clostridium difficile* colitis (fCDC) occurs in 2-8% of patients with CDC, and carries a high mortality. Prompt surgery may reduce mortality. Our aim was to determine whether a standardized hospital-wide protocol for surgical referral in CDC would result in earlier surgical consultation, earlier identification of patients who could benefit from surgical therapy, and reduced mortality from fCDC.

Methods: A multidisciplinary team developed consensus criteria for surgical consultation. Compliance with the referral protocol was evaluated by prospective chart review of all inpatient *C. difficile* cases. Outcomes of the prospective cohort were compared to an historic control group, comprised of patients from an earlier study performed at our institution.

Results: From November 1, 2010 – October 31, 2012, we identified 1106 inpatients with CDC; 339 patients matched the consultation criteria, of who 213 received a surgical consultation, resulting in an overall compliance rate of 62.8%. Of 46 patients with fCDC, 11 (23.9%) died. All fulminant cases received a surgical consultation, with a median time to surgical referral of 3 hours. The adjusted mortality was significantly lower in the prospective group compared to the historical group (18.3% vs. 34.8%, p=0.031). The mortality rate was 14.7% when excluding patients with limitations of care and those transferred to our institution in a fulminant state.

Conclusions: A hospital-wide protocol with established criteria for surgical consultation resulted in a 31.5% relative reduction in mortality from fCDC compared to historical controls. The overall mortality rate for fCDC patients without limitations of life-sustaining treatment who presented to our emergency department or developed fCDC while admitted to our hospital was 14.7%.

INTRODUCTION

Clostridium difficile infections afflict up to 10% of all hospitalized patients and up to 20% of such patients receiving antibiotics.[1-8] A study using the Nationwide Inpatient Sample showed a 109% increase in incidence of *C. difficile* infections between 1993 and 2003.[8] More recent national data showed that the rate of *C. difficile* hospitalizations per 1,000 non-maternal, adult discharges increased from about 5.6 in 2001 to 12.8 in 2012, with annual costs in the U.S. estimated in the billions of dollars.[9, 10] Two to eight percent of patients with *C. difficile* infection will develop fulminant disease, defined as *C. difficile* colitis (CDC) with significant systemic toxic effects and shock, resulting in the need for intensive care unit (ICU) admission, colectomy or death.[8, 11-17] Mortality rates for fulminant CDC (fCDC) range between 13.8% - 80%.[11-13, 16-34] A retrospective study in our own institution identified a 35% mortality rate for fCDC.[11] This study and others have suggested that admission to a surgical service and prompt colectomy may reduce mortality in fCDC.[11, 12, 16-19, 23, 27, 31, 32] In spite of these data suggesting an important role for surgical consultation and surgery in the management of patients with fCDC, and guidelines recommending that colectomy be considered before severe shock is established,[1, 13, 18, 27, 35] delays in surgical consultation are common. This may be due in part to a lack of clear criteria for surgical consultation.

In order to address this gap, we developed a hospital-wide protocol based on consensus-driven criteria for surgical referral of patients with CDC. We hypothesized that this protocol would result in earlier surgical consultation, earlier identification and treatment of fCDC patients, and reduced mortality from fCDC.

METHODS

Design:

This study has a before-after design across the time of implementation of a hospital-wide surgical referral protocol for patients with severe CDC. Data on fCDC patients after the protocol (POST group) was recorded prospectively. Data on fCDC patients before the protocol (PRE group) were extracted retrospectively from the database of a previous study from our institution.[11]

Protocol development:

Based on our review of hospital data, the three main sources of fCDC patients were the general medical wards, the Emergency Department, and the medical intensive care unit. Between August and October 2010 we coordinated a series of meetings with representatives of these departments. Retrospective data from our hospital[11] and other

sites were reviewed, and consensus was reached about appropriate criteria for surgical consultation. These criteria were based upon several predictors of mortality identified in previous studies from our institution,[11, 12] as well as in studies from other institutions.[13, 18-20, 27, 30, 31, 33, 36] The resulting protocol called for immediate surgical consultation for patients with known or suspected CDC, and any of the additional criteria listed in Table 1 indicating possible severe CDC. The protocol initially called for consultation for every patient with a single criterion. At a four-month interim analysis we found that no patients with only one criterion had developed fCDC. Within the multidisciplinary study group, it was decided that the threshold for consultation should be increased to two criteria. The consensus criteria for surgical consultation were disseminated through departmental meetings and conferences, the Massachusetts General Hospital intranet, and emails to staff members, fellows, and residents throughout September and October 2010. Starting November 1, 2010 the protocol was applied to all patients arriving to the Emergency Department or already hospitalized in any hospital unit.

Table 1. Consensus criteria for surgical referral in patients with confirmed or suspected fulminant *Clostridium difficile* colitis (any two of the following):

1	ICU admission
2	Temperature > 101 F
3	WBC count > 15,000 cells/mm^3 or < 4000, or bands > 10%
4	HR > 120 beats/min
5	Systolic BP < 90 mmHg and/or need for vasopressors
6	> 12 bowel movements/day
7	Peritonitis on exam or abdominal pain not improving within 24 hours
8	Evidence of shock (decreased mental status, new organ failure, lactate > 2.0)

Abbreviations: ICU, Intensive Care Unit; F, Fahrenheit; WBC, White Blood Cell; bands, bandemia; HR, heart rate; BP, blood pressure.

Compliance with the protocol:

To monitor compliance with the protocol, we prospectively identified all patients with positive *C. difficile* immunoassays from our Infection Control Registry, ascertained whether those patients reached the threshold of two criteria (or one criterion during the first 4 months of the study), and recorded whether a surgical consult was called. Compliance to the protocol was promoted through departmental meetings and conferences, and the intranet throughout the complete study period. Additionally, the representatives from each department included in the study were charged with ongoing education to maintain compliance with the agreed upon management protocol. Individual cases of non-consultation or delayed consultation were reviewed and fed back to the responsible clinicians by their departmental representatives.

Definitions and measurements:

CDC was defined by the identification of *C. difficile* in symptomatic patients. During the first 22 months of the study, the type of diagnostic test that was used to detect *C. difficile* infection, was the toxin A/B enzyme immunoassay. This was changed in the last 2 months of the study (September and October 2012) to a membrane enzyme immunoassay that detects both *C.difficile* glutamate dehydrogenase antigen and toxins A and B. In specimens with discordant glutamate dehydrogenase antigen and toxin results by the new test, an additional PCR test for toxigenic *C. difficile* was performed. Fulminant CDC was defined by the presence of septic shock[37], need for intubation and/or vasopressors, or admission to the ICU owing to CDC. Subtotal colectomy was performed in patients with fCDC who were determined to be too toxic for a trial of non-operative therapy or were treated medically, but deemed to have failed medical therapy. In patients undergoing subtotal colectomy, CDC was confirmed by histopathologic analysis of the surgical specimen.

Data collection:

The following data were collected prospectively from November 1, 2010 until October 31, 2012 for the POST group: demographics; important comorbidities, measured by the age-adjusted Charlson Comorbidity Index[38] (CCI); history of hospitalization and antibiotic therapy during the 2 months before the current admission; prior CDC in the 6 months before the current admission; vital signs; physiologic parameters; abdominal examination findings; mental status; radiographic and/or endoscopic findings; medical intervention (antibiotics, intubation, and vasopressors); surgical intervention (type of operation); time interval between diagnosis (defined as a confirmed/suspected CDI and 2 positive criteria) and surgical consultation; time interval between diagnosis and surgical intervention; indication for surgical intervention; surgical findings; final pathology; intensive care unit (ICU) and hospital length of stay; mortality; admission source; admitting service; referral source; primary department that provided care; and discharge disposition. We also recorded whether the patients had any limitations of care, defined as a refusal by the patient or legal representative to undergo surgery or other life-sustaining treatments. Patients who were transitioned to comfort measures after failure of an aggressive course of treatment were not considered to have limitations of care. The exact same data were recorded for the PRE group (January 1, 1996 to December 31, 2007).

Outcomes:

The primary outcome was in-hospital mortality and secondary outcomes included ICU and hospital length of stay, time to surgical consultation and to surgery. The time was measured from either arrival to the Emergency Department with severe CDC symptoms or the time from which patients met consultation criteria if they were already hospitalized for other reasons.

Statistical analysis:

We compared the PRE and POST group to identify differences in patient characteristics and outcomes. Subgroup analyses were performed based on surgery status (colectomy vs. no-colectomy) and admitting service (surgical vs. non-surgical). Continuous variables were summarized using mean ± standard deviation and compared by Student t-tests, when variables had normal-like distributions, or summarized using median (interquartile range) and compared by Wilcoxon rank sum tests, when variables could not be assumed to be normally distributed. Categorical variables were compared by Fisher's exact test. Statistical significance was considered at a two-sided $p<0.05$. All statistical analyses were performed using SAS version 9.3 (The SAS Institute, Cary, NC). This study was approved by our Institutional Review Board.

RESULTS

Over a 2-year period of prospective data collection 1106 patients had a positive toxin assay for *C. difficile* in our tertiary care center. Of those patients, 339 met our criteria for surgical consultation. A total of 213 patients were referred per protocol to the surgical service, resulting in an overall compliance rate of 62.8%. During the first 4 months of the study, when the threshold for surgical consultation required one criterion, compliance with the protocol was 53.6%. This increased to 65.2% after we changed the threshold for consultation to at least 2 criteria. In total, 48 patients with fCDC were included in the POST group. The overall incidence of fCDC in the period following protocol implementation was 4.3% (48/1106). We excluded 2 patients from the analysis who were treated with an experimental procedure (loop ileostomy with colonic lavage) as part of another research study. All 46 patients included in the analysis underwent surgical consultation, resulting in a compliance rate of 100% for patients with fCDC. The median time from diagnosis to consultation was 3 hours (IQR, 1-7.75 hours). The majority of patients with fCDC met either 4 (34.8%) or 5 (26.1%) criteria upon surgical consultation (Figure 1). No patient had only 1 or all 8 criteria.

The overall mean age of the fCDC patients in the POST group was 69.3 ± 16.4 years. Fifty-nine percent were male with an average age-adjusted Charlson Comorbidity Index of 6.3 ± 2.7. Half of the patients were admitted directly to the surgical service and 63% had CDC as their primary diagnosis. The median hospital stay for our entire cohort was 13.5 days (IQR: 7-22 days), and the median ICU stay was 4 days (IQR: 2-9 days). No significant differences in the main outcomes (mortality, ICU length of stay, hospital length of stay) were found when comparing patients admitted to the surgical service to those admitted to a non-surgical service. Comparing the PRE- and POST groups, the POST-group had a significantly higher age-adjusted CCI, while the PRE-group had a higher

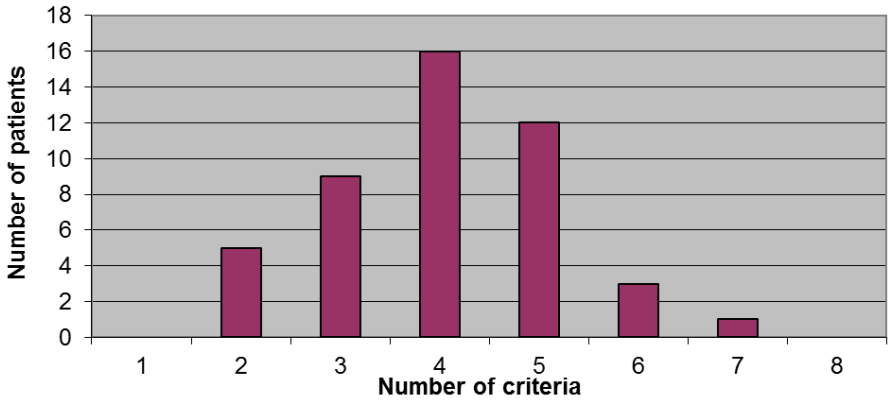

Figure 1. Number of criteria met by fulminant *Clostridium difficile* colitis patients upon surgical consultation

mean white blood cell (WBC) count and lower mean serum albumin (see Table 2). Additionally, patients in the POST group were treated more often with enteral vancomycin or received combination therapy with vancomycin and metronidazole. After our intervention a higher percentage of patients were directly admitted to the surgical service (50% POST vs. 15.2% PRE, p=<0.0001), and there was a shorter time interval between hospital admission and surgical intervention in patients undergoing surgery (median 1.5 days (IQR, 0-3) vs. 3 days (IQR, 1-11), p=0.018).

Mortality, our primary outcome, was decreased by a relative 31.5% after implementing the protocol (34.8% vs. 23.9%, PRE vs. POST, p=0.15). The difference in mortality was statistically significant when adjusting for the difference in CCI between the two groups (adjusted rate 34.8% vs. 18.3%, p=0.031). The mortality rate dropped even further when excluding those with limitations of care (unadjusted rate 30.3% vs. 18.6%, p=0.13; adjusted rate 30.3% vs. 15.3%, p=0.047) and when excluding both patients with limitations of care and those that were transferred to our institution in a fulminant state (unadjusted rate 31% vs. 14.7%, p=0.055; adjusted rate 31% vs. 12.8%, p=0.033). There were no significant differences in median hospital LOS and median ICU LOS (Table 3). The percentage of patients undergoing subtotal colectomy with ileostomy did not differ significantly between the PRE and POST group (37.9% PRE vs. 41.3% POST). Limiting our analysis only to those patients that received a colectomy, we did not find any significant difference in mortality, ICU or hospital length of stay. However, we found that patients in the POST group were admitted to the ICU sooner after admission to the hospital than patients in the PRE group (median 0 vs. 1 day, p=0.034). There was also a shorter interval between admission and surgical intervention for those that required surgery in the POST group (median 1.5 vs. 3 days, p=0.018). Comparing patients admitted to the surgical service to those admitted to a non-surgical service, in the PRE-group the time intervals

Table 2. Comparison of fulminant *Clostridium difficile* colitis patients before (PRE) and after (POST) implementation of the surgical referral protocol

Parameter	PRE N=198	POST N=46	P value
Age, mean (SD), y	68.6 ± 14.9	69.3 ± 16.4	0.79
Age ≥ 70 years, No. (%)	117 (59.1)	25 (54.3)	0.56
Male, No. (%)	95 (48)	27 (58.7)	0.19
CCI, mean (SD)	5.1 ± 2.3	6.3 ± 2.7	0.008
Risk factors, No. (%)			
Diabetes mellitus	59 (29.8)	12 (26.1)	0.62
Renal disease	50 (25.3)	12 (26.1)	0.91
Immunosuppression	99 (50)	16 (34.8)	0.063
Recurrent *C. difficile* colitis (within last 6 months)	65 (32.8)	12 (26.1)	0.38
Recent hospitalization (within last 2 months)	173 (87.4)	36 (78.3)	0.11
Recent antibiotic usage (within last 2 months)	181 (91.4)	41 (89.1)	0.63
Clinical features, No. (%)			
WBC count, mean (SD), /μL	31.9 ± 21	25.7 ± 14.7	0.02
Neutrophil bands, mean (SD), %	18 ± 15.2	18.7 ± 11.3	0.74
Albumin, mean (SD), mg/dL	2 ± 0.6	2.5 ± 0.6	0.0001
Creatinine, mean (SD), mg/dL	2.2 ± 1.6	1.8 ± 2.0	0.25
Intubation, No. (%)	85 (42.9)	16 (34.8)	0.31
Vasopressors, No. (%)	92 (46.5)	25 (54.3)	0.34
CT results*, No. (%)			
Abnormal scan	140 (70.7)	36 (78.3)	0.75
Colonic wall thickening	126 (63.6)	33 (71.7)	0.66
Colonic dilation	34 (17.2)	7 (15.2)	0.57
Ascites	79 (39.9)	19 (41.3)	0.77
Perforation	6 (3)	0	0.21
Admission source, No. (%)			0.011
Home	82 (41.4)	20 (43.5)	
Outside hospital	34 (17.2)	11 (23.9)	
Nursing home	16 (8.1)	5 (10.9)	
Rehabilitation facility	66 (33.3)	8 (17.4)	
Other	0	2 (4.3)	
Hospital transfer in fulminant state, No. (%)	18 (9.1)	9 (19.6)	0.041
Surgery as admitting service, No. (%)	30 (15.2)	23 (50)	<0.0001
Admission with CDC as primary diagnosis, No. (%)	135 (68.2)	29 (63)	0.5
Operation (subtotal colectomy with ileostomy), No. (%)	75 (37.9)	19 (41.3)	0.67
Interval hospital admission - ICU admission, median (IQ1-3), d	0 (0-4)	0 (0-1)	0.098
Interval hospital admission - surgical intervention†, median (IQ1-3), d	3 (1-11)	1.5 (0-3)	0.018
Interval ICU admission - surgical intervention†, mdian (IQ1-3), d	0 (0-2)	1 (0-2)	0.35
Limitation of care, No. (%)	13 (6.6)	3 (6.5)	0.99
Metronidazole (both PO and IV), No. (%)	182 (91.9)	41 (89.1)	0.54
Oral vancomycin, No. (%)	86 (43.4)	41 (89.1)	<0.0001
Combination of metronidazole and vancomycin, No. (%)	80 (40.4)	40 (87)	<0.0001

* CT was not performed for 48 from the PRE group and 8 from the POST group

† Limited to the patients who received surgical intervention

Abbreviations: SD, standard deviation; CCI, Charlson Comorbidity Index; WBC, white blood cell; CT, computed tomography; IQ, interquartiles; ICU, intensive care unit; PO, per oral; IV, intravenous.

between hospital admission and surgical intervention, and between ICU admission and surgical intervention (measured in days) were significantly shorter in patients admitted directly to the surgical service. In the POST-group, such differences were not found. The mortality rate dropped significantly on non-surgical services (37.5% PRE vs. 13% POST, p=0.02), but at the same time there was a trend towards higher mortality on the surgical service (20% PRE vs. 34.8% POST, p=0.23).

Table 3. Outcomes of fulminant *Clostridium difficile* colitis patients before (PRE) and after (POST) implementation of the surgical referral protocol

Outcomes	PRE N=198	POST N=46	P value
Mortality, all subjects, No. (%)	69 (34.8)	11 (23.9)	0.17
After adjusting for CCI, %	34.8	18.3	0.031
Mortality, excluding limitations of care, No. (%)	56 (30.3)	8 (18.6)	0.14
After adjusting for CCI, %	30.3	15.3	0.047
Mortality, excluding limitations / transfers, No. (%)	52 (31)	5 (14.7)	0.062
After adjusting for CCI, %	31	12.8	0.033
Hospital length of stay, median (IQ1-3), days	16 (8-32)	13.5 (7-22)	0.089
ICU length of stay, median (IQ1-3), days	4 (2-10)	4 (2-9)	0.34

Abbreviations: CCI, Charlson Comorbidity Index; ICU, intensive care unit; IQ, interquartiles.

DISCUSSION

With 3 million new cases every year in the US, and rising prevalence, *C. difficile* is now the leading cause of nosocomial diarrhea in both North America and Europe. CDC is not only increasingly common, but has also become more severe with the emergence of multiple hypervirulent strains linked to increasing morbidity and mortality.[1, 6, 8, 11, 16, 30, 39-43] As severe infections have become more common, the role of surgery in their management has been refined. Current guidelines recommend surgery only for severe, complicated disease, but recommend performing it before severe shock or irreversible organ damage has intervened.[35] Studies by Sailhamer[11], Hall[12], Seder[33], and Ali[18] suggest improved outcomes, including mortality benefits, when surgical intervention is performed early in the course of fulminant disease. Still, a study from our own institution showed that surgical consultation was often undertaken relatively late, sometimes days after the occurrence of multisystem organ failure.[11] Our current study shows that by implementing a standardized protocol for surgical consultation in CDC the time from diagnosis to surgical consultation can be reduced – in this case to a median of 3 hours for patients with fCDC - and the adjusted mortality rate decreased.

Currently, there are no evidence-based guidelines for when to obtain surgical consultation in cases of CDC, though a number of criteria have been suggested to be risk fac-

tors for transition to fCDC. These include older age (>70 years), profound leukocytosis, comorbidities including immunosuppression, history of inflammatory bowel disease, and intravenous immunoglobulin treatment, surgery within 30 days of presentation with CDC, and evidence of peritoneal signs on physical exam.[15, 16, 20, 44] Our consultation criteria were developed through multidisciplinary consensus, and based largely on our own retrospective data.[11, 12] Our priority was to identify patients who would develop fulminant disease, early in their course. We consciously developed criteria that we believed would be highly sensitive for fCDC, at the cost of some specificity. Hospital-wide compliance to our protocol was almost 65% over the 24-month study period. As expected, some clinicians were reluctant to place surgical consultations in patients who, in spite of meeting consultation criteria, appeared clinically well or improving. However, all patients who developed the fulminant disease were caught early in their disease course, with a median time to surgical consultation of 3 hours, resulting in 100% compliance in that group, which was the primary goal of our initiative. Further work might attempt to identify the most important clinical factors predicting the development of fulminant disease to allow further refinement of the consultation criteria.

We found a statistically significant risk-adjusted relative mortality reduction of 31.5% when comparing our post-protocol study cohort to historic controls. Our POST cohort had more comorbid disease than the PRE group, as shown by the higher age-adjusted CCI score. Although the mean peak WBC counts were higher and the mean lowest recorded albumin levels were lower in the PRE group, these discrepancies can be explained by the fact that patients under our protocol were recognized and treated earlier in the course of disease, before their WBC counts rose or serum albumin levels fell further. The unadjusted mortality was 23.9% in the new cohort. This dropped to 18.6% when excluding patients with limitations of care (refusal of mechanical ventilation, vasopressors, or surgery), and fell to 14.7% when we, in addition to excluding patients with limitations of care, also excluded those that were transferred in a fulminant state to our center. We believe this latter exclusion is relevant in a study focusing on early surgical consultation, since patients transferred to our institution in a fulminant state that may have lasted for days could not be expected to benefit from an early referral protocol. The overall mortality for fCDC for patients presenting de novo to our institution, or contracting the disease while admitted to our hospital is 14.7%. This is among the lowest mortality rates reported in the literature, where, over the last decade, most studies report mortality rates between 35-55%.[8, 11, 17-20, 23, 24, 26-28, 31-33]

In patients who required a total abdominal colectomy, the time interval between hospital admission and surgical intervention was measured, since multiple studies have suggested improved outcomes with shortened intervals.[13, 18, 19, 27] Compared to the PRE cohort, the time interval from admission to surgical intervention was cut in half (median of 1.5 days vs. 3 days, p=0.024) for patients requiring colectomy, without increasing the

overall percentage of fCDC patients undergoing colectomy (37.9% PRE vs. 41.3% POST). The fact that approximately the same number of patients underwent colectomy, suggests that the improved outcomes were a result of performing colectomies earlier in the course of disease rather than a result of performing colectomies more frequently, and that early surgical consultation does not necessarily lead to increased rates of colectomy.

There has also been debate in the literature about whether patient outcomes could be improved by direct admission to a surgical service in severe CDC cases.[11, 13, 18, 19, 27] Sailhamer et al.[11] showed a lower mortality rate in patients admitted to a surgical vs. a non-surgical service (12.8% vs. 39.3%), both in all CDC patients, and in those undergoing colectomy. However, a study by Byrn and colleagues[13] showed no difference in mortality based on admitting service. Our results showed a significantly higher percentage of fCDC patients directly admitted to the surgical service after implementation of the protocol (15.2% PRE vs. 50% POST, p=0.67), but no differences in outcomes between patients admitted to the medical or surgical services. When comparing PRE vs. POST implementation of the protocol, stratifying by admitting service, the mortality rate within the medical service significantly decreased, while there was a trend towards increasing mortality on the surgical service. This can be explained in two ways. First, due to our intervention, patients admitted to non-surgical services in the POST group were more likely to have early surgical consultation and all its associated benefits. Second, it is probable that in the PRE cohort a highly selected subgroup of patients likely to benefit from surgery were the only ones admitted directly to the surgical service. This is in contrast with the POST cohort, where early surgical consultation resulted in more surgical admissions, even of patients who were less likely to undergo surgery. This second contention is further supported by the fact that in the PRE cohort 66.7% of patients admitted to the surgical service underwent colectomy, compared to only 52.2% of patients in the POST cohort. It is likely that patients with severe CDC can be managed equally effectively on either a surgical or medical service as long as appropriate medical therapy is administered, close communication is maintained, and the need for surgical intervention is constantly reevaluated.

Our study has a number of limitations. Our primary intervention was only adhered to 65% of the time. As discussed above, we accepted a lower specificity in the consultation criteria in the effort to capture all potential cases with severe CDC. We included all CDC patients in the analysis, not only those for whom surgical consultation was obtained, thus the entire prospective POST cohort can be considered on an intention-to-treat basis. Further studies could seek to identify the most important criteria or factors associated with the transition to fCDC, to further refine the consultation criteria. Although our POST cohort was identified prospectively, the mortality benefit we describe is in comparison to historical controls collected retrospectively over a number of years during which the epidemiology and treatment of CDC evolved considerably. The more frequent use of

enteral vancomycin and general advances in critical care in recent years would tend to bias the results in favor of our intervention, suggesting a benefit to early surgical consultation that may not exist. Conversely, the preponderance of more virulent *C. difficile* strains in recent years might bias the results against our intervention. We controlled for patient comorbidities, but given the lack of complete microbiologic data on specific *C difficile* strains and resistance patterns, we could not adequately control for all of these confounders. Additionally, our institution has generated publications advocating early surgical consultation in CDC from both our General Surgery and Trauma and Acute Care Surgery services.[11, 12] Our previously published historical controls represent one of the better mortality rates in the published literature for fulminant CDC. The relatively low mortality before intervention and an institutional environment in which awareness of the importance of surgical consultation in CDC may have been higher than is typical even before our intervention, would both bias our results towards the null hypothesis.

As the first prospective study of early surgical consultation for CDC, our study shows that a hospital-wide protocol with established criteria for surgical consultation lowers mortality from fCDC. The overall mortality rate for fCDC patients without limitations of life-sustaining treatment was 14.7%, one of the lowest reported. Further studies are needed to refine the referral criteria and to determine whether this type of intervention will be effective in other institutions.

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Chapter 4

Antibiotic Regimen after a Total Abdominal Colectomy with Ileostomy for Fulminant *Clostridium Difficile* Colitis: a Multi-Institutional Study

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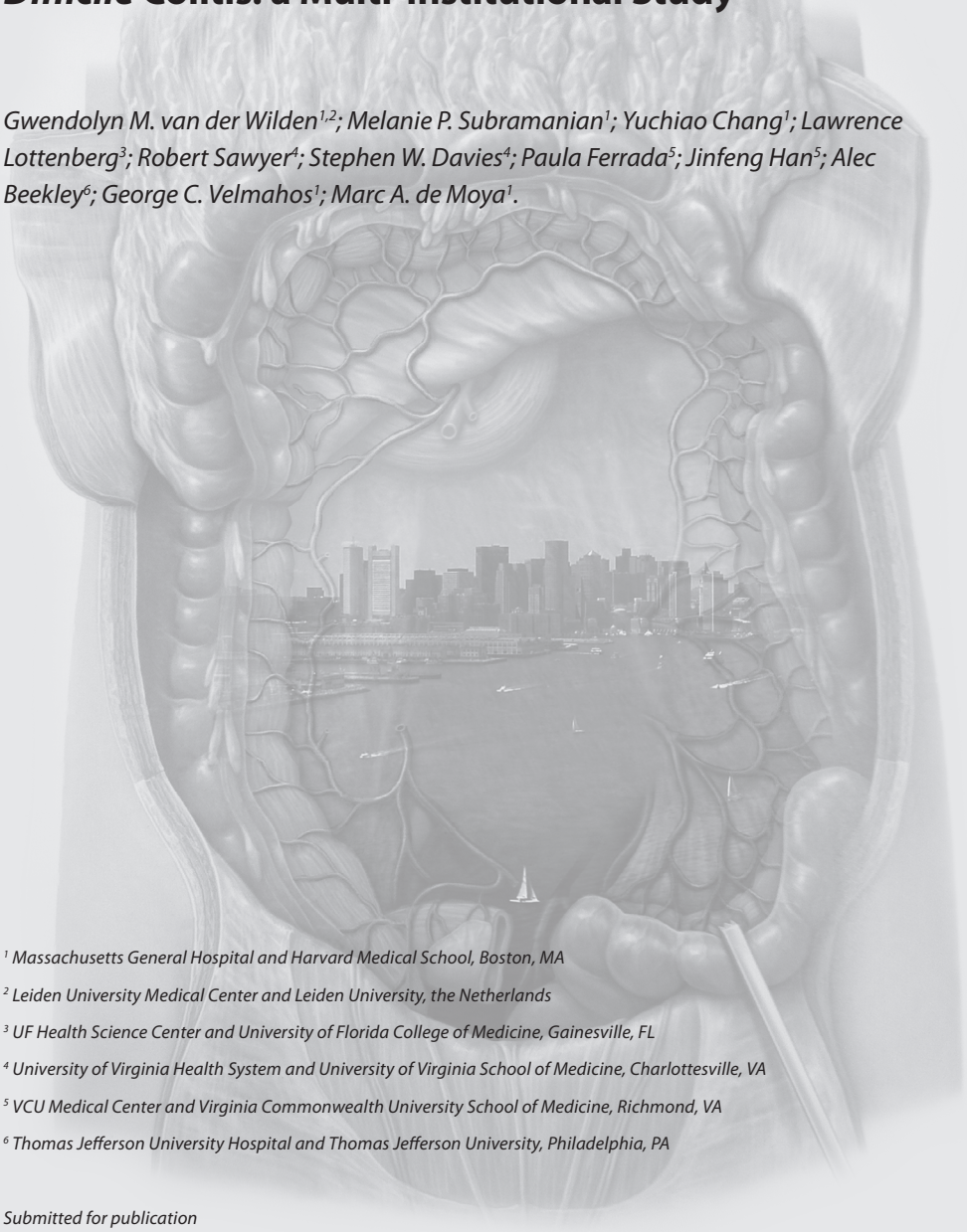

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Submitted for publication

ABSTRACT

Background: Fulminant *Clostridium difficile* colitis (fCDC) is a highly lethal disease with mortality rates ranging between 12% - 80%. Although often these patients require a total abdominal colectomy (TAC) with ileostomy, there is no established management protocol for post-operative antibiotics. In this study we aim to make some recommendations for post-operative antibiotic usage, while describing the practice across different institutions.

Methods: Multi-institutional retrospective case series including fCDC patients who underwent a TAC between January 1, 2007 – June 30, 2012. We first analyzed the complete cohort and consecutively performed a survivor analysis, comparing different antibiotic regimens. Additionally we stratified by time interval (antibiotics for ≤7 days, or ≥8 days). Primary outcome was in-hospital mortality. Additional secondary outcomes included hospital length of stay (HLOS), ICU LOS, number of ventilator-free days, and occurrence of intra-abdominal complications (proctitis, abscess, sepsis, etc.). Finally, a multivariate logistic regression analysis was performed to identify predictors of mortality.

Results: A total of 100 fCDC patients that underwent a TAC were included across 5 institutions. Four different antibiotic regimens were compared; A (metronidazole IV + vanco PO), B (metronidazole IV), C (metronidazole IV + vanco PO and PR), and D (metronidazole IV + vanco PR). The combination of IV metronidazole with or without PO vancomycin showed superior outcomes in terms of a shorter ICU length of stay and more ventilator-free days. However, when comparing metronidazole alone vs. metronidazole and any combination of vancomycin, no significant differences were found. The addition of neither vancomycin enema, nor the time interval changed outcomes. Requiring a vasopressor before the operation, and the total units of FFP transfused during hospital admission were found to be risk factors for mortality.

Conclusion: Patients, after a TAC for fCDC, may be placed on either IV metronidazole or PO vancomycin depending upon local antibiograms, and proctitis may be treated with the addition of a vancomycin enema (PR). There was no data to support routine use of more than 7 days.

INTRODUCTION

Colonization with *Clostridium difficile* can result in a wide range of disease patterns from asymptomatic colonization, to a mild infection (CDI), and sometimes even a severe, fulminant, colitis.[1, 2] Fulminant *C. difficile* colitis (fCDC) is a disease of increasing incidence, with high morbidity and mortality.[3-5] Often these patients require surgical treatment, namely a total abdominal colectomy (TAC). Although this procedure has been performed and described many times[4-17], not much has been written about the post-operative antibiotic course of these patients. There is literature describing post-operative complications such as enteritis and surgical site infections[12, 13, 18], however there is no established antibiotic management protocol for patients with fCDC that underwent a TAC. For almost three decades now, vancomycin and metronidazole have been the two most frequently used antimicrobial agents for the treatment of CDI[19], but no guidelines recommend one specific antibiotic regimen for patients after a TAC. In this study the practice across different institutions is described. Our aim is to make some recommendations for post-operative antibiotic usage.

METHODS

Design

This is a multi-institutional retrospective case series including fCDC patients who underwent a total abdominal colectomy (TAC) between January 1, 2007 and June 30, 2012. The primary outcome was in-hospital mortality. Secondary outcomes included hospital length of stay (HLOS), ICU LOS, number of ventilator-free days, and occurrence of intra-abdominal complications (proctitis, abscess, sepsis, etc.).

Definitions and data collection

Fulminant CDC is defined as[4] CDC with significant systemic toxic effects and shock, resulting in need for ICU admission, colectomy, or death. Normally, a TAC is performed in patients with fCDC who were determined to be too toxic for a trial of non-operative management or who failed medical therapy. In all patients undergoing a TAC, CDC was confirmed by histopathologic analysis of the surgical specimen.

The focus was on the post-operative course of these patients, and initially we compared patients that received antibiotics post-operatively for ≤7 days, or ≥8 days. The following variables from patient electronic records were collected: 1) age, gender, race, and ethnicity; 2) Charlson Comorbidity Index[20], APACHE II score, vasopressor requirement, transfusion requirements, P/F ratio, and total fluid balance; 3) laboratory values: red blood cell count, white blood cell count, platelets, hemoglobin, hematocrit, sodium,

potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, and glucose; 4) hospital length of stay, ICU length of stay, ventilator-free days, time to full enteral feeds, mortality, and discharge disposition; and 5) complications: proctitis, sepsis, abscess, breakdown of rectal staple line, and surgical site infection.

Statistical analysis:

Descriptive statistics were tabulated to give an overview of our study cohort. When comparing groups, continuous variables were summarized as mean ± standard deviation, and compared by t-tests when variables were normally distributed. Otherwise, data were summarized as median (interquartile range [IQR]), and compared by Wilcoxon rank sum tests. Categorical variables were compared by Fisher's exact test. To examine the outcomes in the post-operative course, we conducted an additional analysis limited to survivors. We compared outcomes between antibiotic regimen, length of treatment, and with and without the addition of an enema. We also compared antibiotic groups stratified by length of treatment. Additionally we compared survivors vs. non-survivors, and variables significant at 0.1 level were considered as candidates for a multivariable logistic regression model to identify independent predictors of mortality. Due to the small number of events, the final model included the two predictors significant at 0.05 level and adjusted odds ratios (aOR) with 95% confidence intervals (CI) were reported. A two-tailed P <0.05 was considered to be significant for all analyses. All analyses were performed in SAS version 9.3 (The SAS Institute, Cary, NC). This study was approved by our Institutional Review Board.

RESULTS

A total of 100 patients from five institutions were collected. All patients underwent a total abdominal colectomy (TAC) for fCDC. The mean (± standard deviation) age was 66 ± 15 years, and 58% were male. The average age-adjusted Charlson Comorbidity Index (CCI) was 4.4 ± 2.7. Pre-operatively, the mean APACHE score was 18 ± 9, 43% required a vasopressor, the mean P/F ratio was 332 ± 147 mmHg, and median total fluid balance (TFB) was 2.6 L positive (IQR 0.6-5.4 L). Our primary outcome, mortality, was 26% (26/100) overall. The median (IQR) hospital length of stay (LOS) was 19 days (11-37), with a median ICU LOS of 6.5 days (3-15), and a median ventilator-free days of 25 (0-27). All other variables, including the intra- and post-operative status, as well as the complications that occurred, can be found in Table 1.

The antibiotics studied in the post-operative course of fCDC patients were metronidazole (per oral , PO, and intravenous, IV) and vancomycin (PO and per rectum, PR). In total, 14 different combinations could be made (Table 2). There was a significant amount of variability within institutions and across institutions in preferred regimen and length

Table 1. Overall cohort with fulminant *Clostridium difficile* colitis (fCDC), managed with a total abdominal colectomy (TAC)

Parameter	Overall cohort (n=100)
Demographics	
Age, mean (SD), y	66.3 ± 15.3
Age > 70 years, No. (%)	44 (44)
Male, No. (%)	58 (58)
Race, No. (%)	
Caucasian	86 (86)
African-American	12 (12)
Asian	1 (1)
Unknown	1 (1)
Hispanic, No. (%)	4 (4)
Charlson Comorbidity Index (CCI), mean (SD)	4.4 ± 2.7
Pre-operative status	
APACHE score, mean (SD)	18.3 ± 8.6
Vasopressor requirement, No. (%)	43 (43)
PF ratio, mean (SD), mmHg	331.7 ± 146.7
TFB, median (IQR), mL	2584 (608-5384)
Intra-operative status	
EBL, median (IQR), mL	250 (100-500)
Blood transfusions, median (IQR), units	0.5 (0-3.5)
Post-operative status	
Vasopressor requirement, No. (%)	65 (65)
PF ratio 24 h post-op, mean (SD), mmHg	302.4 ± 126.8
TFB post-op day 1, median (IQR), mL	7438 (4771-11659)
TFB post-op day 2, median (IQR), mL	9181 (5221-13095)
TFB post-op day 3, median (IQR), mL	8245 (4610-14174)
Outcomes	
Hospital length of stay, median (IQR), days	19 (11-37)
ICU length of stay, median (IQR), days	6.5 (3-15)
Ventilator free days, median (IQR), days	25 (0-27)
Time to full enteral feeds, median (IQR), days	4 (2-6)
Proctitis + Pouchitis, No. (%)	6 (6)
Sepsis, No. (%)	28 (28)
Abscess, No. (%)	7 (7)
Breakdown rectal staple line, No. (%)	3 (3)
Surgical Site Infection, No. (%)	8 (8)
Mortality, No. (%)	26 (26)
Discharge disposition, No. (%)	
Home	32 (32)
Deceased	28 (28)
Rehabilitation	26 (26)
Nursing home	14 (14)

Abbreviations: SD, standard deviation; APACHE, Acute Physiology and Chronic Health Evaluation; PF ratio, PaO2 (partial pressure of oxygen) / FiO2 (fraction of inspired oxygen); mmHg, millimeters of mercury; TFB, total fluid balance; mL, milliliter; EBL, estimated blood loss; IQR, interquartile range; RBC, red blood cells; FFP, fresh frozen plasma; ICU, intensive care unit.

of treatment. When dividing the length of treatment into two groups, ≤ 7 days and ≥ 8 days, we found that a majority of the centers (57% of patients) preferred post-operative antibiotic treatment for ≥ 8 days. There was a significant difference in in-hospital mortality between patients that received antibiotics for ≤ 7 days vs. ≥ 8 days (41.7% vs. 17.5%, p=0.016). In the survivor analysis, there were no significant differences in outcomes between patients that received antibiotics for ≤ 7 days vs. ≥ 8 days.

Due to low numbers in some of the subgroups, we decided to compare the four largest groups; subgroup A (metronidazole IV + vancomycin PO), B (metronidazole IV), C (metronidazole IV + vancomycin PO and PR), and D (metronidazole IV + vancomycin PR). None of the combinations turned out to be superior in mortality. When comparing groups A and C, as well as A and D, a shorter ICU LOS and more ventilator free days were found in favor of group A. The same results were found when comparing ICU LOS between groups B and C, as well as B and D, with group B being superior. No significant differences were found between groups A and B or between groups C and D (Table 3).

Additionally we compared patients per time interval (≤ 7 days vs. ≥ 8 days), stratified by antibiotic regimen (group A-D), with no significant differences found. Similarly, there were no significant differences when comparing metronidazole alone vs. metronidazole with any combination of vancomycin (with and without stratification by time interval). An extra focus was the addition of a rectal enema of vancomycin to the antibiotic regimen. Overall, patients that received an enema in addition to IV/PO vancomycin or metronidazole had a longer ICU LOS (median (IQR) of 11 days (6-19) vs. 5 days (2-11), p=0.001), and a higher incidence of

Table 2. Different combinations of antibiotics and number of treatment days

Combination of antibiotics	Total (n=100)	Treatment 1-7 days (n)	Treatment > 8 days (n)
Metronidazole IV and Vancomycin PO	26	12	14
Metronidazole IV	21	11	10
Metronidazole IV and Vancomycin PO + PR	12	1	11
Metronidazole IV and Vancomycin PR	12	4	8
Metronidazole PO + IV and Vancomycin PR	7	2	5
Metronidazole PO + IV	6	2	4
Metronidazole PO + IV and Vancomycin PO	3	1	2
Vancomycin PO	2	1	1
Metronidazole PO + IV and Vancomycin PO + PR	2	0	2
Metronidazole PO	1	0	1
Metronidazole PO and Vancomycin PO + PR	1	0	1
Vancomycin PR	1	1	0
Vancomycin PO + PR	1	1	0
No antibiotics at all or unknown	5	-	-

Abbreviations: IV, intravenous; PO, per oral; PR, per rectum.

proctitis (13.9% vs. 0%, p=0.006). When stratified by time interval, adding an enema to any antibiotic regimen of ≤ 7 days was associated with a delay to full enteral feeds (median (IQR) of 6 days (5-7) vs. 3 days (2.5-4), p=0.047). Receiving antibiotics including an enema for ≥ 8 days was associated with a longer ICU LOS (median (IQR) of 11.5 days (9-22) vs. 5 days (4-13), p=0.008), and a higher percentage of patients with proctitis (13.9% vs. 0%, p=0.019). Similar results were observed when the analyses were limited to survivors.

In the multivariate logistic regression analysis for mortality, we identified two predictors significant at 0.05 level: requiring a vasopressor before the operation increased the risk of mortality significantly (OR, 6.46), as well as the total units of FFP transfused during hospital admission; for every extra unit of FFP the odds of dying increased with 17% (Table 4). The final model had a c statistic of 0.81 with no evidence of lack of fit (Hosmer-Lemeshow Goodness-of-Fit Test, p=0.21). The combination of antibiotics however, did not turn out to be a risk factor for mortality.

Table 3. Comparison of antibiotic regimen

	A (n=26)	B (n=21)	C (n=12)	D (n=12)	P value
Mortality, No. (%)	10 (38)	7 (33)	3 (25)	4 (33)	None
Hospital length of stay, median (IQR), days	17 (9-31)	21 (11-46)	19.5 (14.5-29.5)	16.5 (10-29)	None
ICU length of stay, median (IQR), days	4.5 (1-15)	4.5 (2-10.5)	11.5 (9.5-29)	11.5 (4.5-17.5)	A vs. C: 0.017 B vs. C: 0.009
Ventilator free days, median (IQR), days	24.5 (0-28)	25.5 (0-27)	16 (0-25.5)	12 (0-22)	None
Limited to Survivors	**A (n=16)**	**B (n=14)**	**C (n=9)**	**D (n=8)**	
Hospital length of stay, median (IQR), days	16.5 (11-28)	22.5 (13-46)	20 (19-33)	21 (11-29)	None
ICU length of stay, median (IQR), days	4 (0-5.5)	5 (3-8)	11 (10-29)	13.5 (7-17.5)	A vs. C: 0.007 A vs. D: 0.031 B vs. C: 0.01 B vs. D: 0.038
Ventilator free days, median (IQR), days	26.5 (25-28)	27 (25-27)	22 (12-26)	17.5 (8.5-25.5)	A vs. C: 0.021 A vs. D: 0.021

Group A: Metronidazole IV + Vancomycin PO
Group B: Metronidazole IV
Group C: Metronidazole IV + Vancomycin PO + Vancomycin PR
Group D: Metronidazole IV + Vancomycin PR

Abbreviations: IV, intravenous; PO, per oral; PR, per rectum; N.S., not significant; IQR, interquartile range; ICU, intensive care unit; LOS, length of stay; SSI, surgical site infection.

Table 4. Independent predictors of mortality

Predictor	Odds Ratio	95% CI	P value
Vasopressor requirement pre-operative	6.46	1.96 – 21.24	0.0021
Total units of FFP transfused during hospital admission	1.17	1.06 – 1.3	0.0021

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma.

DISCUSSION

In this multicenter study of 100 fCDC patients that underwent a TAC, we looked at the differences in antibiotic regimen postoperatively. Four different combinations of metronidazole and vancomycin were compared, and the combination of IV metronidazole with or without PO vancomycin showed superior outcomes in terms of a shorter ICU length of stay and more ventilator-free days. However, when comparing metronidazole alone vs. metronidazole and any combination of vancomycin, no significant differences were found. The majority of patients (57%) within our study were treated for ≥ 8days, but that did not result in any significant differences in outcomes. In addition we showed that adding an enema (PR) of vancomycin did not improve outcomes.

For the past 30 years, vancomycin and metronidazole have been the two drugs of choice for the treatment of CDI.[21-23] Current guidelines recommend metronidazole for the treatment of an initial episode of mild to moderate CDI, as well as for a first recurrence, while vancomycin (with or without the addition of metronidazole) is the antibiotic of choice for more severe and complicated episodes, and a second recurrence.[19] These recommendations are supported by studies of Belmares and Zar that looked specifically into disease severity stratification and found superior results for vancomycin in more severe cases.[24, 25]

Early studies have shown that metronidazole and vancomycin are equally efficient, and have similar relapse rates in regular CDI, with a side note that metronidazole is more economical than vancomycin.[22] The efficacy of metronidazole was more recently challenged by a study of Vardakis et al., who showed in a systematic review that metronidazole had a higher treatment failure rate than vancomycin.[26] Additionally, Musher and colleagues also showed higher recurrence rates in patients treated with metronidazole.[27]

However, vancomycin has been shown to have varying results as well; Pepin et al. reported that vancomycin lost its superiority over metronidazole, coinciding with the emergence of NAP1/027 in the early 2000s, implying that vancomycin would not work as well in severe cases.[28] A Cochrane database review in 2011 concluded that when looking at both symptomatic and bacteriologic cure, there was no overwhelming evidence that either metronidazole or vancomycin was superior in treating CDI. One explanation of discrepancies was small sample size.

Regarding our study, there is no literature on the ideal post-operative antibiotic regimen. Although vancomycin might be recommended for severe disease, patients that

have undergone a TAC are technically moving away from their complicated course, since the source of infection is removed. Given there is no difference in outcome measures when comparing metronidazole alone vs. metronidazole and any combination of vancomycin, and considering that CDI is being caused by antibiotic usage in the first place[1, 2], for postoperative patients it is reasonable to place them on either IV metronidazole or PO vancomycin depending upon local antibiograms. Complications such as proctitis or pouchitis should be treated with the addition of an enema (PR) of vancomycin (500 mg Q8). Regarding duration of postoperative antibiotic treatment, we found no data to support routine use of more than 7 days.

We have to emphasize that our study has its limitations. First, this is a retrospective review of patients with a complicated disease course; although many variables were collected, certain causality cannot be ascertained. However, our goal was to create some guidelines since this matter normally is decided only based on physician discretion. The sample size was small and therefore we were unable to evaluate all antibiotic regimens. And lastly, new drugs such as fidaxomicin were not included in this study, since this drug was only approved in 2011. Although good results in two trials (fidaxomicin was found to be equally effective to vancomycin in achieving a clinical response at end of therapy but superior in preventing a recurrence), future studies are warranted to test the usage of fidaxomicin in the post-operative course after a TAC for fCDC.[29, 30]

Despite these limitations this is the first study to show a detailed multi-institutional overview of fCDC patients after a TAC. We described the overall state of health of this complex population, and showed that these patients gradually improve in the first week after surgery. In conclusion, there is no justification for mandated use of vancomycin versus IV metronidazole in the postoperative period and routine duration of therapy should not exceed 7 days unless warranted by clinical status.

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Chapter 5

Vitamin D Status and Severity of *Clostridium difficile* Infections in Hospitalized Adults

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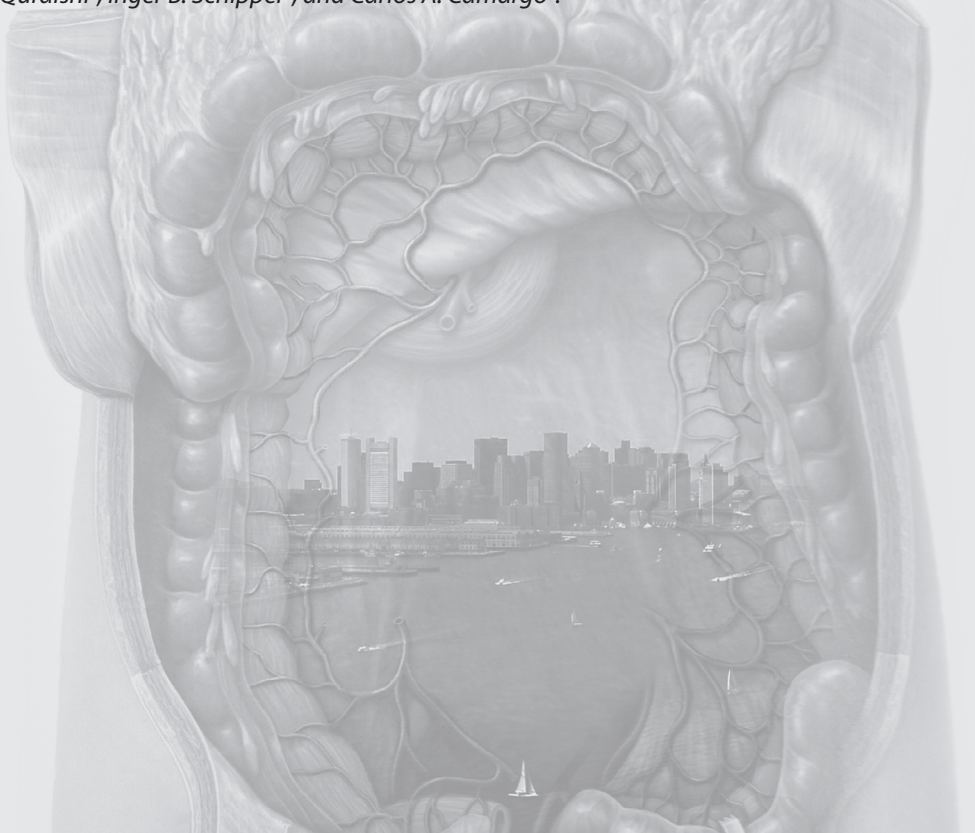

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Submitted for publication

ABSTRACT

Background: *Clostridium difficile* is the most common cause of nosocomial diarrhea, affecting up to 10% of hospitalized patients. Preliminary studies suggest an association between vitamin D status and *Clostridium difficile* infections (CDIs). Our goal was to investigate whether serum 25-hydroxyvitamin D [25(OH)D] levels are associated with CDI severity.

Methods: We prospectively enrolled patients diagnosed with CDI and divided them into two severity groups: group A (positive toxin A/B enzyme immunoassay only) and group B (positive toxin A/B enzyme immunoassay plus abdominal CT consistent with colitis). Serum 25(OH)D levels [D_3, D_2, and total 25(OH)D] were measured on all patients after diagnosis of CDI. We performed multivariable logistic regression analysis to examine the association between 25(OH)D levels and CDI severity, while adjusting for age, Deyo-Charlson Comorbidity Index, recent hospitalization, and vitamin D supplementation.

Results: 100 patients were enrolled between July 2011 and February 2013. The mean (SD) cohort age and Deyo-Charlson comorbidity index was 62 (19) years and 4 (3), respectively; 54% of patients were male. Mean serum total 25(OH)D level was 22 (10) ng/ml; 43% of patients had 25(OH)D <20ng/mL. Mean 25(OH)D_3 level was significantly higher in group A (n=71) than in group B (n=29): 21 (1) ng/mL versus 15 (2) ng/mL, respectively (P=0.005). Multivariable logistic regression showed that 25(OH)D_3 levels were associated with CDI severity [aOR: 0.92; 95%CI: 0.87-0.98].

Conclusions: We found a significant inverse association between 25(OH)D_3 levels and CDI severity. Further studies are needed to determine whether vitamin D supplementation can improve outcomes in patients with CDI.

INTRODUCTION

Clostridium difficile is the leading cause of healthcare-associated diarrhea in North America. It affects up to 12.8 per 1000 hospitalized patients, and the infection incidence continues to increase.[1, 2] Colonization with *C. difficile* can range from a simple asymptomatic intestinal colonization to diarrhea, and ultimately colitis. Excess annual healthcare expenditures attributable to nosocomial *Clostridium difficile* infections (CDIs) range from $1-3 billion, and the average hospital length of stay is prolonged by 3-6 days.[3-6] In hospitalized patients, CDIs may result in mild, moderate, or fulminant colitis, which is typically associated with significant morbidity and mortality.[7-9] While the overall mortality rate for CDIs is approximately 9%,[1, 2, 10] with fulminant *C. difficile* colitis (fCDC), it may be as high as 30%-80%.[10-13]

Clostridium difficile is an opportunistic pathogen, which typically leads to disease if the normal gastrointestinal flora is perturbed.[8] Suboptimal host immune responses appear to play a critical role in symptomatic CDI.[14] Recently, the role of vitamin D in regulating key elements of the immune system has become an area of intense scientific investigation.[15, 16] Indeed, vitamin D status, as measured by serum 25-hydroxyvitamin D [25(OH)D] levels, may play an important role in patient susceptibility to nosocomial infections such as CDIs.[17, 18] Vitamin D status is typically determined by accounting for both 25(OH)D_3 and 25(OH)D_2 (cholecalciferol and ergocalciferol, respectively); the majority of 25(OH)D in humans is comprised from cholecalciferol. While emerging evidence suggests an association of vitamin D status with the risk of developing hospital-acquired CDI[19], it remains unclear whether patients with lower 25(OH)D levels are at risk for developing more severe CDIs. Therefore, our goal was to investigate whether vitamin D status is associated with the severity of CDI in hospitalized patients.

METHODS

We prospectively enrolled patients with confirmed CDI at the Massachusetts General Hospital between July 2011 and February 2013. Potential subjects were identified through the hospital's Infection Control Registry, which includes a daily audit of patients who test positive for *Clostridium difficile*. After obtaining informed consent, a blood sample was collected, and patients were followed until hospital discharge. Our primary focus was the association of 25(OH)D_2, 25(OH)D_3, and total 25(OH)D levels with CDI severity. Partners Human Research Committee approved the study.

Definitions and measurements:

Serum 25(OH)D levels were measured by liquid chromatography-tandem mass spectrometry (LC-MS). The method used was an isotope dilution, LC-MS assay optimized in the hospital's clinical research laboratory based on published procedures.[20] The limit of detection is 2 ng/mL for 25(OH)D_2 and 3 ng/mL for 25(OH)D_3; to convert from ng/mL to nmol/L multiply by 2.496. The intra- and inter-assay coefficients of variability for total 25(OH)D were both <10%. We reported serum levels of 25(OH)D_3, 25(OH)D_2, and total 25(OH)D (D_3+D_2) levels. Based on published guidelines[21], we categorized total 25(OH)D levels into 4 groups: <10 ng/mL, 10-19.9 ng/mL, 20-29.9 ng/mL, and ≥30 ng/mL. Fresh blood samples were sent immediately to the clinical research lab where vitamin D levels (D_2, D_3, and total vitamin D) were determined.

Between July 2011 and September 2012, diagnosis of CDI was based on toxin A/B enzyme immunoassay. From September 2012 onwards, the hospital changed to a membrane enzyme immunoassay (EIA), which detects *C. difficile* glutamate dehydrogenase antigen (GDA) and the A/B toxins. In specimens with discordant GDA and toxin results by the new test, an additional PCR test for toxigenic *C. difficile* was performed. When the PCR test was positive, the diagnosis of CDI was officially confirmed. Only patients diagnosed with CDI by the GDA/toxins EIA from the latter cohort were included; those that were diagnosed by PCR were excluded to avoid a potential bias when compared to the original test (toxin A/B enzyme immunoassay). All measurements were performed in the hospital's clinical core laboratory (for CDI testing) and research core laboratory (for vitamin D testing); both are Clinical Laboratory Improvement Amendments (CLIA)-certified facilities and maintain rigorous quality control standards.

Patients were divided into two CDI severity groups: group A was defined as patients with a mild CDI, confirmed by a positive toxin assay, and with a normal abdominal computed tomography (CT) scan, while group B was defined as patients with a more severe CDI, confirmed by a positive toxin assay, and with an abnormal abdominal CT scan. An abnormal CT scan was defined as an image demonstrating abnormal findings of pancolitis, ascites, colonic wall thickening, and/or dilation. Fulminant CDC was defined as CDC with significant systemic toxic effects and shock, resulting in need for ICU admission, requirement of colectomy, or death.[13] Patients with fCDC were included in group B.

Data collection:

We collected the following data from a combination of patient electronic records and personal interviews: 1) age, gender, race, ethnicity; 2) admission source, admitting service, hospitalization within 2 months of the current admission; prior CDI within 6 months of the current admission; 3) antibiotic therapy within 2 months of the current admission, proton-pump inhibitor (PPI) use, vitamin D supplementation (type and dose in international units); 4) physiologic parameters: white blood cell count with differential,

albumin levels, and creatinine levels; 5) physical exam findings: presence of abdominal pain or distention, diffuse abdominal tenderness, and peritoneal signs; 6) abdominal CT scan findings; and 7) hospital length of stay, 28-day mortality, and discharge disposition. Information contained within the electronic medical records was used to calculate a Deyo-Charlson Comorbidity Index score for each patient.[22]

Statistical analysis:

Descriptive statistics were used to compare patients in group A versus group B. When normally distributed, continuous variables were reported as mean (standard deviation), and compared by t-tests. Otherwise, non-parametric data were reported as median (interquartile range [IQR]), and compared by Wilcoxon rank sum tests. Categorical variables were compared by Fisher's exact test. We examined the association of 25(OH)D levels with CDI severity using multivariable logistic regression. Biologically plausible covariates entered into the model included: age, recent hospitalization, prior CDI, vitamin D supplementation, and Deyo-Charlson Comorbidity Index. Serum 25(OH)D levels were treated as continuous variables, while CDI severity was treated as a dichotomous variable (either mild or severe). To test the robustness of the multivariable model, we then performed stepwise logistic regression using forward and backward selection methods. Variables considered for entry or removal in the stepwise approach included: age, recent hospitalization, prior CDI, recent antibiotic use, vitamin D supplementation, CDI as primary diagnosis, albumin, Deyo-Charlson comorbidity index, and type of assay used to confirm a diagnosis of CDI. Based on prior studies[19], we assumed that the mean 25(OH)D level in CDI patients was 20 ng/mL. To detect a clinically meaningful difference in 25(OH)D levels (20 ng/mL vs. 15 ng/mL), with a shared standard deviation of 5 ng/mL, alpha set at 0.05, and beta set at 0.8, would require a minimum of 16 patients in each CDI severity group. Results are reported as odds ratios (OR) with 95% confidence intervals (CI). All analyses were performed in STATA 11.2 (StataCorp LP, College Station, Texas). A two-tailed $P < 0.05$ or 95% CI that did not span a value of 1 was considered to statistically significant.

RESULTS

Over a period of 20 months, we enrolled 100 consecutive patients. The mean (SD) age of the patients in the study cohort was 62 (19) years and 54% were male. The average Deyo-Charlson Comorbidity Index was 4 (3). The majority of patients were admitted directly from home (65%). While CDI was the primary diagnosis for admission in 21% of the study cohort, for 20% of patients, this was a recurrent CDI and 61% had been hospitalized for various other reasons within 2 months of enrollment into the current

Table 1. Comparison of patients with a 'simple' *Clostridium difficile* infection (group A) vs. patients with a 'severe' *Clostridium difficile* infection (group B).

	Group A (n=71)	Group B (n=29)	P value
Vitamin D status			
≥ 30 ng/mL, No. (%)	19 (26.8)	5 (17.3)	0.31
20 – 29.9 ng/mL, No. (%)	24 (33.8)	9 (31)	0.79
10 – 19.9 ng/mL, No. (%)	22 (30.9)	12 (41.4)	0.32
< 10 ng/mL, No. (%)	6 (8.5)	3 (10.3)	0.76
Vitamin D levels			
25(OH)D level, mean (SD), ng/ml	23 (1.2)	20 (2)	0.13
$25(OH)D_3$ level, mean (SD), ng/ml	21.1 (1.1)	15.2 (1.5)	0.005
$25(OH)D_2$ level, mean (SD), ng/ml	1.9 (0.5)	4.2 (1.4)	0.051
Vitamin D supplementation, No. (%)	19 (27)	11 (38)	0.27
International Units daily, mean (SD), IU	227 (109)	221 (83)	0.98
Age, mean (SD), y	63 (2.3)	60 (3.4)	0.55
Age ≥ 70 years, No. (%)	29 (41)	9 (31)	0.36
Male, No. (%)	42 (59)	12 (41)	0.11
CDI as primary diagnosis, No. (%)	11 (15)	10 (34)	0.03
Deyo Charlson Comorbidity Index (DCI), mean (SD)	3.9 (0.3)	3.8 (0.5)	0.87
Admission source, No. (%)			0.4
Home	43 (61)	22 (76)	
Nursing home	3 (4.2)	1 (3.5)	
External acute care facility	14 (20)	2 (6.9)	
Rehabilitation	11 (15)	4 (14)	
Hospital length of stay, mean (SD), days	20 (3.2)	25 (5.1)	0.38
Mortality, No. (%)	3 (4.2)	1 (3.5)	0.86
Recurrent *C. difficile* colitis (within last 6 months), No. (%)	14 (20)	6 (21)	0.91
Recent hospitalization (within last 2 months), No. (%)	40 (56)	21 (72)	0.14
Recent antibiotic usage (within last 2 months), No. (%)	54 (76)	23 (79)	0.73
Proton Pump Inhibitors (PPI), No. (%)	34 (48)	15 (52)	0.73
White blood cell (WBC) count, mean (SD), /μL	16 (1.9)	19 (2.3)	0.32
Neutrophil bands, mean (SD), %	8.4 (1.8)	14 (2.9)	0.11
Albumin, mean (SD), mg/dL	2.9 (0.1)	2.5 (0.1)	0.007
Creatinine, mean (SD), mg/dL	1.7 (0.2)	1.5 (0.3)	0.57
Abdominal pain or distention on physical exam, No. (%)	6 (8.5)	11 (38)	-
Peritoneal signs on physical exam, No. (%)	-	1 (3.5)	0.12
Diffuse abdominal tenderness on physical exam, No. (%)	5 (7)	11 (38)	-
Abnormal abdominal CT scan, No. (%)*	-	29 (100)	-

* CT: Computed Tomography (only 46 scans made)
Definitions: Deficiency = D < 20 ng/mL; Insufficiency = D < 30 ng/ml; Severe deficiency = D < 10 ng/ml.
Abbreviations: SD, standard deviation; CDI, *Clostridium difficile* infection; fCDC, fulminant *Clostridium difficile* colitis; IQR, interquartile range.

study. In addition, 77% of patients had used more than one antibiotic within 2 months of enrollment, and 49% of patients were using PPIs prior to hospital admission.

Clinical features of our study cohort over the course of their hospitalization was notable for: 1) a mean highest white blood cell count of 17 (15) per µL with an average bandemia of 10 (11)%; 2) a mean lowest serum albumin level of 2.7 (0.6) mg/dL; and 3) a mean highest creatinine level of 1.7 (1.8) mg/dL. Overall, 20% of the cohort had a physical exam positive for abdominal pain, distention, or diffuse abdominal tenderness, while peritoneal signs were detected in only one patient; three patients progressed to fCDC. Median hospital length of stay was 11 days [IQR: 7-22 days] and overall in-hospital mortality was 4%. Regarding 25(OH)D levels, in a majority of patients, the blood sample was collected between days 2 and 5 after confirmed diagnosis of CDI. Nine per cent of patients were <10 ng/ml, 34% were 10-19 ng/ml, 33% were 20-29 ng/ml, and 24% were 30 ng/ml or higher. The mean total 25(OH)D level was 22 (10) ng/mL; mean $25(OH)D_3$ level was 19 (10) while mean $25(OH)D_2$ was 2.6 (5.5) ng/mL. Almost one third of patients were on vitamin D supplementation, prior to hospitalization, and the majority of them continued therapy over the course of the study (median daily dose of 400 [IQR 400-800] IU). None of the patients were started on vitamin D supplementation during hospitalization. All these results are presented relative to CDI severity in Table 1. When dividing the patients (n=100) into two groups according to CDI severity, 71% was diagnosed with a positive toxin assay for CDI, but with a normal abdominal CT-scan (group A), while 29% had an abnormal CT-scan and were assigned to group B.

In the multivariable regression model, two factors were associated with CDI severity: $25(OH)D_3$ levels (adjusted OR, 0.92; 95%CI: 0.87-0.98) and recent hospitalization (OR, 3.9; 95%CI: 1.23-12.4) (Table 2). Stepwise regression analysis did not materially change the association of $25(OH)D_3$ with CDI severity (adjusted OR 0.93; 95%CI: 0.88-0.98). The final model had a power of 0.79, with an observed R^2 of 0.12. We did not observe an association of either $25(OH)D_2$ or total 25(OH)D with CDI severity. Further adjusting for the type of assay used to confirm the diagnosis of CDI did not materially change these results.

Table 2. Multivariable regression analysis to investigate the association of 25-hydroxyvitamin D levels with the severity of *Clostridium difficile* infection.

Variable	Odds Ratio	95% Confidence Interval	P value
$25(OH)D_3$ level (ng/mL)	0.92	0.87 - 0.98	0.008
Vitamin D Supplementation	1.73	0.63 – 4.79	0.29
Age	0.99	0.96 – 1.02	0.44
Deyo-Charlson Comorbidity Index	0.98	0.79 – 1.22	0.85
Recent hospitalization (within last 2 months)	3.9	1.23 - 12.4	0.02

Total n=100, 71 cases in group A (mild), vs. 29 cases in group B (severe)

DISCUSSION

In this study, we investigated whether serum 25(OH)D levels were associated with CDI severity. While it has been hypothesized that vitamin D status may play an important role in the pathogenesis of various nosocomial infections (including *C. difficile*)[23, 24], recent evidence confirms that 25(OH)D levels may be a modifiable risk factor for CDI.[19] Our study provides further novel information and suggests that every 1 ng/mL increase in $25(OH)D_3$ was associated with an 8% decrease in risk of CDI severity. These findings support the idea that vitamin D supplementation may be an important adjuvant therapy in the care of patients with CDI. However, due to the observational nature of our study, our ability to draw causal inferences is limited.

Over the last decade, due to multiple outbreaks and the emergence of more virulent *C. difficile* strains, there has been a renewed focus on treatment options for severe CDI.[10, 25-31] Though various factors influence virulence, the immune response to *C. difficile* toxins appears to play a major role in determining host susceptibility to CDIs.[32, 33] As such, it has been postulated that the immunomodulatory effects of vitamin D may be an important consideration in the care of patients with CDIs.[18, 24] Indeed, cells of the innate and adaptive immune system express the vitamin D receptor (VDR)[34]; higher levels of vitamin D have been shown to suppress adaptive immunity, but to potentiate the innate immune response, enabling the cells to combat infection.[16, 18] Vitamin D interacts with macrophages and can affect the production of cytokines, as well as neutrophil motility and phagocytic function.[16] The active form of vitamin D, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] has been shown to activate macrophages through up-regulated expression of cathelicidin and B-defensin 2 in neutrophils, monocytes, natural killer cells, and epithelial cells. These antimicrobial peptides are effective against both gram-positive and gram-negative bacteria, fungi, and mycobacteria at a variety of sites, including the gastrointestinal system.[15, 35] In addition, preliminary evidence suggests that vitamin D can interfere with the pathogenesis of CDI by attenuating the expression of NLRP3 (which normally produces IL-1B). This helps to protect macrophages against death induced by *C. difficile* toxins A and B, and therefore may limit inflammation and colonic damage.[36]

We focused on both $25(OH)D_3$ and $25(OH)D_2$, in addition to total 25(OH)D levels in the current study. Despite a significant difference in $25(OH)D_2$ levels between CDI severity groups in an unadjusted analysis (Table 1), this relationship did not persist in the final multivariable regression model (Table 2). Since the relationship between $25(OH)D_2$ and CDI severity is only seen when supplementation status is taken out of the model, it confirms that ergocalciferol (vitamin D_2) supplementation is the primary driver behind the observed 25(OH)D2 levels. This is an important observation since recent evidence has shown that $25(OH)D_3$ exhibits a higher affinity for vitamin D receptors (VDR) and

vitamin D binding protein than $25(OH)D_2$, thereby suggesting that $25(OHD)_2$ may not be as biologically significant as $25(OH)D_3$. Moreover, the hydroxylation steps involved in processing dietary vitamin D yield distinct end-products, such that the metabolism of cholecalciferol (vitamin D_3) results in a compound with significantly longer biological activity when compared to the metabolism of ergocalciferol.[17, 37, 38] These are important considerations for future studies, especially in terms of the need to potentially measure both $25(OH)D_2$ and $25(OH)D_3$ in cohort studies and the choice of supplements for randomized, placebo-controlled trials.

Our study is not without potential limitations. The study was conducted at a single teaching hospital, where care is often provided to some of the sickest patients from around New England. As such, the generalizability of these patients to other hospitals is unclear. Since blood samples for vitamin D status assessments were drawn after the diagnosis of CDI, reverse causation cannot be ruled out. While vitamin D status may be affected by acute illness[39], the majority of our samples were collected within 4 days after a diagnosis of CDI, which limits the degree of potential derangement from baseline levels. And finally, although we did attempt to control for the burden of chronic disease by adjusting for the Deyo-Charlson Comorbidity Index in our multivariable analysis, we were unable to control for other important confounders and covariates that may reflect the influence of overall state of health. All of these limitations will need to be addressed in future investigations to extend and build upon the current study.

In summary, this study of 100 patients with a diagnosed *C. difficile* infection suggests that the 25(OH)D level is a modifiable risk factor for CDI severity. We hypothesize that vitamin D sufficiency is associated with optimal expression of endogenous antimicrobial peptides and may regulate cytokine expression to limit the inflammatory cascade associated CDIs. In turn, these may attenuate the effect of barrier site disruptions that are characteristic of CDIs. Further prospective studies are needed to replicate our findings, to assess the potential benefit of optimizing vitamin D status in patients with active infection or at high risk for CDIs, and to identify the mechanism by which vitamin D sufficiency may confer protection against CDI and other nosocomial infections.

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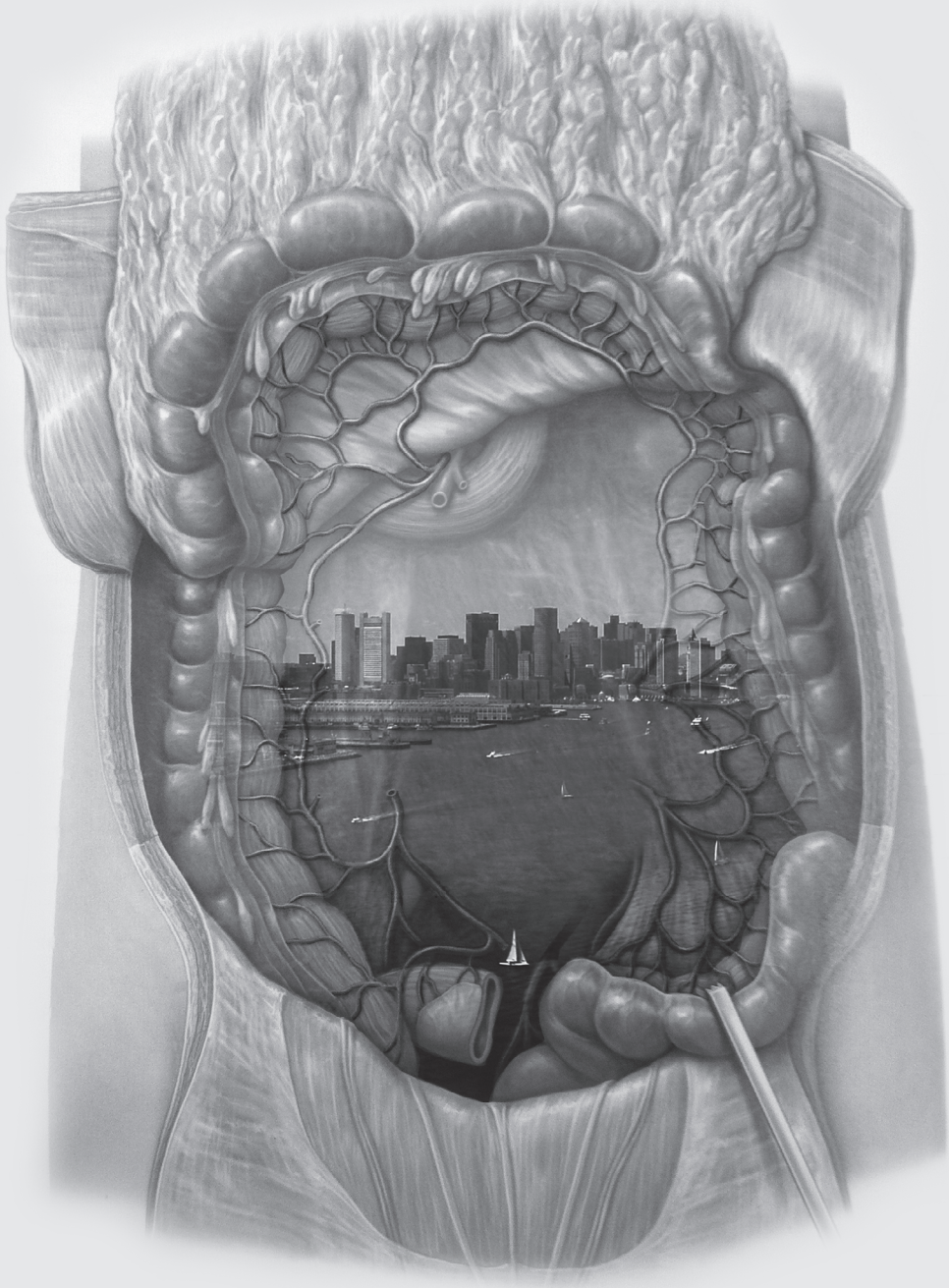
Part II

Severe abdominal trauma



Chapter 6

Successful non-operative management of the most severe blunt kidney injuries: a multicenter study of the Research Consortium Of New England Centers for Trauma

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JAMA Surg. 2013 Oct 1;148(10):924-31

ABSTRACT

Objective: To determine the rate, causes, predictors, and consequences of failure of non-operative management (NOM) in grade IV and V blunt renal injuries (BRI).

Design: Retrospective case series.

Setting: Twelve Level I and II trauma centers in New England

Patients: 206 adult patients with a grade IV or V BRI who were admitted between January 1, 2000, and December 31, 2011.

Main Outcome Measures: Failure of NOM, defined as the need for a delayed operation or death due to renal-related complications during NOM.

Results: Fifty-two patients (25.2%) were operated on immediately and 154 (74.8%) were managed non-operatively (with the assistance of angiographic embolization in 25 patients). NOM failed in 12 patients (7.8%) and was related to the kidney injury in 10 (6.5%). None of these 10 patients suffered complications because of the delay in BRI management. The time from admission to failure was 17.6 ± 27.4 hours (median: 7.5; range 4.5-102 hours), and the cause was hemodynamic instability in 83.3% of the cases. Multivariate analysis identified 2 independent predictors of NOM failure: Age > 55 years and road traffic crash as the mechanism of injury. When both risk factors were present, NOM failure occurred in 27.3% of the patients; when both were absent, there were no NOM failures. Among patients successfully managed by NOM, 46 (32.4%) developed renal-related complications, including hematuria (24), urinoma (15), urinary tract infection (8), renal failure (7), and abscess (2). These were managed successfully with no loss of renal units. The renal salvage rate was 76.2% for the entire population, and 90.3% among patients selected for NOM.

Conclusions: Hemodynamically stable patients with grade IV and V BRI were safely managed by NOM. Only 6.5% failed NOM due to renal-related injuries and three fourths of the entire population retained their kidneys.

INTRODUCTION

Up to 10% of patients with blunt abdominal trauma have renal injuries.[1] Over the last few decades non-operative management (NOM) has become increasingly popular, especially for low-grade (I-III) blunt renal injuries (BRI). The published evidence is unclear about the role of NOM for higher grades (IV and V). In short, grade IV injuries indicate lacerations which extend to the renal pelvis and grade V injuries indicate a shattered kidney or renal artery injuries with parenchymal devascularization. Santucci et al[2] showed in a meta-analysis of 16 studies that approximately 90% of grade IV BRI could be managed without an operation. Even for grade V injuries there is evidence that NOM can be successful.[3-6] Because grade IV and V injuries are uncommon, most of these studies lack an appropriate sample size to uncover statistical significances and make valid recommendations.

The Research Consortium of New England Centers for Trauma (ReCONECT) includes level 1 and 2 trauma centers in the region and has produced, so far, four studies.[7-10] In particular it has evaluated injuries of low prevalence, which can only be analyzed by a multicenter collaboration. The objective of the current study is to determine the rate and predictors of failure of NOM in patients with severe blunt renal injuries. We hypothesize that such injuries can be safely managed without an operation, but that the rate of complications, following operative and non-operative management of BRI, and the need for subsequent interventions is high.

METHODS

Patients

This is a retrospective case series including all adult patients with a grade IV or V BRI, who were admitted from January 1, 2000, to December 31, 2011, in twelve New England trauma centers. Renal injuries were graded based on computed tomography (CT) findings and according to the American Association for the Surgery of Trauma Organ Injury Scale (Table 1).[11] Ten centers were verified by the American College of Surgeons Committee on Trauma as Level I (9 centers) or II (1 center) trauma centers; two additional centers were accredited as Level II trauma centers by their state but not the American College of Surgeons. Exclusion criteria were: age < 15 years, an urgent operation in an outside hospital, and death before or on arrival at the receiving hospital.

Definitions

The patients were divided into those who received an immediate operation (IO) and those managed by NOM. Hemodynamic instability and peritonitis were indications for

Table 1. Grading of Kidney Injury According to the American Association for the Surgery of Trauma Organ Injury Scale[11]

Grade*	Type of injury	Description of injury	AIS-90
I	Contusion	Microscopic or gross hematuria, urologic studies normal	2
	Hematoma	Subcapsular, nonexpanding without parenchymal laceration	2
II	Hematoma	Nonexpanding perirenal hematoma confirmed to renal retroperitoneum	2
	Laceration	<1.0 cm parenchymal depth of renal cortex without urinary extravasation	2
III	Laceration	<1.0 cm parenchymal depth of renal cortex without collecting system rupture or urinary extravasation	3
IV	Laceration	Parenchymal laceration extending through renal cortex, medulla, and collecting system	4
	Vascular	Main renal artery or vein injury with contained hemorrhage	4
V	Laceration	Completely shattered kidney	5
	Vascular	Avulsion of renal hilum which devascularizes kidney	5

*Advance one grade for bilateral injuries up to grade III

IO. Patients were included in the NOM group if there was a clear note in the record to that effect or an operation was booked more than 3 hours after the diagnosis of BRI. The decision to use the cutoff point of 3 hours in order to define NOM has been used in previous ReCONECT studies.[8,10] Because the decision-making about an operation versus NOM was not always clear from the review of the medical records, we were obliged to make some arbitrary assumptions. Based on the infrastructure of our trauma centers, we believe that longer than 3 hour-intervals, between the diagnosis of BRI and the booking of an operation, indicated that the patient was initially managed by NOM. It would be extremely unlikely that a decision for IO was made after 3 hours from diagnosis. On the other hand it is possible that shorter periods of NOM (e.g. 2 hours) were labeled as IO in this study. Failure of NOM (f-NOM) was defined as the need for surgery after a trial of NOM or as death due to renal-related complications during NOM; if none of this happened, NOM was considered successful (s-NOM).

Data and Outcomes

The following data were collected: demographics, mechanism of injury (road traffic crash, fall, assault, or other), associated injuries, admission hemodynamics, Injury Severity Score (ISS), computed tomography (CT) findings, renal injury grade (IV or V), presence of free abdominal blood on CT (recorded as diffuse or confined around the kidney), type of management (NOM or IO), indication for operative intervention, operative procedures, operative findings, any other interventions required, intensive care unit (ICU) and hospital stay, morbidity, and mortality.

The primary outcome was f-NOM, classified as renal-specific and non-renal-specific according to the reason for which the patient failed NOM. The secondary outcome was complications of NOM and the interventions required to treat those complications.

Statistical Analysis

Patients with IO were compared to those with NOM. Additionally; f-NOM and s-NOM patients were compared. We dichotomized certain continuous variables across clinically meaningful values: Age was dichotomized at 55 years; Injury Severity Score at 25; systolic blood pressure at 100 mmHg; heart rate at 100 beats per minute; and hematocrit level at 30%. Continuous variables were summarized using mean values with standard deviations (SD) and compared using two-sample t-tests, or summarized using median values with interquartiles and compared using Wilcoxon rank sum tests. Categorical variables (reported as counts and proportions) were compared using chi-square test or Fisher's exact test. Logistic regression was performed to identify independent predictors of f-NOM. Odds ratios and 95% confidence intervals were reported for each predictor. The incidence of f-NOM based on different combinations of independent predictors of f-NOM was examined. $P \leq .05$ indicated statistical significance. SAS version 9.2 (SAS Institute, Cary NC) was used for the entire analysis. The study was approved by the Institutional Review Boards of all participating hospitals.

RESULTS

In total, 206 patients were identified, 154 (74.8%) with grade IV and 52 (25.2%) with grade V BRI. Of those, 52 (25.2%) were managed by IO and 154 (74.8%) by NOM.

The mean age of the population was 36.2 + 18.3 years (median: 30 years; range: 15-90), with 84% being under the age of 55. Seventy-five percent were male, with a mean Injury Severity Score of 25.7 + 13.1 (median: 24; range 4-75). Sixty-four percent of all injuries were caused by road traffic crashes. Other injuries besides the BRI were found in 164 (79.6%) patients, including splenic injuries in 62 (30.1%), liver injuries in 57 (27.7%), and other abdominal injuries in 29 (14.1%).

Among the 160 patients (77.7%) who required intensive care, the average ICU stay was 8 + 17.8 days (median: 2.5; range: 0-204 days). The average hospital stay for the entire population was 15.7 + 23.6 days (median: 8; range: 1-210 days). Overall, 17 patients (8.3%) died; 3 (1.4%) deaths were related to the kidney injury. The renal unit was preserved in 157 (76.2%) patients, including 18 of 52 IO patients (34.6%), 135 of 142 s-NOM patients (95.1%), and 4 of 12 f-NOM patients (33.3%).

NOM vs. IO

Of the 52 IO patients, 34 renal units were lost. Thirty (57.7%) were subjected to nephrectomy and one (1.9%) to a partial nephrectomy. Of the remaining four patients three died within 24 hours after admission and one patient had a non-perfused kidney for eight hours due to a prolonged transfer from another hospital; a damage control operation was performed and the kidney was left in situ.

Of the 154 NOM patients, 33 (21.4%) received angiography during the acute stage, 25 (16.2%) proceeded to angiographic embolization for bleeding control, and 2 (1.2%) required repeat embolization. Additionally, 13 patients (8.4%) received a ureteral stent early after the injury.

As expected, there were multiple differences in injury characteristics and physiologic stability between IO and NOM patients (Table 2). Morbidity and mortality were higher in IO patients and ICU and hospital stays were longer. There were 4 independent predictors of IO: ISS (OR: 1.06; 95% CI: 1.03-1.09), the presence of diffuse intra-peritoneal blood (OR: 5.86; 95% CI: 2.38-14.41), active vascular extravasation on CT (OR: 3.45; 95% CI: 1.45-8.15), and associated abdominal injuries (OR: 8.73; 95% CI: 2.97-25.67).

s-NOM vs. f-NOM

Failure of NOM was detected in 12 of 154 NOM patients (7.8%), without a difference in failure rates between grade IV (7.6%) and V (7.8%) patients. Ten of 12 f-NOM patients failed due to renal-related reasons (renal-related failure rate: 6.5%). The two remaining patients failed NOM due to their liver injuries. Operative intervention took place at 17.6 + 27.4 hours after admission (median: 7.5; range: 4.5-102 hours). Hemodynamic instability was the indication for operation in 10 of 12 f-NOM patients (83.3%); one patient received an operation because of peritonitis and one more because of abdominal compartment syndrome. Eight patients were subjected to a nephrectomy, one to a partial nephrectomy, and one to renal repair. The remaining 2 patients had no renal procedures; one had a decompressive laparotomy and the other received a liver resection and cholecystectomy. One patient (8.3%) died 2 days after operative intervention due to multisystem organ failure. This patient failed NOM after 7 hours and received a nephrectomy and adrenalectomy.

Patients with f-NOM were older, had active extravasation on CT more frequently, and had a higher rate of general complications (Table 3). Their hospital and ICU stays were longer. Two independent predictors of f-NOM were identified: Age ≥ 55 years (OR: 5.99; 95% CI: 1.58-22.61) and road traffic crash as the mechanism of injury (OR: 5.62; 95% CI: 1.09-28.86). When both risk factors were present, f-NOM occurred in 27.3% of the patients; when both were absent, the s-NOM rate was 100%.

Table 2. Comparison between patients who received an Immediate Operation (IO) and those offered a trial of Non-operative Management (NOM)

Characteristic	IO (n=52)	NOM (n=154)	P Value
Age, y, mean (SD)	36.3 (16.2)	36.2 (19.1)	0.97
Male sex, No. (%)	39 (75)	115 (74.7)	0.96
Type of injury, No. (%)			0.053
Motor vehicle crash	41 (78.9)	90 (58.4)	
Fall	8 (15.4)	36 (23.4)	
Assault	1 (1.9)	10 (6.5)	
Other	2 (3.8)	18 (11.7)	
Injury Severity Score, mean (SD)	34.3 (16.9)	22.8 (10.1)	<0.0001
Systolic blood pressure on admission, mmHg, mean (SD)	105.1 (31.2)	120.8 (25.3)	0.002
Heart rate on admission, beats/min, mean (SD)	107.4 (24.7)	89 (21.5)	<0.0001
Hematocrit on admission, %, mean (SD)	33.1 (7.4)	36.5 (6.3)	0.004
Hemoglobin on admission, gm/dl, mean (SD)	11.3 (2.3)	13 (3.6)	0.0003
Glasgow Coma Scale Score, mean (SD)	10.6 (5.4)	13.4 (3.6)	0.0009
Associated injuries, No. (%)	49 (94.2)	115 (74.7)	0.002
Liver injury, No. (%)	19 (36.5)	38 (24.7)	0.098
Splenic injury, No. (%)	26 (50)	36 (23.4)	0.0003
Other abdominal injuries, No. (%)	16 (30.8)	13 (8.4)	<0.0001
CT grade of renal injury, No. (%)			<0.0001
4	26 (50)	128 (83.1)	
5	26 (50)	26 (16.9)	
Presence of free abdominal blood on CT, No. (%)			<0.0001
Diffuse	29 (55.8)	34 (22.1)	
Confined around kidney	17 (32.7)	113 (73.4)	
Unknown	6 (11.5)	7 (4.5)	
Active extravasation, No. (%)	25 (48.1)	44 (28.6)	<0.0001
Urinary extravasation, No. (%)	13 (25)	47 (30.5)	0.015
Morbidity, kidney-related, No. (%)	12 (23.1)	49 (31.8)	0.23
Morbidity, general, No. (%)	23 (44.2)	26 (16.9)	<0.0001
Mortality, No. (%)	12 (23.1)	5 (3.2)	<0.0001
Hospital length of stay, days, mean (SD)	23.4 (32.5)	13.1 (19.2)	0.004
Intensive Care Unit length of stay , days, mean (SD)	13.8 (17.2)	6.1 (17.6)	0.0004
Hospital length of stay in survivors, days, mean (SD)	28.2 (35.2)	11.9 (11.4)	<0.0001
Intensive Care Unit length of stay, in survivors, days, mean (SD)	16.2 (18)	4.8 (7.3)	<0.0001

Abbreviations: SD, standard deviation; CT, computed tomography.

Table 3. Comparison between patients with successful (s-NOM) and failed non-operative management (f-NOM)

Characteristic	s-NOM (n=142)	f-NOM (n=12)	P Value
Age, y, mean (SD)	35.2 (18.3)	47.6 (24.7)	0.11
Age ≥ 55 y, No. (%)	21 (14.8)	5 (41.7)	0.017
Male sex, No. (%)	107 (75.4)	8 (66.7)	0.51
Type of injury, No. (%)			0.26
Motor vehicle crash	80 (56.3)	10 (83.3)	
Fall	34 (23.9)	2 (16.7)	
Assault	10 (7)	-	
Other	18 (12.7)	-	
Injury Severity Score, mean (SD)	22.6 (10.3)	25.5 (7.8)	0.25
Injury Severity Score > 25, No. (%)	51 (35.9)	5 (41.7)	0.69
Systolic blood pressure on admission, mmHg, mean (SD)	121.4 (25.2)	114.3 (26.9)	0.39
Systolic blood pressure on admission, ≤ 100 mmHg, No. (%)	26 (18.3)	4 (33.3)	0.21
Heart rate on admission, beats/min, mean (SD)	89.3 (21.3)	84.9 (25.3)	0.57
Heart rate on admission > 100 beats/min, No. (%)	41 (28.9)	2 (16.7)	0.37
Hematocrit on admission, mean (SD)	36.6 (6.3)	35.4 (5.5)	0.51
Hematocrit level on admission ≤ 30%, No. (%)	22 (15.5)	1 (8.3)	0.5
Hemoglobin on admission, gm/dl, mean (SD)	13.1 (3.6)	11.8 (2.7)	0.36
Glascow Coma Scale Score, mean (SD)	13.5 (3.5)	12.3 (4.9)	0.39
Associated injuries, No. (%)	104 (73.2)	11 (91.7)	0.16
Liver injury, No. (%)	34 (23.9)	4 (33.3)	0.47
Splenic injury, No. (%)	32 (22.5)	4 (33.3)	0.4
Other abdominal injuries, No. (%)	11 (7.7)	2 (16.7)	0.29
CT grade of renal injury, No. (%)			0.98
4	118 (83.1)	10 (83.3)	
5	24 (16.9)	2 (16.7)	
Presence of free abdominal blood on CT, No. (%)			0.097
Diffuse	31 (21.8)	3 (25)	
Confined around kidney	106 (74.6)	7 (58.3)	
Unknown	5 (3.5)	2 (16.7)	
Active extravasation, No. (%)	39 (27.5)	5 (41.7)	0.001
Urinary extravasation, No. (%)	44 (31)	3 (25)	0.078
Morbidity, kidney-related, No. (%)	46 (32.4)	3 (25)	0.6
Morbidity, general, No. (%)	20 (14.1)	6 (50)	0.001
Mortality, No. (%)	4 (2.8)	1 (8.3)	0.3
Hospital length of stay, days, mean (SD)	12.5 (19.4)	20.1 (15.4)	0.058
Intensive Care Unit length of stay , days, mean (SD)	5.8 (18.1)	10 (9.8)	0.008
Hospital length of stay in survivors, days, mean (SD)	11.1 (10.8)	21.6 (15.2)	0.014
Intensive Care Unit length of stay, in survivors, days, mean (SD)	4.4 (6.9)	10.6 (10)	0.007

Abbreviations: SD, standard deviation; CT, computed tomography.

Complications

Renal-related complications developed in 12 IO patients (23.1%) compared to 49 NOM patients (31.8%, p = 0.23) (Table 2). Persistent or recurrent hematuria was the most common complication and occurred in 26 patients (12.6%), including 1 IO patient (1.9%) and 25 NOM (16.2%) patients (Table 4). In the majority of patients the hematuria was self-limited but 5 (19.2%) required angiographic embolization. The second most common complication was urinoma. It developed in 21 patients (10.2%) of who 5 received IO (9.6%) and 16 received NOM (10.3%). The IO patients were managed with a ureteral stent (3) or a percutaneous nephrostomy (2), whereas the NOM patients had a stent (8), percutaneous nephrostomy (2), or no intervention (6). Thirteen patients (6.3%) with a urinary tract infection were managed with antibiotics. A perirenal abscess was identified in 3 patients (1.4%) and drained percutaneously. Renal dialysis was required in 3 patients (1.4%); an additional 7 patients had transient serum creatinine elevations, which returned to normal in all patients. Of other general complications, pneumonia and deep venous thrombosis were the most frequent.

Follow-up

Eighty-two (39.8%) patients returned for a clinic visit, 15 IO (28.8% of all IO) and 67 NOM (43.5% of all NOM) patients. Four NOM patients were reported with persistent hematuria upon follow-up, while one patient remained to have a poor function of the kidney due to hydronephrosis. An additional patient was hypertensive after a partial infarction of the kidney. None of the IO patients that were seen in the clinic had long-term sequelae. Of them 7 IO and 40 NOM patients had a repeat CT scan and only 2 (both NOM) had a small urinoma. No action was taken on any of these patients, based on the repeat CT scan.

Table 4. Renal-related and general complications

Complications	IO (n=52)	NOM overall (n=154)	S-NOM (n=142)	F-NOM (n=12)
Urinoma, No. (%)	5 (9.6)	16 (10.4)	15 (10.6)	1 (8.3)
Persistent hematuria, No. (%)	1 (1.9)	25 (16.2)	24 (16.9)	1 (8.3)
Local abscess, No. (%)	1 (1.9)	2 (1.3)	2 (1.4)	0
Urine tract infection, No. (%)	4 (7.7)	9 (5.8)	8 (5.6)	1 (8.3)
Renal failure, No. (%)	2 (3.8)	7 (4.5)	7 (4.9)	0
Other renal-related complications, No. (%)	3 (5.8)	5 (3.2)	5 (3.5)	0
General complications, No. (%)	23 (44.2)	26 (16.9)	20 (14.1)	6 (50)
Pneumonia	13	7	5	2
Deep venous thrombosis	4	6	5	1
Wound infection	3	0	0	0

DISCUSSION

NOM has become the preferred way of managing BRI, even for high-grade injuries. [2, 3, 12-24] Of 206 grade IV and V BRI patients, analyzed in our multicenter study, 74.8% were offered NOM, which was successful in over 92%. The failure related to the BRI was 6.5%. These findings agree in general with the existing literature evidence, consisting typically of limited cases series, often with disparate results. Altman et al[3] managed 13 patients with grade V BRI, offering NOM successfully to six patients. All of them had functioning renal parenchyma upon repeat CT. Buckley and McAnninch[25] reported successful NOM in one third of patients with grade IV blunt and penetrating renal injuries; none of them required a delayed nephrectomy. Shariat et al[26] used NOM without failures in 80% of 51 patients with grade IV BRI. In a systematic review of the literature Umbreit et al[27] examined 95 children with grade IV BRI. No intervention was possible in 72% and partial renal preservation in 95%. In contrast to that, Rogers et al[28] reported on 10 children with grade IV and 10 with grade V BRI. While 80% of the grade IV injuries were managed successfully by NOM, all grade V injuries required IO and only 30% achieved long-term preservation of renal function. In our study, among patients who received an IO, 34.6% had a renal-salvage procedure (defined as a functioning renal unit of 50% or more[25]). Of NOM patients, 90.3% preserved the renal function of the injured kidney; the rate was 95.1% among s-NOM patients.

Angiographic embolization has been a valuable adjunct of NOM and was used in 16.2% of our NOM patients with a 92% initial success rate for bleeding control and 100% after a repeat attempt. Similarly, Hagiwara et al[17] has shown excellent bleeding control in 7 of 8 patients with high-grade BRI and active extravasation. The effectiveness of angiographic embolization was lower in a study of 22 BRI patients by Menaker et al[16], who experienced 7 failures (27%). Similarly, Hotaling et al[31] analyzed the National Trauma Data Bank® and reported that 29% of patients with angiographic embolization required a repeat embolization.

Multiple predictors of f-NOM have been identified in the literature, most of them expressing common sense. Toutouzas et al[12] found ISS, fluid and blood requirements, and diagnostic findings to be predictive of f-NOM. Associated abdominal injuries, age, ISS, ongoing blood transfusions, and worsening acidosis are additional predictors of f-NOM in other studies.[2, 5, 19, 25, 32] Age ≥ 55 years and road traffic crash as the mechanism of injury were the two independent predictors in our study and they both increased the odds of f-NOM by nearly 6-fold. Although an older age does not come as a surprise, the specific mechanism of injury requires further exploration. In a study by Kuan et al[33], reporting on 115 BRI patients from the Crash Injury Research and Engineering Network, 36 patients were found to have grade III-V injuries. In frontal collisions the seatbelt was deemed to be related to the injury, whereas side door intrusion and armrest seemed to be the

causative factors in lateral collisions. It may, therefore, be true that road traffic crashes with or without seatbelts predispose patients to BRI more than other mechanisms of injury.

The complications following high-grade BRI are significant[34] even when the patients are managed by NOM. Starnes[13] showed that the incidence of complications in severe BRI (Grades III-V) were similar between patients who underwent renal exploration (7.3%) or NOM (7.9%). Nephrorrhaphy was associated with the highest rate of complications. Similarly, Shariat et al[26] showed non-significantly different rates of complications between NOM (28%) and IO patients (13%) with grade IV BRI. Obviously, these results may be misleading since renal-related complications are harder to develop after nephrectomy, and one could argue that the ultimate complication is the loss of the kidney. In our study persistent hematuria and urinomas were the most frequent complications. An intervention was required in 19.2% of patients with persistent hematuria (angiographic embolization) and 71.4% of patients with urinoma (ureteral stenting, percutaneous nephrostomy, and percutaneous drainage of collection).

Long-term follow-up is the Achilles heel of every trauma study. We only had data on 39.8% of patients who returned to follow-up and on even fewer who had repeat CT scans. The study was not designed to address the speed of the healing process of high-grade BRI nor the common questions of return to work or athletic activities. We could not comment on long-term sequelae in this population, such as nephrogenic hypertension. Other limitations of this retrospective review included the lack of standardized protocols across all participating centers for the management of BRI, resulting in significantly different practices. Analyzing these differences made no statistical sense because the number per center became prohibitively low. Finally, as it happens in such unfunded, multicenter collaborations, we compromised certain fields in order to improve participation. Not all desirable details were requested because the primary intent was to allow centers to collect data without an unreasonable effort.

Despite the above limitations, this study presents the highest number of grade IV and V BRI to date. NOM was safely applied without risking unnecessary renal unit loss or disastrous complications. Almost three fourths of the population was offered NOM, with an f-NOM rate of less than 8% and similar between grade IV and V injuries. Two independent predictors of f-NOM were detected: an age greater than 55 years and road traffic crash; if both predictors were absent, there was a 100% success rate of NOM. Renal-related complications were significant, primarily in the form of hematuria or urinoma, but successfully managed by additional interventions. At the end, 76.2% of patients with a grade IV or V BRI (and 90.3% of those treated by NOM) preserved renal function of the injured renal unit. Appropriate patients with these most severe kidney injuries can be confidently managed by NOM.

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Chapter 7

Successful non-operative management of the most severe blunt liver injuries: a multicenter study of the Research Consortium Of New England Centers for Trauma

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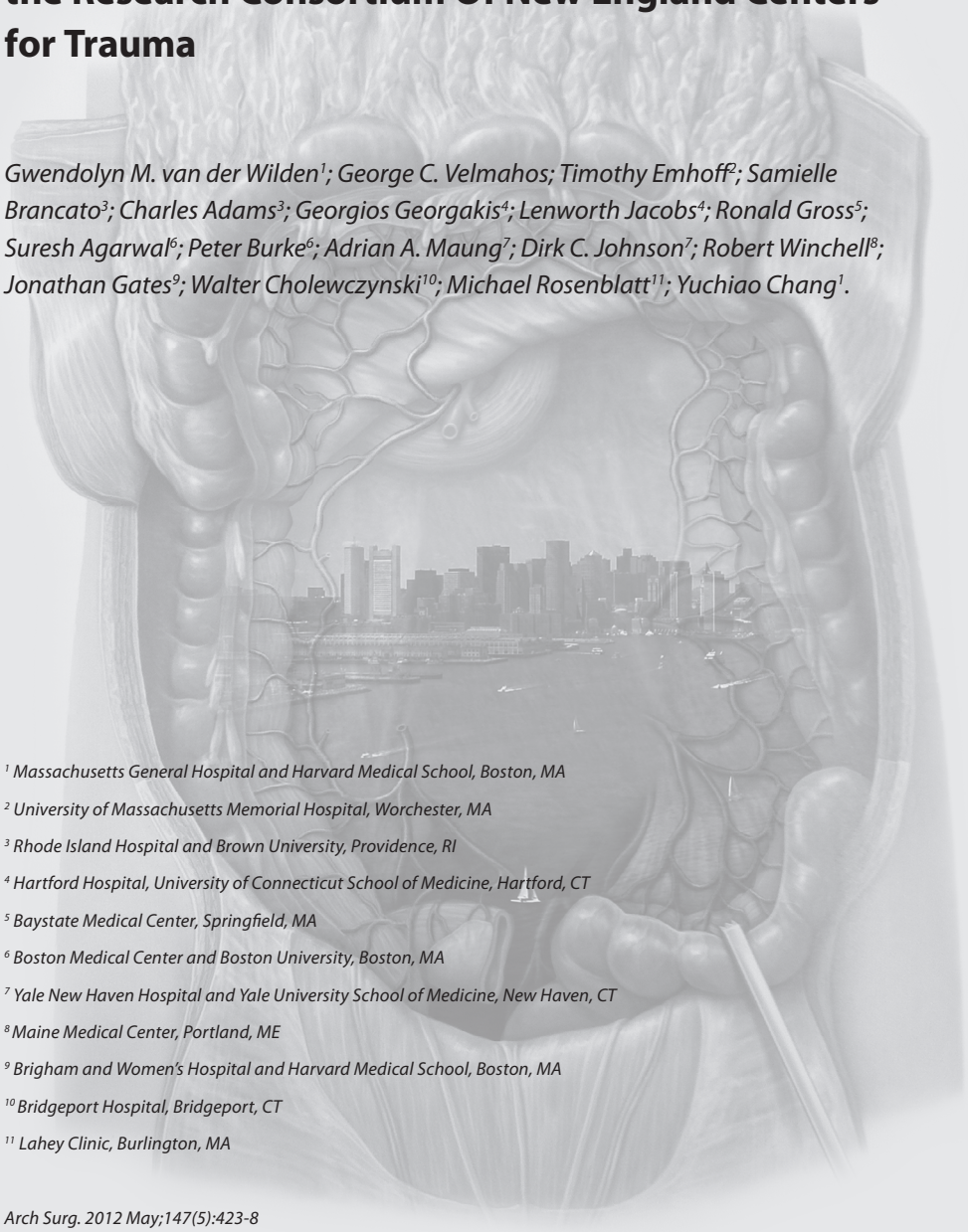

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Arch Surg. 2012 May;147(5):423-8

ABSTRACT

Objective: To determine the rate and predictors of failure of non-operative management (NOM) in grade IV and V blunt liver injury (BLI).

Design: Retrospective case series.

Setting: Eleven Level I and II trauma centers in New England.

Patients: Three hundred and ninety-three adult patients with a grade IV or V BLI who were admitted between January 1, 2000, and January 31, 2010.

Main Outcome Measures: Failure of NOM (f-NOM), defined as the need for a delayed operation.

Results: A total of 131 (33%) patients were operated on immediately, typically because of hemodynamic instability. Of the remaining 262 (67%) patients who were offered a trial of NOM, treatment failed in 23 patients (9%) but only in 17 (6%) because of the liver (ongoing bleeding in 7, biliary peritonitis in 10). Multivariate analysis identified 2 independent predictors of f-NOM: Systolic blood pressure on admission ≤ 100 mmHg and other abdominal organ injury. f-NOM was observed in 23% of the patients with both independent predictors and in 4% of those with none of the two predictors. None of the f-NOM patients suffered life-threatening events because of f-NOM, and the mortality rate was similar between successful NOM (5%) and f-NOM patients (9%, $p = 0.52$). Of the patients with successful NOM, liver-specific complications developed in 10% and were managed definitively without major sequelae.

Conclusions: NOM was offered safely in two thirds of grade IV and V BLI with a 91% success rate. Only 6% of NOM patients required a delayed operation because of liver-related issues, and none suffered life-threatening complications because of the delay.

INTRODUCTION

Over the last decades non-operative management (NOM) of blunt liver injuries (BLI) has become the standard of care for hemodynamically stable patients, who account for approximately 85% of all those with blunt hepatic trauma[1-5]. With increasing experience, even severe BLI have been managed by NOM. The splenic paradigm has shown that the literature offered an overenthusiastic picture about NOM success across all grades. Because the few high-grade splenic injuries were often diluted within the many low-grade injuries, the overall high success rates of NOM were misleadingly perceived as applicable to all grades[6]. A multi-center study from our ReCONECT (Research Consortium of New England Centers for Trauma) group in 2010 showed that 38% of non-operatively managed grade IV and V splenic injuries eventually failed NOM. It also documented that 64% of all high-grade injuries required splenectomy either emergently or after failed NOM[7].

Anecdotal experience shows that severe BLI are more hemostatic than severe splenic injuries. In a study of 206 patients, the successful NOM to the liver was 17% higher than the successful NOM to the spleen[2]. The only study referring exclusively to high-grade liver injuries reports successful NOM in 41% of the patients but is limited by the low number of grade V injuries (only 10% of the entire population) [8].

The ReCONECT group has combined the collective experience of multiple trauma centers in order to increase the sample size on injuries of low frequency [9,10]. The objective of the current study is to determine the rate and predictors of failure of NOM in patients with grade IV and V BLI. Our hypothesis is that such high-grade BLI can be safely managed by NOM.

METHODS

Patients

We retrospectively included all adult patients with a grade IV or V BLI, who were admitted from January 1, 2000, to January 31, 2010, in eleven New England trauma centers. Grading was based on computed tomographic (CT) findings and according to the American Association for the Surgery of Trauma Organ Injury Scale[11] (Table 1). For patients who were taken to the operating room and given a different intraoperative grade than CT's, we recorded the intraoperative grade. All centers are verified by the American College of Surgeons Committee on Trauma as level I (9 centers) or II (2 centers) trauma centers. Patients under the age of 15, patients who received an urgent operation in an outside hospital, and patients who were already dead at the scene or on arrival were excluded**.** Similarly, patients with a grade VI injury (liver avulsion) were not included, since such patients rarely arrive at the hospital alive, and if they do, they usually die within a few hours.

Table 1. Grading of Liver Injury According to the American Association for the Surgery of Trauma Organ Injury Scale[11]

Grade*	Type of injury	Description of injury	AIS-90
I	Hematoma	Subcapsular, <10% surface area	2
	Laceration	Capsular tear, <1 cm parenchymal depth	2
II	Hematoma	Subcapsular, 10% to 50% surface area	2
	Laceration	Capsular tear, 1-3 cm parenchymal depth, <10 cm in length	2
III	Hematoma	Subcapsular, >50% surface area of ruptured subcapsular or parenchymal hematoma; intraparenchymal hematoma >10 cm or expanding	3
	Laceration	>3 cm parenchymal depth	3
IV	Laceration	Parenchymal disruption involving 25% to 75% hepatic lobe or 1-3 Couinaud's segments	4
V	Laceration	Parenchymal disruption involving >75% of hepatic lobe or >3 Couinaud's segments within a single lobe	5
	Vascular	Juxtahepatic venous injuries; ie, retrohepatic vena cava/central major hepatic veins	5
VI	Vascular	Hepatic avulsion	6

*Advance one grade for multiple injuries up to grade III

Definitions

Patients were categorized as receiving NOM or an immediate operation (IO). Hemodynamic instability and signs of peritonitis were indications for IO. NOM was defined by either a clear note in the medical record committing the patient to NOM or by the fact that an operation was booked later than 3 hours from the diagnosis of BLI. The decision to use 3 hours as the threshold of NOM definition was selected by consensus, based on the infrastructure of the participating centers, which typically allowed for expeditious transfer to the operating room. We also wanted to account for patients with complex multiple trauma who spent an initial period of active resuscitation and diagnostic evaluation before a final decision was made about IO versus NOM.

Failure of NOM (f-NOM) was defined as the need for surgery after a trial of NOM or as death due to BLI while the patient was managed non-operatively. NOM was considered successful (s-NOM), if the patient did not receive an abdominal operation during the index hospital stay nor did he/she succumb to the liver injury.

Data and Outcomes

We collected data on demographics, mechanism of blunt trauma (motor vehicle-related crash, fall, assault or other), associated injuries, admission hemodynamics, Injury Severity Score (ISS), liver injury grade (IV or V), CT findings, presence of free abdominal blood on CT (recorded as diffuse or only around the liver), type of management (NOM or IO), indication for operative intervention, operative procedure, operative findings, intensive

care unit (ICU) and hospital stay, morbidity, and mortality. The outcome measure was f-NOM. It was further classified as liver-specific f-NOM, indicating that the operation was performed to treat bleeding, leak, or infection from the liver injury, or non-liver-specific f-NOM, indicating an operation for other intra-abdominal injuries (e.g. bleeding from the spleen).

Statistical Analysis

Patients who received NOM or IO were compared. Additionally, f-NOM patients were compared with s-NOM patients. Selected continuous variables were dichotomized across clinically meaningful values: Age was dichotomized at 55 years; Injury Severity Score at 25; systolic blood pressure at 100 mmHg; heart rate at 100 beats per minute; and hematocrit at 30%. Continuous variables were summarized using mean values with standard deviations (SD) and compared using two-sample t-tests, or summarized using median values with interquartiles and compared using Wilcoxon rank sum tests. Categorical variables (reported as counts and proportions) were compared using chi-square test or Fisher's exact test. Logistic regression was performed to identify independent predictors of f-NOM significant at the .05 level. Odds ratios and 95% confidence intervals were reported for each predictor. The incidence of f-NOM based on different combinations of independent predictors of f-NOM was examined. $P \leq .05$ indicated statistical significance. SAS version 9.2 (SAS Institute, Cary NC) was used for the entire analysis. The study was approved by the institutional review boards of all participating hospitals.

RESULTS

During the study period of 10 years, 393 patients with grade IV and V BLI were included in the 11 ReCONECT hospitals that participated in this study. An immediate operation (IO) was performed in 131 (33%) patients, while 262 (67%) patients were managed non-operatively. Of the 131 patients, 105 (80%) received damage control operations with packing of the liver.

The mean age of the population was 33 + 16 years (median: 28 years; range: 15-95 years) and Injury Severity Score was 32 + 14 (median: 29; range: 4-75). Fifty-four percent were males, 44% had other intra-abdominal organ injuries, 14% had a brain injury, and 32% had major fractures. The average ICU stay for the 324 patients who required critical care was 9 + 17 days (median: 3 days; range: 0-164 days) and average hospital stay of the total population was 16 + 22 days (median: 8 days; range: 1-204 days). Mortality was 21% (84 patients), including 60 patients who died within 24 hours, 11 patients who died between the second and seventh day, and 13 patients who died later.

NOM vs. IO

Except for age, heart rate on admission, the presence of major fractures, and other extra-abdominal injuries, all recorded variables were significantly different between IO and NOM patients**.** Not surprisingly, morbidity and mortality were higher in IO patients. ICU and hospital stays were similar between the two groups when all patients were evaluated but were longer in IO patients when only survivors were analyzed (Table 2).

s-NOM vs. f-NOM

NOM failed in 23 of 262 patients (9%) The rate of failure was 8% among grade IV and 14% among grade V patients (p=0.28). Patients with f-NOM had a lower blood pressure on admission; higher rates of associated abdominal organ injuries, hepatic angiography, and morbidity; and a longer ICU and hospital length of stay (Table 3). Of the 23 f-NOM patients, 17 failed because of liver-related reasons (7 due to recurrent liver bleeding and 10 due to biliary peritonitis). Of the 7 with recurrent bleeding, 5 received packing of the liver and 2 had non-anatomical resections. The remaining 6 f-NOM patients had non-liver related issues (small bowel injury in 3 patients, colon injury in 1, duodenal injury in 1, and gallbladder necrosis in 1). Therefore, the liver-related f-NOM was 6%.

The 17 patients with liver-related f-NOM received their operations at an average of 6 (7) days (range: 0-26 days) after admission, 2 (2) days (range 0-17 days) for those who had liver bleeding and 9 (8) days (range: 1-26 days) for those with biliary peritonitis. All but 2 of the 7 f-NOM patients who required an operation for liver bleeding, received an exploratory laparotomy within 24 hours of admission. No liver-related morbidity was recorded as a direct consequence of f-NOM and none of these patients died.

Two independent predictors of failure of NOM were identified: systolic blood pressure ≤ 100 mmHg on admission and the presence of associated abdominal organ injury (Table 4). If both independent risk factors were present, 23% had f-NOM, as opposed to 11% if 1 factor was present, and 3.5% if none was present. The negative predictive value of the absence of both risk factors for f-NOM was 96%.

Interventions

Of 262 NOM patients 94 patients (36%) received hepatic angiography and 65 (25%) were embolized. Among the 239 s-NOM patients, 79 (33%) received angiography and 55 were embolized (23%). Three of these 55 patients (5%) developed recurrent bleeding which was controlled by re-embolization in 2 and ceased spontaneously in 1. Of the 7 patients who failed NOM due to ongoing bleeding, 5 had angiography and 4 of were embolized before the operation. The success rate of embolization (including repeat embolization) was 93% (55 of 59).

Endoscopic retrograde cholangiopancreatography (ERCP) was performed in 16 NOM patients for biliary leaks. Three of them failed NOM. An additional 5 patients received

ERCP after IO. Percutaneous drainage for abdominal collections was performed in 14 NOM and 6 IO patients.

In the end, 39% of the total study population (154 of 393) received an operation, including 131 IO and 23 f-NOM patients. Of them 64% had grade IV and 36% had grade V BLI. Two f-NOM patients had laparoscopy, 1 for biliary peritonitis and 1 for a small bowel injury; all other patients received an exploratory laparotomy.

Table 2. Comparison between patients who received an Immediate Operation (IO) and those offered a trial of Non-operative Management (NOM)

Characteristic	IO (n=131)	NOM (n=262)	P Value
Age, y, mean (SD)	33 (15)	33 (17)	0.88
Male sex, No. (%)	86 (66)	125 (48)	0.003
Type of injury, No. (%)			0.021
Motor vehicle crash	108 (82)	213 (81)	
Fall	6 (5)	26 (10)	
Assault	7 (5)	2 (1)	
Other	10 (8)	20 (8)	
Injury Severity Score, mean (SD)	41 (15)	27 (11)	< 0.0001
Systolic blood pressure on admission, mmHg, mean (SD)	102 (32)	122 (25)	< 0.0001
Heart rate on admission, beats/min, mean (SD)	103 (33)	97 (21)	0.087
Hematocrit on admission, %, mean (SD)	31 (7)	37 (26)	0.0003
Glascow Coma Scale, mean (SD)	8 (6)	13 (4)	< 0.0001
Brain injury, No. (%)	27 (21)	28 (11)	0.008
Major fracture, No. (%)	43 (33)	82 (31)	0.76
Other abdominal organ injury, No. (%)	45 (34)	127 (48)	0.008
Other extra-abdominal injury, No. (%)	103 (79)	216 (82)	0.36
CT grade of liver injury, No. (%)			< 0.0001
4	79 (60)	234 (89)	
5	52 (40)	28 (11)	
Contrast extravasation on CT (n=228), No. (%)	28 (21)	70 (27)	0.0001
Free blood on CT, No. (%)			< 0.0001
No Blood / Perihepatic	77 (59)	79 (30)	
Diffuse	54 (41)	183 (70)	
Morbidity, No. (%)	112 (85)	114 (44)	< 0.0001
Mortality, No. (%)	69 (53)	15 (6)	< 0.0001
Hospital stay, d, mean (SD)	17 (24)	16 (21)	0.62
ICU stay, d, mean (SD)	5 (9	24 (25)	0.30
Hospital stay in survivors, d, mean (SD)	33 (26)	14 (16)	< 0.0001
ICU stay, in survivors, d, mean (SD)	20 (19)	7 (12)	< 0.0001

Abbreviations: SD, standard deviation; CT, computed tomography; ICU, intensive care unit.

Table 3. Comparison between patients with successful (s-NOM) and failed non-operative management failed (f-NOM)

Characteristic	s-NOM (n=239)	f-NOM (n=23)	P Value
Age, y, mean (SD)	33 (17)	31 (13)	0.41
Age ≥ 55 y, No. (%)	26 (11)	1 (4)	0.32
Male sex, No. (%)	109 (46)	16 (70)	0.087
Type of injury, No. (%)			0.98
Motor vehicle crash	194 (81)	19 (83)	
Fall	24 (10)	2 (9)	
Assault	2 (1)	-	
Other	18 (8)	2 (9)	
Injury Severity Score, mean (SD)	27 (11)	29 (7)	0.15
Injury Severity Score > 25, No. (%)	122 (51)	15 (65)	0.2
Systolic blood pressure on admission, mmHg, mean (SD)	124 (25)	110 (21)	0.007
Systolic blood pressure on admission, ≤ 100 mmHg, No. (%)	40 (17)	9 (39)	0.01
Heart rate on admission, beats/min, mean (SD)	97 (21)	97 (21)	0.95
Heart rate on admission > 100 beats/min	103 (43)	9 (39)	0.68
Hematocrit on admission, mean (SD)	37 (27)	36 (6)	0.51
Hematocrit level on admission ≤ 30%, No. (%)	43 (18)	3 (13)	0.53
Glascow Coma Scale, mean (SD)	13 (4)	14 (3)	0.5
Brain injury, No. (%)	26 (11)	2 (9)	0.75
Major fracture, No. (%)	75 (31)	7 (30)	0.93
Other abdominal organ injury, No. (%)	110 (46)	17 (74)	0.011
Other extra-abdominal injury, No. (%)	194 (81)	22 (96)	0.081
CT grade of liver injury, No. (%)			0.28
4	215 (90)	19 (83)	
5	24 (10)	4 (17)	
Contrast extravasation on CT (n=228), No. (%)	61 (26)	9 (39)	0.34
Free blood on CT, No. (%)			0.061
Perihepatic	76 (32)	3 (13)	
Diffuse	163 (68)	20 (87)	
Morbidity, No. (%)	91 (38)	23 (100)	< 0.0001
Mortality, No. (%)	13 (5)	2 (9)	0.52
Hospital stay, d, mean (SD)	13 (15)	41 (46)	0.009
ICU stay, d, mean (SD)	6 (11)	29 (41)	0.015
Hospital stay in survivors, d, mean (SD)	13 (13)	32 (29)	0.008
ICU stay, in survivors, d, mean (SD)	6 (9)	21 (27)	0.023

Abbreviations: SD, standard deviation; CT, computed tomography; ICU, intensive care unit.

Table 4. Independent Predictors for Failure of Non-operative Management

Predictor	OR (95% CI)	P value
Systolic blood pressure on admission, ≤ 100 mmHg	2.70 (1.07 - 6.77)	0.03
Other abdominal organ injury	2.92 (1.10 – 7.76)	0.03

DISCUSSION

The shift towards NOM of BLI has been profound over the last few decades. From the early articles of near-mandatory operation for all liver injuries[12,13] to recent recommendations of managing most BLI non-operatively[14], there is clearly a major change in the standard of care. As it usually happens with new methods, the rapidly growing enthusiasm for NOM of solid visceral injuries allowed an overstatement of its scope and outcomes. For example, the unchecked optimism about the success of NOM on the injured spleen is balanced by recent evidence showing that over one third of severe splenic injuries fail NOM[7].

The liver is known to respond well to NOM[1,2,4,8,14-19]. However, as it had happened with the spleen, the studies describing high non-operative success rates have included primarily low-grade liver injuries. The severe injuries of the liver were typically treated with an operation. For example, among 128 patients with grade IV and 31 with grade V BLI, described by Kozar et al, only 40% with grade IV and 4% with grade V injury were offered NOM[17]. In 1996 a multicenter study from the Western Trauma Association revealed a very low number of NOM failures[20]. Of 404 BLI patients managed non-operatively 58 had grade IV or V injuries. There were only 6 NOM failures (1.5%) and only 3 of them were related to the liver. The manuscript did not specify the grade of injury in these 6 patients nor the number of patients with grade IV or V injuries managed with IO. In a study of 55 BLI patients managed by NOM at the Los Angeles County hospital, 8 patients failed NOM (14.5%) although none of them for liver-related reasons. Interestingly, 6 of the 8 failures were on patients with liver injury grade of III and higher[14]. Other groups have reported on high-grade injuries but focused either on operations only[5] or did not distinguish between those who were operated on immediately and those who were operated on after NOM failed[8].

Our consortium of 11 New England Trauma Centers focused exclusively on the highest grades of injury, IV and V. One third of the patients were immediately taken for an operation and the remaining two thirds were offered NOM. Over 90% of the NOM patients left the hospital without a midline laparotomy. The liver was the cause of NOM failure only in 7% of the patients. Interestingly, 7 of the 17 liver-related f-NOM patients had ongoing bleeding and the remaining 10 had bile leaks. None of the 7 patients who bled experienced complications that could be attributed to f-NOM and none of them died.

The very high s-NOM rate was in part due to control of bleeding via angiographic embolization. One quarter of NOM patients were embolized with a 93% success rate for bleeding control. Multiple other studies have shown that liver embolization for trauma is safe and stops bleeding effectively[21-23]. In our population most angiographies were performed within the first 24 hours of admission, attesting to the fact that embolization was used as an important element of the NOM strategy.

Additional interventions, such as ERCP, stenting, or percutaneous drainage of collections have been recommended as effective tools to control bile leaks following severe liver trauma[24]. Laparoscopic drainage of biliary collections has been used to ameliorate a severe inflammatory response in selected NOM patients, who remain tachycardic and febrile 3-5 days after injury[25]. In our study, we used ERCP and percutaneous drainage in 6% and 5% of the population respectively.

Our multi-institutional collaboration enhances the sample size of a relatively uncommon injury but affects the ability to collect important details, particularly in view of its retrospective design. Therefore, precise information about decision-making is missing. We accepted an arbitrary number of hours from admission, beyond which an operation was offered because of f-NOM. It is possible that some of these patients were never offered NOM but deteriorated during the period of evaluation. In this context, "failure" of NOM should not be attributed to the inability of trauma surgeons to triage patients appropriately but rather to the natural history of some injuries, which continue to bleed despite optimal management. We could not find patients who were clearly harmed by f-NOM. Although, undoubtedly, such patients exist, f-NOM does not seem to set up patients for an increased risk of complications and death. Close observation and monitoring is, of course, a prerequisite of subjecting such severe injuries to NOM. Finally, we could not make statements about issues which are widely debated and continue to remain without answers: How long should these patients remain in the hospital? When should they be allowed to return to strenuous activities? What is the role of routine repeat scanning? Our study was not designed to answer these questions.

In summary, grade IV and V liver injuries respond well to NOM. In contrast with splenic injuries of similar grade, many of which are destined to fail[7], the majority of severe BLI can be managed without an operation. High-grade liver injuries seem to behave in a dichotomous way. They either bleed immediately and dramatically, and are in obvious need of surgical intervention or they do not bleed and can be managed reliably by NOM with a very low likelihood of subsequent bleeding. There is little reason to intervene surgically on those hemodynamically stable patients, no matter how awe-striking the CT scan may be. In this multicenter study 67% of patients with grade IV and V BLI were offered NOM, which was successful in 91% of them. Only 6% of the non-operatively managed patients, failed NOM because of the liver injury.

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Chapter 8

Trauma Whipple: Do or Don't after severe pancreatoduodenal injuries? An Analysis of the National Trauma Data Bank (NTDB)

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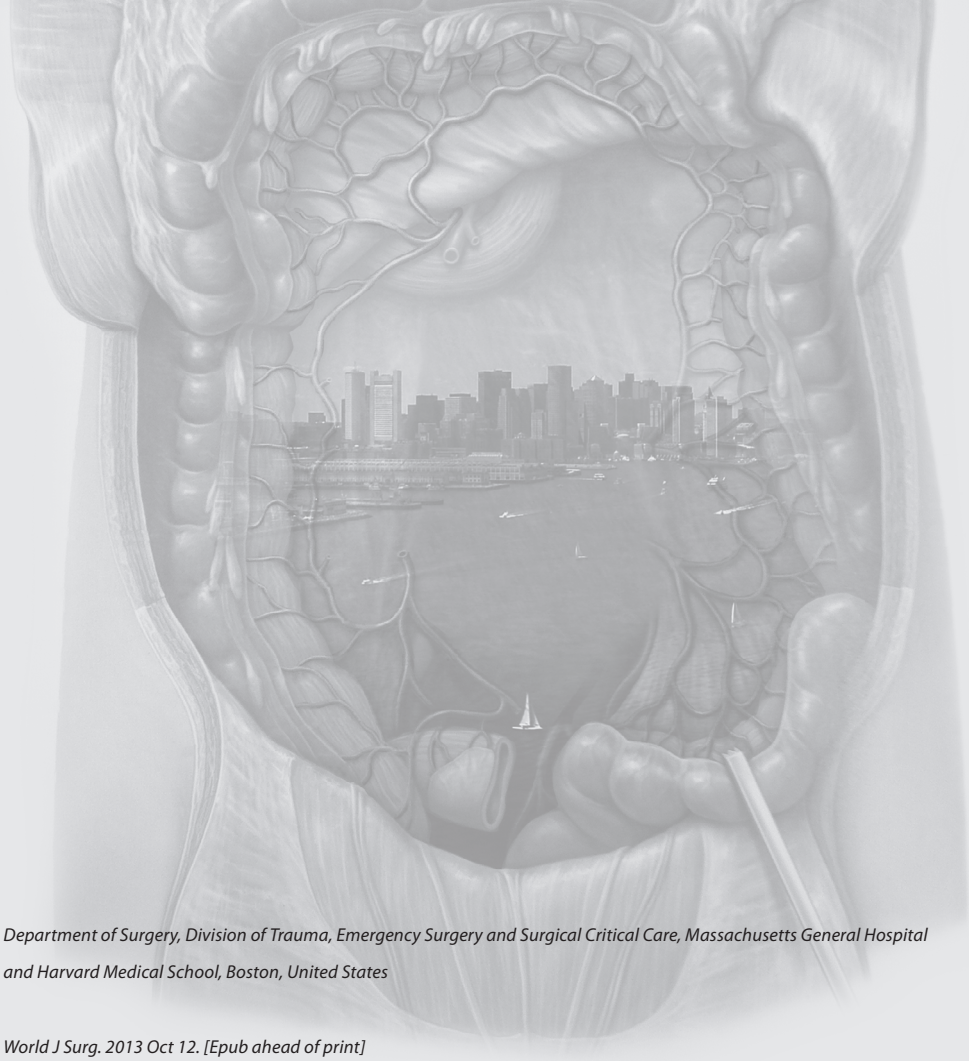

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World J Surg. 2013 Oct 12. [Epub ahead of print]

ABSTRACT

Background: Pancreatoduodenectomy for trauma (PDT) is a rare procedure, reserved for severe pancreatoduodenal injuries. Using the National Trauma Data Bank (NTDB),our aim was to compare outcomes of PDT patients to similarly injured patients who did not undergo a PDT.

Methods: Patients with pancreatic or duodenal injuries treated with PDT (ICD-9-CM 52.7) were identified in the NTDB 2008-2010 Research Data Sets, excluding those receiving delayed PDT (> 4 days). The PDT group (n=39) was compared to patients with severe combined pancreatoduodenal injuries (grade 4 or 5) who did not receive a PDT (non-PDT group, n=38). Patients who died in the emergency department or did not undergo a laparotomy were excluded. Our primary outcome was mortality; secondary outcomes were ICU length of stay, hospital length of stay and total ventilator days. A multivariate model was used to determine predictors of in-hospital mortality within each group, and in the overall cohort.

Results: The non-PDT group had a significantly lower SBP and GCS at baseline, and more severe duodenal, pancreatic, and liver injuries. There were no significant differences in outcomes between the two groups. The Injury Severity Score (ISS) was the only independent predictor of mortality among PDT patients (OR 1.12, 95% CI: 1.01-1.24) and in the entire cohort (OR 1.06, 95% CI: 1.01-1.12). The method of operation did not influence any of the outcomes.

Conclusions: Compared to non-PDT, PDT did not result in improved outcomes despite a lower physiologic burden among PDT patients. More conservative procedures in high-grade injuries of the pancreatoduodenal complex may be appropriate.

INTRODUCTION

The pancreatoduodenectomy, as a single stage procedure, was first reported by Whipple in 1935 for the elective resection of periampullary carcinoma.[1] While the operative mortality rate of this radical procedure has been improved to <5%, it is still associated with a 40% complication rate and a poor (<10%) 5-year survival when performed for adenocarcinoma of the pancreatic head.[2,3]

Thirty years elapsed, before this procedure was first reported in trauma patients.[4,5] The frequency of duodenal and pancreatic injuries is low compared to other abdominal organ injury. Isolated duodenal injuries are very rare, and no adequate documentation of the exact incidence can be found. A review of Asensio on duodenal injuries[6], estimated the incidence at 4.3% of all patients with abdominal injuries (range 3.7-5.0%), while pancreatic trauma is present in only 3%.[7]

Combined pancreatoduodenal injuries are equally uncommon. Eighty percent are caused by a penetrating mechanism, morbidity is high, and mortality ranges from 18-30%.[8-10] Pancreatoduodenectomy for trauma (PDT) therefore is a very rare procedure and is usually reserved for the most severe pancreatoduodenal injuries (grade 4 or 5, according to the organ injury scale of the American Association for the Surgery of Trauma, Table 1)[11]. The largest study on PDT to date consists of only 18 patients from a single center.[12]

In this study we examined this uncommon operation at a national level, using the National Trauma Data Bank (NTDB). Our aim was to evaluate the outcomes of PDT patients in comparison to similarly injured patients without PDT.

Table 1. Grading of Pancreas and Duodenum Injury According to the American Association for the Surgery of Trauma Organ Injury Scale[11]

Pancreas			
Grade*	Type of injury	Description of injury	AIS-90
I	Hematoma	Minor contusion without duct injury	2
	Laceration	Superficial laceration without duct injury	2
II	Hematoma	Major contusion without duct injury or tissue loss	2
	Laceration	Major laceration without duct injury or tissue loss	3
III	Laceration	Distal transection or parenchymal injury with duct injury	3
IV	Laceration	Proximal transection or parenchymal injury involving ampulla	4
V	Laceration	Massive disruption of pancreatic head	5

*Advance one grade for multiple injuries up to grade III.

Duodenum

Grade*	Type of injury	Description of injury	AIS-90
I	Hematoma	Involving single portion of duodenum	2
	Laceration	Partial thickness, no perforation	3
II	Hematoma	Involving more than one portion	2
	Laceration	Disruption <50% of circumference	4
III	Laceration	Disruption 50-75% of circumference of D2; Disruption 50-100% of circumference of D1,D3,D4	4 4
IV	Laceration	Disruption >75% of circumference of D2 Involving ampulla or distal common bile duct	5 5
V	Laceration	Massive disruption of duodenopancreatic complex	5
	Vascular	Devascularization of duodenum	5

*Advance one grade for multiple injuries up to grade III. D1-first position of duodenum; D2-second portion of duodenum; D3-third portion of duodenum; D4-fourth portion of duodenum.

METHODS

The NTDB is a database containing data on trauma patients, submitted on a voluntary basis by trauma centers in the United States. It was designed and is maintained by the American College of Surgeons, Committee on Trauma, and has been running since 1997. Currently, the data set includes over 5 million cases from over 900 trauma centers of all levels of designation. We used NTDB version 7.2, and focused on the Research Data Sets for 2008, 2009, and 2010, since 2008 was the year that a new and more complete dataset was introduced.

Patients undergoing pancreatoduodenectomy for trauma (PDT) were identified, using the International Classification of Diseases, 9th Revision (ICD-9) procedure code 52.7 (radical pancreatoduodenectomy). A total of 47 patients were found. Because the focus of this study is on outcomes of patients who received PDT acutely (either at the initial operation or within 4 days from admission), we excluded three patients who received delayed PDT beyond 4 days. Five additional patients were excluded because their ICD-9 diagnosis codes did not include pancreatic or duodenal injuries. The final PDT sample comprised 39 patients (PDT group, Figure 1). This group was compared with patients who had severe combined pancreatoduodenal injuries (grade 4 or 5 in both organs, according to the organ injury scale (OIS) of the American Association for the Surgery of Trauma (AAST), Table 1)[11] but did not receive PDT (non-PDT group, Figure 1). Patients who died in the emergency department (ED) or did not receive a laparotomy for their abdominal injuries were excluded in the non-PDT group.

Data that were collected included: demographics, Injury Severity Score (ISS), Abbreviated Injury Scores (AIS), physiologic status upon arrival at the receiving hospital, associated injuries, and performed procedures. Our primary outcome was mortality, and

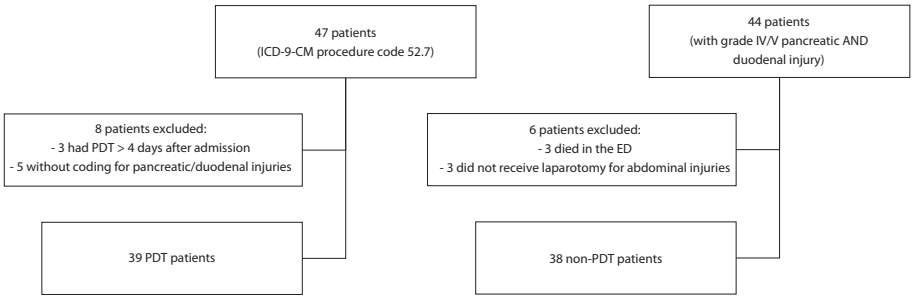

Figure 1. PDT group vs. non-PDT group

additional secondary outcomes were hospital length of stay (HLOS), intensive care unit length of stay (ICU LOS), and ventilator days.

Univariate analysis was performed to compare the two groups. We dichotomized certain continuous variables across clinically meaningful values: Injury Severity Score at 25; systolic blood pressure at 90 mmHg and 110 mmHg; and heart rate at 100 beats per minute. Continuous variables were summarized using mean values with standard deviations (SD) and compared using two-sample t-tests, or summarized using median with range and compared using Wilcoxon rank sum tests. Categorical variables (reported as counts and proportions) were compared using Fisher's exact test. Logistic regression analysis was performed to identify independent predictors of mortality significant at a 0.05 level for each group, and in the overall cohort. Odds ratios and 95% confidence intervals were reported for each predictor and $p \leq .05$ indicated statistical significance. SAS version 9.3 (SAS Institute, Cary NC) was used for the entire analysis. The study was approved by our institutional review board.

RESULTS

In three years (2008-2010) of NTDB data, a total of 39 patients were found to have received a Trauma Whipple (PDT-group) in the acute phase for severe pancreatoduodenal injuries. Their mean age was 34 ± 18 years (median: 27 years; range 16-80), with only 10.3% being over 55 years of age. Seventy-four percent were male, and 77% had a penetrating trauma as mechanism of injury. The mean Injury Severity Score (based on AIS) was 27 ± 13 (median 25; range 4-59). This group was compared to patients that had severe pancreatoduodenal injuries, but did not receive a PDT. As shown in Table 2, no significant differences were found in any demographical data.

Comparing physiologic status at baseline (Table 2), the non-PDT group had significantly more patients with a lower systolic blood pressure, both when dichotomized at 90mmHg (PDT vs. non-PDT, respectively 15% vs. 21%, p=0.028), and at 110 mmHg (28% vs. 53%, p=0.01). No significant difference was found in heart rate, but there was a dif-

ference in Glasgow Coma Scale score (14 ± 3 vs. 10 ± 6, p=0.002). When comparing AIS scores though, no difference in head and neck AIS was found (p=0.85).

Patients in the non-PDT group had significantly higher abdominal AIS, a higher percentage of patients with duodenal and pancreatic injuries, and more severe liver injuries. Surprisingly, of the patients that did receive a PDT, only 79% had either a severe (grade 4 or 5) duodenal or severe pancreatic injury. In the non-PDT group this percentage was 100%, since that was one of the inclusion criteria for this group (Table 2).

There were no significant differences in outcomes. Mortality was 33% vs. 37%, respectively, for the PDT and the non-PDT group (p=0.81). The hospital and ICU length of stay did not differ significantly between the two groups. Similarly, there was no significant difference in the number of minutes spent in the ED and the number of ventilator days (Table 3). No difference in the incidence of reported complications was found (PDT vs. non-PDT, respectively 51% vs. 55%, p=0.82). Looking at the time of death in both the PDT and non-PDT group, our results showed that patients that received a PDT died at a median of 7 days (range 1-180 days), while the patients in the non-PDT group died much earlier, at a median of 1 day (range 1-85 days).

Table 2. Descriptives of PDT group and non-PDT group

Parameter	PDT (n=39)	non-PDT (n=38)	P value
Age (years)	34 ± 18	30 ± 14	0.26
Male, No. (%)	29 (74)	30 (79)	0.79
ISS (AIS based)	27 ± 13	30 ± 10	0.21
ISS >25, No. (%)	16 (41)	22 (58)	0.17
Penetrating trauma, No. (%)	30 (77)	26 (68)	0.45
Systolic Blood Pressure (mmHg)	118 ± 36	101 ± 47	0.22
SBP <90 mmHg, No. (%)	6 (15)	8 (21)	0.028
SBP <110 mmHg, No. (%)	11 (28)	20 (53)	0.01
Heart rate (beats/min)	96 ± 31	97 ± 42	0.90
HR >100 beats/min, No. (%)	16 (41)	19 (50)	0.19
GCS, mean (SD)	14 ± 3	10 ± 6	0.002
AIS head/neck, mean (SD)	0.2 ± 0.7	0.2 ± 0.7	0.85
AIS abdomen, mean (SD)	3.8 ± 0.8	4.7 ± 0.5	<0.0001
Severe duodenal and/or pancreatic injuries (IV-V), No. (%)	31 (79)	38 (100)	0.005
Severe duodenal injuries (IV-V), No. (%)	11 (28)	38 (100)	<0.0001
Severe pancreatic injuries (IV-V), No. (%)	28 (72)	38 (100)	0.001
Severe splenic injuries (IV-V), No. (%)	0	4 (11)	0.12
Severe liver injuries (IV-V), No. (%)	7 (18)	16 (42)	0.006
Severe gallbladder injuries (IV-V), No. (%)	4 (10)	0	0.23

Abbreviations: ISS, Injury Severity Score; SBP, Systolic Blood Pressure; HR, Heart Rate; GCS, Glascow Coma Scale; AIS, Abbreviated Injury Scale.

In PDT patients with available operative time data (n=33), the majority of procedures were performed within the first 6 hours after admission (21/33 patients = 64%). In the patients who underwent a PDT but did not have either a severe (grade 4 or 5) injury in the pancreas or duodenum, the majority (5/7 = 71%) also received this intervention during the index operation (Figure 2). There was no trend towards institutional bias in preference of one procedure over another (data not shown). Procedures in the non-PDT group are summarized in Table 4.

Survivors and non-survivors in both groups were compared. As shown in univariate analysis, having received a PDT did not predict mortality (p=0.81). In the non-PDT group there were no predictors significant at 0.05 level in the univariate analysis. Among PDT patients, the SBP was significantly higher and the ISS was significantly lower among survivors, however only the ISS was found to be an independent predictor of mortality in our multivariable model. For every unit increase in ISS, the odds of mortality increased by 1.09 fold (95% CI: 1.01-1.18). For the overall cohort, the ISS remained the only independent predictor of mortality; for every unit increase in ISS, the odds of mortality increased by 1.07 fold (95% CI: 1.01-1.12).

Table 3. Outcomes of comparison PDT group vs. non-PDT group

Outcomes	PDT (n=39)	non-PDT (n=38)	P value
Hospital LOS, days, median (range)	18 (1-180)	12 (1-85)	0.32
ICU LOS, days, median (range)	8 (1-106)	10 (1-85)	0.96
Ventilator days, median (range)	7 (1-90)	8 (1-42)	0.73
ED stay in minutes, median (range)	25 (3-3850)	31 (2-13055)	0.55
Any complications, No. (%)	20 (51)	21 (55)	0.82
Mortality, No. (%)	13 (33)	14 (37)	0.81

Abbreviations: LOS, Length of Stay; ED, Emergency Department.

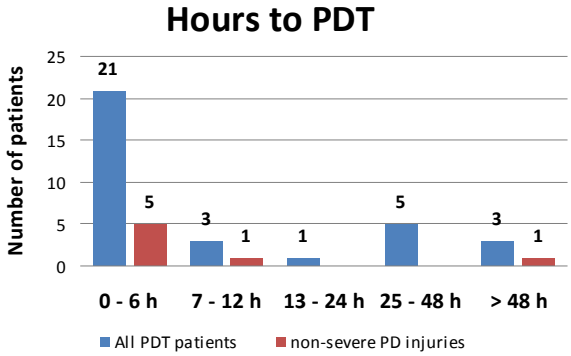

Figure 2. Hours from admission to pancreatoduodenectomy
Abbreviations: PDT, pancreatoduodenectomy for Trauma; non-severe PD injuries = grade I-III.

Table 4. Type of abdominal procedures in non-PDT group

Type of abdominal procedures	non-PDT
Other gastroenterostomy	10
Suture of laceration of duodenum	9
Other partial resection of small intestine	8
Open and other right hemicolectomy	8
Other repair of pancreas	7
Distal pancreatectomy	3
Total pancreatectomy	3
Anastomosis of pancreas	3
Other operations on pancreas	3
Other excision or destruction lesion/tissue of pancreas or pancreatic duct	2
Internal drainage of pancreatic cyst	2
Other partial pancreatectomy	2
Proximal pancreatectomy	1

Abbreviations: PDT, Pancreatoduodenectomy for Trauma.

DISCUSSION

In 1964 Thal and Wilson first described the use of PDT in two trauma patients.[5] Numerous subsequent reports have been published; however, they have all been limited by small sample sizes, ranging between 3-10 patients per study.[4,13-17] The majority of patients sustained a penetrating injury, they were predominantly male, and mortality ranged from 20-100%. Our results are consistent with these prior studies. In a review of all PDTs described in the literature (245 cases)[18] until 1999, the pooled mortality rate was 31%; in our study, mortality was found to be 33%.

In the management of combined pancreatoduodenal injuries, there are several options available. Reviewing the existing published literature[8-10,19], simple repair and drainage was used in 19-44% of patients, repair and exclusion in 34-53%, and a distal pancreatectomy in 3-16%. Trauma Whipple was employed in less than 8% of patients. In a review of pancreatic trauma by Glancy et al.[20], the estimated frequency of PDT was 0.07% in 1407 patients. The question remains, what are the 'hard' indications for performing such a complex procedure?

Subramanian et al[21], in a review of pancreatic trauma, describe the indications for PDT as: extensive trauma to the head of the pancreas, severe combined pancreatoduodenal injury, or destruction of the ampulla of Vater. PDT is also described as a treatment option for isolated grade 5 pancreatic injury[21,22] or isolated grade 5 duodenal injury.[23] In the study by Asensio[12], all 18 patients had injuries to both the pancreas (grade 5 in 17, grade 4 in 1) and duodenum (all grade 5). The indications for PDT in three-quarters of the patients were massive uncontrollable retropancreatic hemorrhage from associated

vascular injuries and massive unreconstructable injuries to both the pancreas and duodenum. In our study, 21% of patients receiving a PDT did not have a grade 4 or 5 injury in either the pancreas or the duodenum, nor did they have significant associated injuries in the abdomen.

If we assume that PDT is being performed for the appropriate indication of severe injury to the pancreatoduodenal complex, it is likely that these patients usually have physiologic derangement or other intra-abdominal injuries requiring attention. Under elective conditions, several authors have recommended enlisting the assistance of an experienced hepatobiliary surgeon when attempting this operation[23-26], and it is not unreasonable to assume that the higher experience-better outcomes relationship is also true in unstable trauma patients. Rather than attempt a rare and complex operation on a coagulopathic, hypothermic, and acidemic patient, it may be prudent to employ modern damage control principles (arrest hemorrhage, temporarily control contamination, restore physiologic balance) and defer a time-consuming and complex reconstruction to more favorable conditions.[27] It is surprising, therefore, to discover that the majority of PDTs were performed within 6 hours of admission. This line of thinking is further supported by the difference in time of death. Patients that received a PDT died much later, while patients with a non-PDT died with a median of only 1 day. As we know, there is a tri-modal distribution of death in trauma, with neurologic and exsanguination deaths occurring immediately, hemorrhagic deaths occurring in the first 24 hours, and septic/multi-organ failure deaths occurring days to weeks later. Reviewing the median time until death, we conclude that most of the non-PDT patients who died, probably died of hemorrhage and that PDT patients who died, likely died of progressive organ failure. This is consistent with the abovementioned finding that non-PDT patients had worse physiologic status upon arrival. We believe that this shows that the surgeon exercised good judgment in deciding not to perform a PDT in these patients, as they were probably very unstable. It is unlikely that performing a PDT would have saved the patient's life. One remaining question is whether patients in the PDT group, dying presumably secondary to progressive organ failure, would have done better with a lesser operation (with presumably less of a physiologic insult), perhaps leading to a higher survival rate. This is a question that should be answered in a new study.

Having shown similar outcomes in patients that were equally injured but managed without a PDT, the question arises whether more conservative procedures are appropriate. A study by Velmahos and colleagues[28] in 2009 demonstrated a failure rate of 10.3% in 97 patients who were managed non-operatively for blunt pancreatic injury (BPI), blunt duodenal injury (BDI), or both. Of those patients, though, only 1 had a grade 4 BPI and the rest were all low grade, mostly grade 1 and 2. A study by Duchesne et al[29] also confirmed that non-operative management (NOM) of patients with low-grade, blunt pancreatic injuries is successful in most patients, with only few complications and a

low mortality (5.7%). However, NOM in high grade injuries is highly unlikely to succeed. Nonetheless, more conservative procedures than PDT, such as primary repair, drainage, duodenal exclusion, or a partial pancreatectomy, are worth considering, since our study demonstrates that outcomes following these procedures are not significantly different compared to those after PDT.

We acknowledge that due to its retrospective design, this study has some limitations. By using a large database we attempted to acquire the largest sample size for this procedure possible; however there are limitations with the NTDB that must be mentioned. The NTDB is a convenience sample that is not completely representative of all trauma centers in the United States. Submission of data is voluntary[30], and this can result in selection bias. Additionally, there is the possibility of inaccurate diagnostic coding, as well as the limitation of included data variables. Regrettably, the NTDB does not include granular detail such as operative reports, intraoperative hemodynamic parameters, surgeon experience, institutional experience, etc. which may factor into the decision whether or not to perform a PDT. Furthermore complications are likely underreported in this database. Despite all these limitations, the NTDB is a very powerful tool and is especially useful in studying injuries of very low incidence. We were able to make an accurate comparison between patients that were managed with PDT versus those that were similarly injured, but were managed without PDT.

CONCLUSIONS

In summary, the Trauma Whipple or PDT is a very uncommon procedure, and even when using the largest available trauma database, over the years 2008-2010 we could only identify 39 patients that received a PDT for severe pancreatoduodenal injuries during the acute phase. Twenty-one percent of PDT may have been performed for inappropriate indications, and in a majority of patients, PDT was performed during the index operation. This, however, did not result in an outcome benefit for patients managed with a PDT when compared to similarly injured patients who were managed without a PDT. More conservative procedures in high-grade injuries of the pancreatoduodenal complex may be appropriate.

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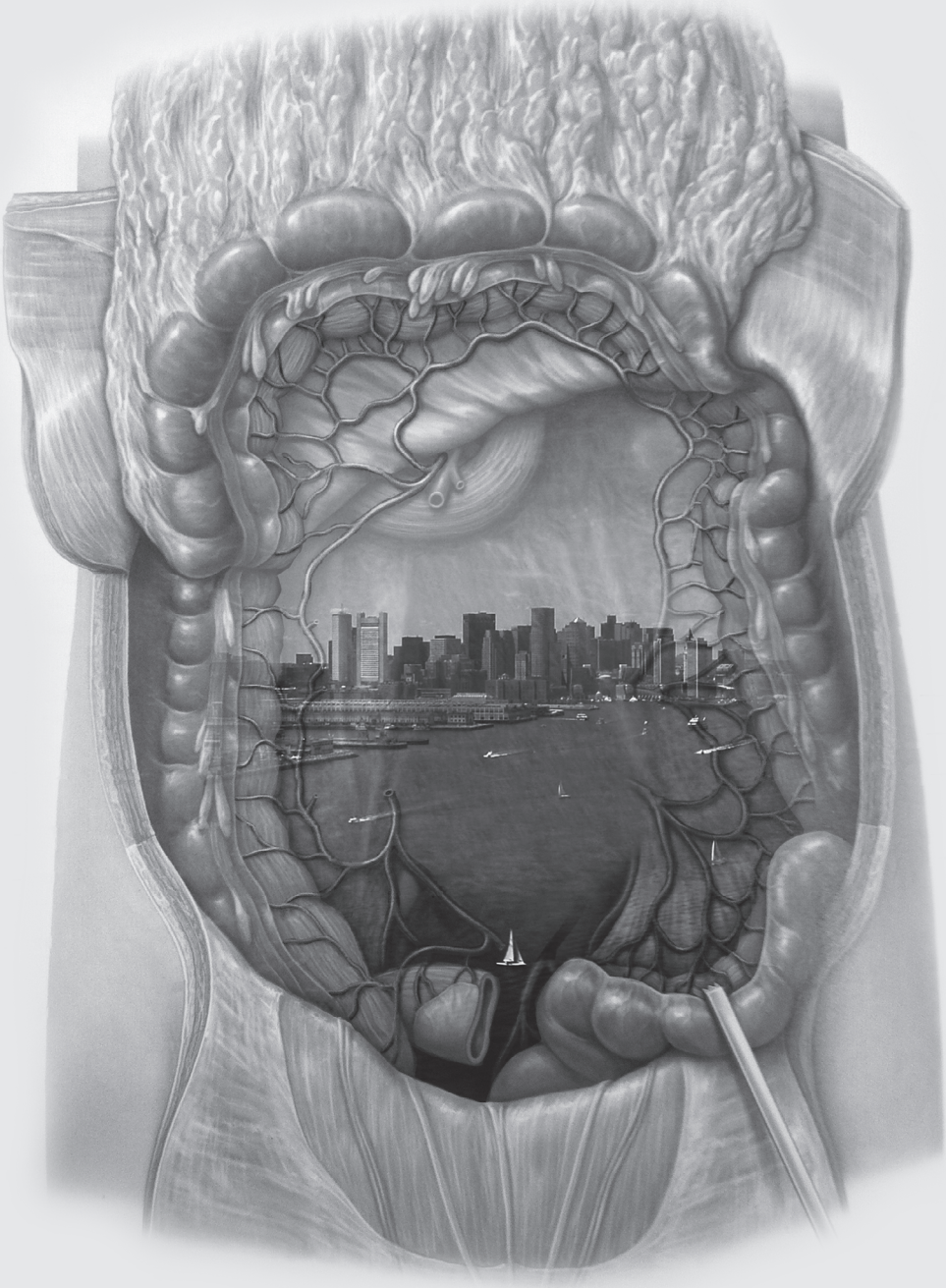
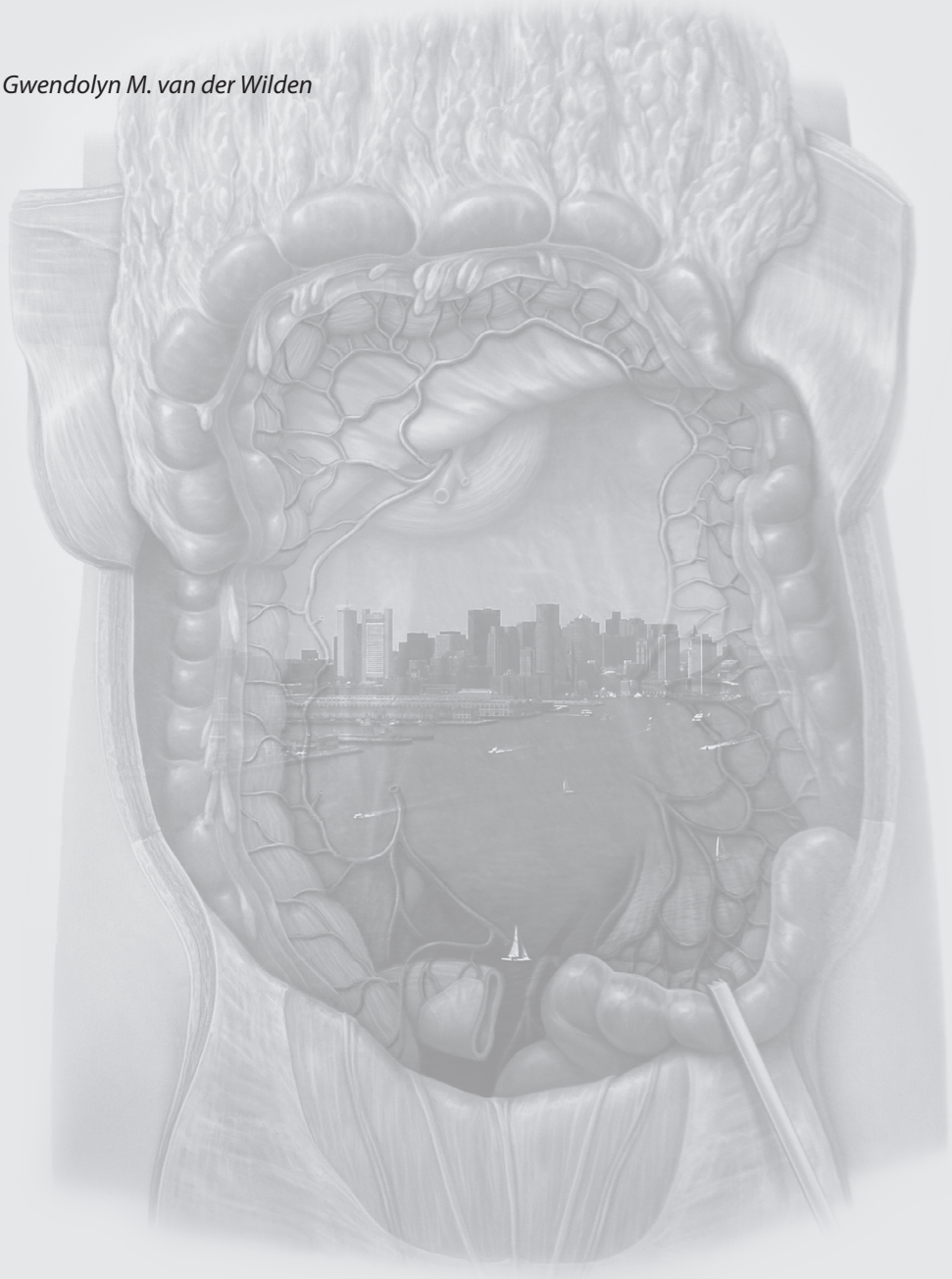
Discussion



Chapter 9

General discussion and future perspectives

Gwendolyn M. van der Wilden



GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Major recent advances in research and patient care have produced enhanced outcomes in complex diseases. fCDC and trauma are not new diseases but continue to claim lives, on many occasions more than in the past. Our ongoing struggle lies not only in new therapeutic strategies but also in preventive methods, which will hopefully allow patients to avoid morbidity and mortality.

The infectious point of view

In this dissertation, the most severe, fulminant, version of *C. difficile* colitis (fCDC) is the hub of attention. Since the early 2000s, CDI is more often being caused by a hypervirulent strain, resulting in an increased incidence of fCDC, accompanied by a higher morbidity and mortality.[1-6] Although appalling mortality rates have required surgeons to focus on this severe colitis, experimental treatment strategies typically target the earlier forms of disease, before it progresses to its fulminant stage. The only recent example of a new treatment option for fCDC is described in a pilot study of Neal et al.[7]; the creation of a diverting loop ileostomy, through which the colon is being lavaged, and post-operatively, is receiving vancomycin enema's in an antegrade fashion (Figure 1). The randomized trial exploring this new option, is currently running, with Massachusetts General Hospital as the leading center in a multi-institutional collaboration. While this trial will provide us with evidence to which extent we can locally, and less invasive, manage this colitis, the question remains whether the answers should be looked for from a different scientific perspective.

Prevention is a key point in optimization of treatment. Looking back at Chapter 1, where SIRS was described as common ground between abdominal emergencies, we

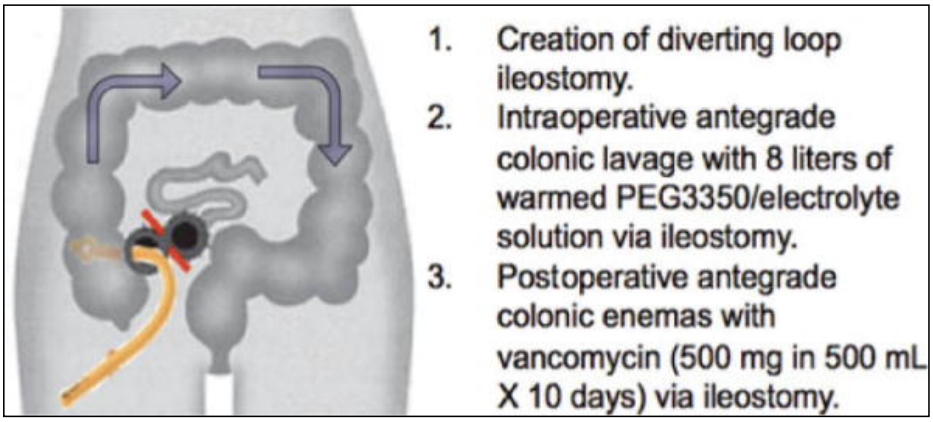


Figure 1. Loop ileostomy with colonic lavage as new treatment of fCDC

know that SIRS can result in secondary MODS, occurring in remote organs. That is the stage in which we would start calling the *C. difficile* colitis, fulminant. Patients can subsequently develop progressive organ failure, which can lead to death.[8] Chapters 2 and 3 describe interferences in the treatment of fCDC by using preventive measures; in this case, not prevention of the initial infection, but of disastrous outcomes from this severe colitis. While the first study focuses on a clinical prediction rule that will help us to identify patients at risk for developing fCDC, the second study describes an intervention; a hospital-wide protocol that facilitates early surgical consultation. Both studies are focused on facilitating treatment at an earlier stage (optimization), which should prevent irreversible events such as mortality.

Chapter 4 focuses on another, yet very important theme in CDI and fCDC; the usage of antibiotics. This study describes the different antibiotic regimen that are used after a total abdominal colectomy for fCDC, and aims to make recommendations about that usage, to optimize treatment and follow-up. This is leading us to an earlier moment in the disease course towards fCDC; the initial CDI. The usage of antibiotics is the biggest risk factor for developing CDI, since it is creating the optimal environment for latent spores to become active and toxic. Although it differs per antibiotic class whether the bacterium is resistant to it or not, the overall use should be reduced to the bare minimum of what is necessary; again, prevention is of the essence here. If we look at the mean incidence of CDI in both the United States (U.S.) and the Netherlands (NL), a huge difference can be detected: 12.5/1,000 admissions in the U.S. vs. 1.5/1,000 admissions in NL.[6, 9-12] This is partially related to the differences in the administration of antibiotics[13-15]; in the U.S. there is a higher risk of prolonged courses, inappropriate use of broad spectrum agents, and lack of appropriate streamlining based on culture data. Although the appropriate use of antibiotics is being promoted by several antimicrobial stewardship programs with good results, there is still a lot that can be done. Antimicrobial stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antibiotics by promoting the selection of the optimal regimen, dose, duration of therapy, and route of administration. The most important goals are to achieve optimal clinical outcomes, minimize toxicity and other adverse events, and reduce the costs.[16-18]

Nevertheless, on certain occasions there is no choice but to prescribe antibiotics. In these cases, we need to make sure that our intestinal microbiota stays balanced, and when needed, to restore it. A technique called fecal transplantation (also known as intestinal microbiota transplantation [IMT]) seems to be the key in future attempts to do so. It has been described since the late fifties[19] but was only recently approved by Medicare and Medicaid and is slowly being accepted as possible treatment by a broader audience. A literature review, including 317 patients across 27 case series and reports, showed that IMT was successful in disease resolution in 92% of cases. Death and other adverse events were both uncommon.[20] The first randomized trial, published recently[21],

confirmed that IMT is very effective in treating (recurrent) CDI; donor feces cured 94% of the patients. In particular patients with multiple relapses (recurrences) of CDI benefitted from this intervention. This treatment interacts with the normal physiology of the colon and its natural inhabitants. However, the question remains: what is the optimal balance of our intestinal microbiota, the ultimate composition of our colonic flora, that will protect us from infections like the one caused by *Clostridium difficile*? More important, once we know the answer to that question, how can we use that knowledge and turn it into a possible treatment for future threats or optimize it in such a way that it will help to also prevent other infections. In short, which germs are friends, and which ones are foes? The elaborate and inspiring article of Michael Pollan in the New York Times[22] addresses that specific question and concluded that one of the keys to good health in this era may involve managing our internal fermentation, anticipating on how our external environment (with factors such as diet, medication, etc.) will interact with our internal environment, in this case, our gastrointestinal tract and its microbiota.

In this same context of optimizing the components of our intestinal microbiota, the study in chapter 5 focuses on the association between vitamin D levels and severity of CDI. Our results show that lower levels of $25(OH)D_3$ are associated with a more severe course of CDI. The next step will be to test in a randomized controlled trial whether adding vitamin D supplementation to the regular treatment of CDI will prevent it from progressing towards a severe colitis. Another study would be to see if optimizing vitamin D levels will also completely prevent the CDI from occurring, something that was suggested in preliminary data.[23] While focusing in this thesis on vitamin D, there are various proteins, biomarkers, and other endogenous substances that might also be relevant in the search for the ultimate composition of the colonic flora.

We are only at the start of discovering the effects of all those individual components within our intestinal microbiota, and although it will be important in future treatments, it will be essential in the prevention of new infections and diseases. To conclude the discussion regarding fCDC related results in this thesis, the 'Holy Grail' of optimization of treatment is closely related to improvement of the logistics of patient care; identifying those patients that are at risk of developing a fulminant colitis at an early stage, and assure that those patients are seen by a surgeon at the earliest moment possible. This may facilitate operative treatment at an earlier moment, when required, at which one can still speak of a life-saving procedure, rather than deteriorating the clinical status of the patient by a 'second hit' through surgical intervention. In addition to that, the focus of future research should include prevention, more specifically the modulation of the causal pathway to prevent a 'simple' CDI from turning into a life-threatening fCDC. Defining the optimal balance of our intestinal microbiota will a prerequisite to accomplish that.

From a different angle: optimization of surgical treatment in abdominal trauma

Trauma is globally the leading cause of death for people between the ages of 5 and 44 years, and has a huge impact on healthcare systems worldwide. With 5.8 million people dying each year as a result of injuries, it accounts for 10% of the world's mortality rate. In addition, many of those who survive acts of violence, accidents, or other causes of injury are left with temporary or sometimes permanent disabilities, both physical and mental (16% of all disabilities globally are caused by injury).[24] Due to heterogeneity in demographics, infrastructure, but also culture, certain aspects of trauma-related injuries differ from country to country. More than 90% of injury-related deaths occur in low- and middle-income countries. But even between high-income countries there are huge differences, for example when comparing the United States, with a population of 316 million, with the Netherlands (population of 17 million). A global overview is given in Table 1; the outcomes can mainly be explained by differences in (access to) healthcare systems, certain legislature (such as gun laws for example), and the impact of crime.

This dissertation focuses on blunt abdominal trauma, an entity that affects up to 13% of trauma patients. Road traffic crashes and falls, as most important causes of blunt trauma, make up for 31% of injury-related mortality worldwide.[24] Management of the, sometimes devastating, injuries is becoming more conservative, and less invasive. In chapter 6 we saw that the most devastating blunt renal injuries, those that are graded as a IV or V by the AAST organ injury scale[25], can be managed safely and effectively without an operation. The same applies to severe blunt liver injuries; outcomes described in chapter 7 show us that non-invasive treatment options should be considered in, again, grade IV and V injuries.[26] Even in the most severe pancreatoduodenal injuries[27], described in chapter 8, that potentially need a pancreatoduodenectomy, we have seen that they can equally effective be managed with more conservative procedures. The explanation for this more conservative trend is probably two-sided; on the one hand we have gained more knowledge over time on how the body responds to certain impacts. A major operation for managing the injuries imposes a significant extra insult on the body, due to often massive pre-operative resuscitation and intra-operative stress. In

Table 1. Global comparison of trauma-related outcomes between the United States and the Netherlands

	United States (per 100,000 residents)	The Netherlands (per 100,000 residents)
Patients treated for traumatic injuries in the Emergency Department annually	10,320 / 100.000	5,120 / 100.000
Trauma-related hospital admissions	790 / 100,000	710 / 100,000
Injury-related mortality	57 / 100,000	31 / 100,000

these cases, the damage control surgery concept applies; delaying the operation to a later moment, or even dividing it into more but smaller procedures, may cause less secondary trauma. Relatively new treatment strategies, operative versus non-operative ones, run parallel to huge improvements in critical care monitoring over the past two decades, which provides us with the opportunity to follow the critically injured patients in detailed fashion, and enables us to identify those patients that need urgent surgical intervention at an early moment.[28, 29]

The question remains: How far can we go? To what extent can we rely on the patients' own reserves to recover from those severe injuries without an invasive intervention? In the case of these abdominal events, we have shown that there will always be patients that require an operation. By the same token, some of these operations are unnecessary, and are offered only because practice is not evidence-based enough yet. The mentality change will be difficult to achieve, since it requires a paradigm shift in our 'mindset', from immediate action and invasive treatments to a more observing role, often with our hands tied, although ready to act whenever necessary. Another part of the shift in surgical mentality is the delayed operation, or so-called damage control surgery, which we briefly touched upon before. The severely injured patients that do need that operation, need it urgently. It will however, only control the hemorrhage (with simultaneously vigorous resuscitation), prevent contamination and further injury, before metabolic failure (triad of acidosis, hypothermia, and coagulopathy) occurs. After that initial operation the patient will go to the ICU where hypothermia and acidosis will be corrected. The definite surgical procedure(s) will follow in the next couple of days (from 24-48 hours after the first procedure), in the window of opportunity between correction of metabolic failure and the onset of signs of SIRS, and possibly MODS.

In conclusion to the second part of the discussion, we can safely limit invasive procedures for acute mesenchymal abdominal injuries and cover trauma patients with more conservative management, even when injuries, according to grading scales, seem devastating. It needs to be emphasized though that there will always be patients with an absolute indication for operation. The focus should be on recognizing those patients at an early moment. So optimization of surgical treatment in abdominal trauma is not only about choosing the right patient for the operation, but to also choose the right time to perform the right procedure. In order to do so, the infrastructure and logistics around these patients need to be optimal at all times, which can be a highly resource competitive endeavor, and requires investment of hospital resources.

More into the future though, it will not only be about preventing those unnecessary procedures, but overall injury prevention will be key when focusing on lowering the current, unacceptably high burden that trauma is causing globally. Public health initiatives play a huge role in this type of prevention, using educational activities such as

drink-driving campaigns and speed limit rules, but also certain legislation mandating a higher standard of car safety, or bicycle helmet laws.

Conclusions

Overall, two themes were dominating this discussion and were present in all studies of this thesis on the value of surgical management in abdominal emergencies; optimization of treatment and prevention. Optimizing the treatment of both trauma patients and patients with fCDC refers to the identification of a possible progressive course at an early stage and improved logistics around this population. But although we have seen before that the systemic response to the insults are quite similar in both fCDC and trauma patients, the road leading to surgical intervention is quite different. In patients with fCDC, SIRS and then sepsis are present by definition, and the surgeon should intervene before the patient enters into the phase of septic shock and MODS. In trauma, sepsis is not present at the early stage although SIRS is rampant. The surgeon's goal is to control bleeding and contamination in order to ameliorate the progress of SIRS. However, a delicate decision making is needed because non-operative treatment may achieve these goals better than an operation in selected patients.

Next to the surgical treatment described, it was shown that more adequate antibiotic usage and an optimal composition of intestinal microbiota will be important in preventing a fulminant course of CDC, and potentially, in prevention of the initial CDI. In patients with blunt abdominal trauma we will need to focus on less invasive treatment, if the clinical situation permits. Public health initiatives can significantly contribute to improved outcomes by implementation of preventive measures.

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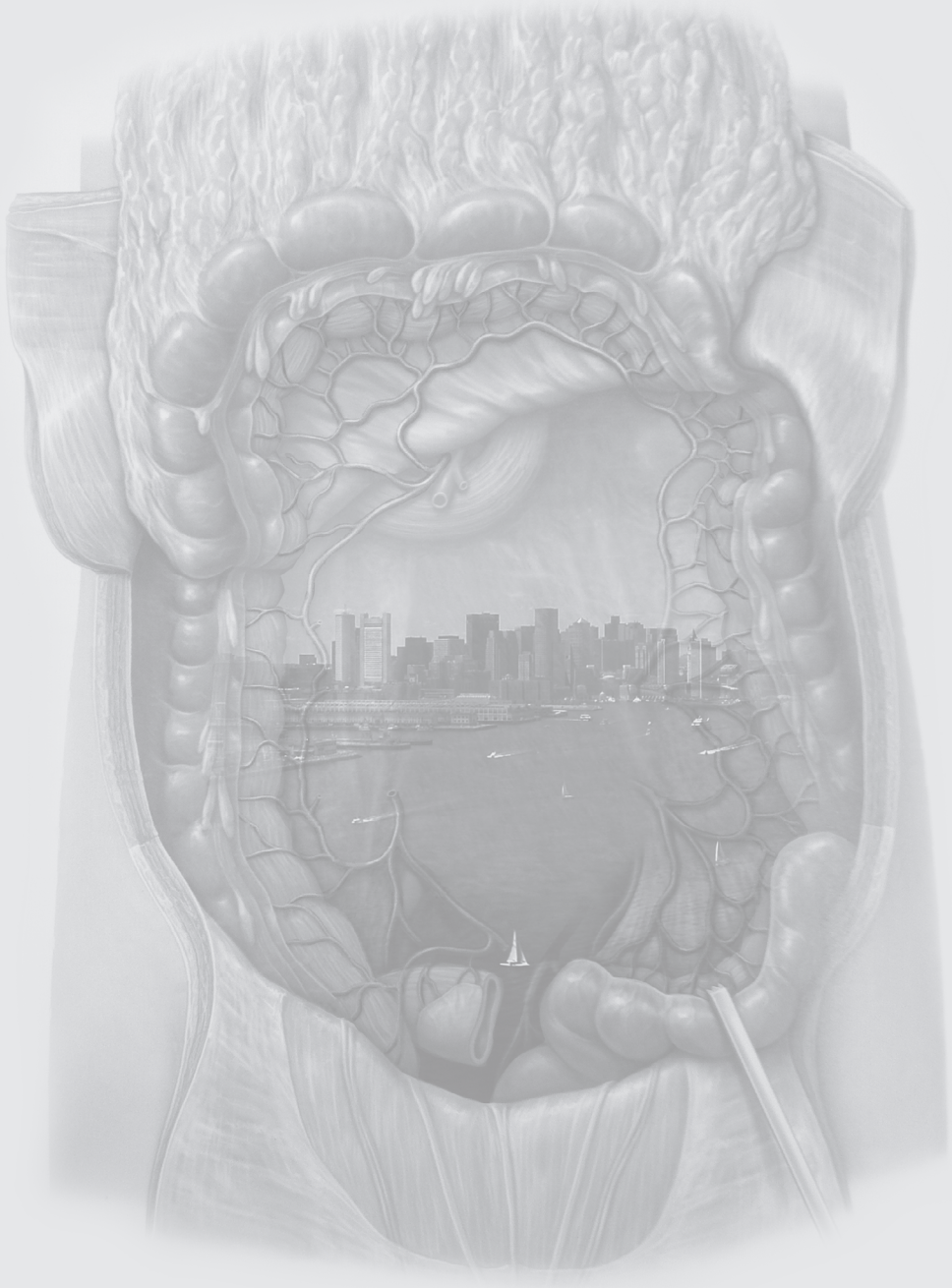
Chapter 10

Summary



SUMMARY

The studies that are part of this thesis focus on abdominal emergencies; fulminant *Clostridium difficile* colitis (**Part I**) and severe abdominal trauma (**Part II**). Several aspects of the optimization of treatment of these severe insults to the abdomen are described. An overall introduction is presented in **chapter 1**.

I. *Clostridium difficile* colitis

The bacterium Clostridium difficile causes an infection (CDI) which nowadays is the leading cause of hospital-acquired diarrhea, both in North America and Europe. While the infection can range from asymptomatic colonization to a severe colitis, it puts pressure on the healthcare system by prolonged hospital stays, rising costs, and increased morbidity and mortality. The research in this thesis concentrates around the fulminant *Clostridium difficile* colitis (fCDC), which develops in 3-8% of patients with CDI. **Chapter 2** describes the development of a risk scoring system (RSS), which enables the clinician to predict which patients are at risk to progress towards a fulminant state. An expert panel reached consensus, using a modified Delphi technique, about four risk factors which were used in the RSS. Based on the log (odds ratio) of each risk factor, the following factors were included and assigned points: age > 70 years (2 points), WBC ≥ 20.000/μL or ≤2.000/μL (1 point), cardiorespiratory failure (7 points), and diffuse abdominal tenderness on physical exam (6 points). The discriminatory value of the MGH RSS (c statistic) was 0.98 (95% confidence interval [CI]: 0.96 – 1). Additionally, the Hosmer and Lemeshow goodness-of-fit test showed a p-value of 0.78, while the Brier score was 0.019. A value of 6 points was determined to be the threshold for dividing low risk (<6) from high risk (≥6) patients. We concluded that the MGH RSS is a valid and reliable tool to identify patients who are at risk of developing fCDC at the bedside. External validation is still needed though, before widespread implementation can occur.

One of the reasons to focus on identification of patients that are at risk of developing fCDC, is the possibility of early intervention. Through a standardized hospital-wide protocol for surgical referral, described in **chapter 3**, we showed that by timely surgical consultation and early identification of patients requiring surgical therapy, we were able to reduce mortality. Criteria developed by a multidisciplinary team were used to trigger a surgical consult, and compliance to this protocol was tested during the 2-year study period. The overall compliance of the protocol was 62.8%. All patients who developed fCDC received a surgical consult, with a median time to consultation of 3 hours. When comparing our 46 fCDC patients after implementation of the protocol with an historic control group (before protocol implementation), the adjusted mortality decreased significantly (18.3% vs. 34.8%, p=0.031). The mortality rate was even lower (14.7%) when excluding patients who were declined an operation due to irreversible conditions. Ad-

ditionally, patients managed under the surgical consultation protocol were admitted to an intensive care unit faster, and the total time from hospital admission to surgical intervention (when required) was shortened.

When patients require an operation, the standard treatment is a total abdominal colectomy (TAC) with ileostomy. Even if this procedure is considered life-saving, it results in high morbidity and a typically prolonged and complex post-operative course. In **chapter 4** that post-operative course is described, with a special focus on post-operative antibiotic usage. A total of 100 fCDC patients who underwent a TAC were included across 5 institutions. Four different post-operative antibiotic regimen were compared: A (metronidazole IV + vancomycin PO), B (metronidazole IV), C (metronidazole IV + vancomycin PO and PR), and D (metronidazole IV + vancomycin PR). Also, the length of treatment was examined (≤ 7 or >7 days). The recommendations, based on this study, are that IV metronidazole and PO vancomycin have similar effectiveness and that proctitis requires the addition of a vancomycin enema (PR). In addition, there is no data to support routine use of more than 7 days of antibiotics. Since prolonged antibiotic use is one of the classic risk factors for developing CDI, this last recommendation is especially important. A multivariate logistic regression was performed as well, and the requirement of a vasopressor before operation (Odds Ratio [OR]: 6.46; 95% CI: 1.96 – 21.24), and the total units of FFP transfused during hospital admission (OR: 1.17; 95%CI: 1.06 – 1.3) were found to be risk factors for mortality.

Chapter 5 extends our CDI research to the association between serum 25-hydroxyvitamin D [25(OH)D] levels and the severity of CDI. Vitamin D has been shown to interact with the immune system in various ways, and we hypothesized that lower levels of 25(OH)D could potentially worsen CDI. In a prospective study, patients diagnosed with CDI were enrolled and divided into two groups, according to severity: group A (positive toxin A/B enzyme immunoassay only) and group B (positive toxin A/B enzyme immunoassay plus abdominal computed tomography imaging consistent with colitis). Serum 25(OH)D levels were measured in 100 patients and showed that the mean 25(OH)D_3 level was significantly higher in group A (n=71) than in group B (n=29): 21 ± 1 ng/mL versus 15 ± 2 ng/mL, respectively (p=0.005). Even after adjusting for clinically relevant covariates, we found that 25(OH)D_3 levels were associated with CDI severity (adjusted OR: 0.92; 95% CI: 0.87-0.98). This study shows that vitamin D interferes with the progress of CDI from a simple infection to a severe colitis and uncovers potential pathways for the origin of the disease. Further studies are warranted to see what the exact function of vitamin D in the pathophysiology of CDI is.

II. Abdominal trauma

In **Part II**, the main focus is on new insights in the treatment of severe blunt abdominal trauma. Practice has shifted over the last decades from operative management to a less invasive approach. The first two studies described in this part are designed as large multi-

institutional studies, including most of the trauma centers in New England (north-east of the United States). This New England collaborative was created to examine injuries, which have a low frequency and no single center can analyze adequately. The last study was conducted, utilizing the largest national trauma database in the United States, the National Trauma Data Bank (NTDB).

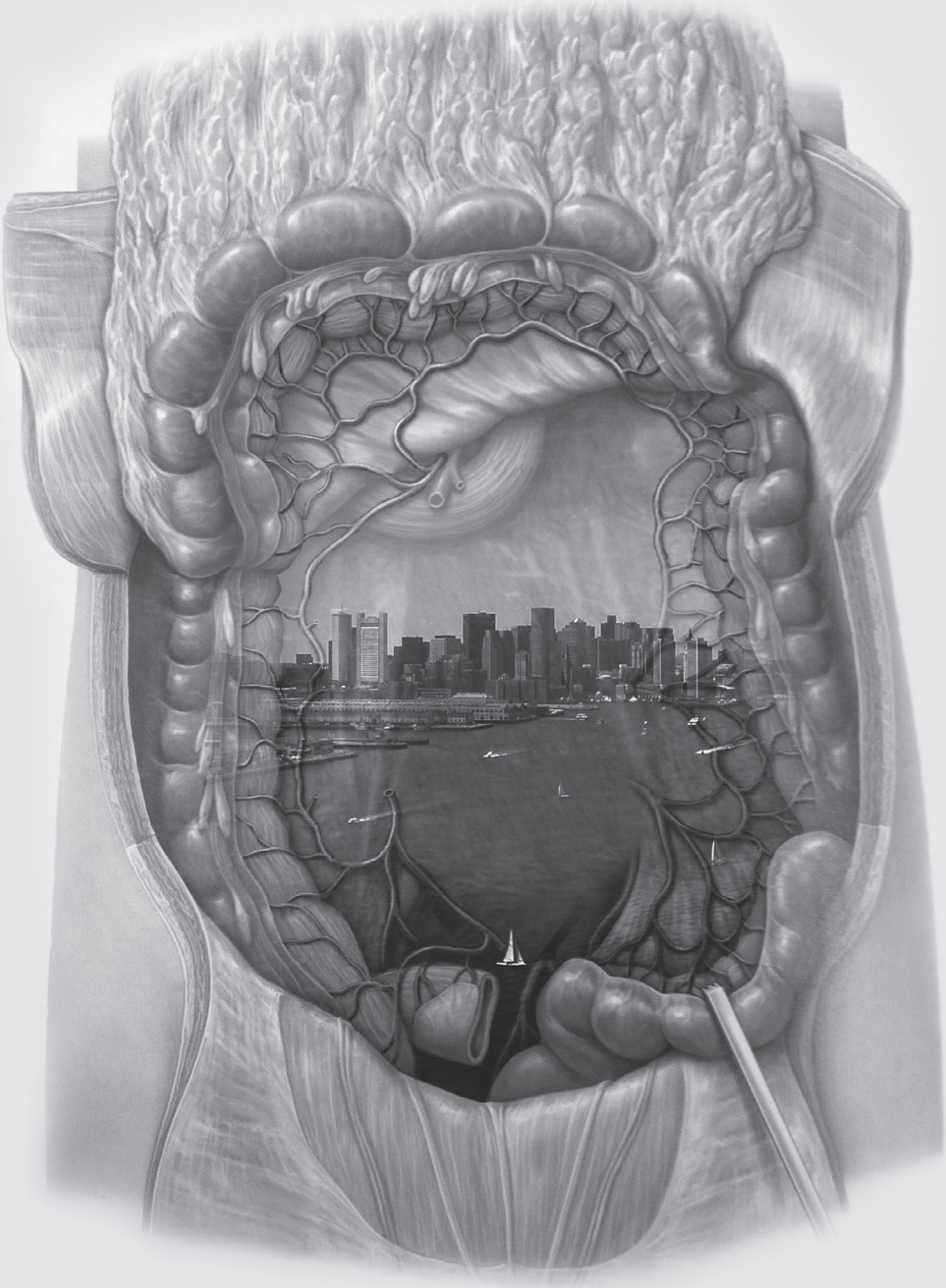
The focus in **chapter 6** is on non-operative management (NOM) of grade IV and V blunt renal injuries, with emphasis on the rate, causes, predictors, and consequences of failure of treatment (f-NOM defined as the need for a delayed operation or death due to renal injury-related complications). In total 206 patients were enrolled across twelve centers between 2000 and 2011. One fourth of the patients was operated on immediately (IO), while the remaining 75% (154 patients) were managed without an operation (angiographic embolization in 25 patients). The overall failure rate of NOM was 7.8% (12 out of 154 patients); in 10 patients related to their kidney injuries. Independent predictors of failure were found to be an age > 55 years and road traffic crash as mechanism of injury. Even though when both factors were present, failure of NOM occurred in only 27.3% of cases. In addition we looked at the occurrence of complications within this population. Around 10-15% of patients with blunt renal injuries will get a complication, most often persistent hematuria or the development of an urinoma. The majority of those complications do not require any operative intervention. Overall, the renal salvage rate was 76.2% (both IO and NOM), and 90.3% among patients selected for NOM. While these results might have been expected due to the regenerating capacity of the kidney, no extensive evidence was available in the literature. This was the case as well for severe blunt liver injuries. Therefore, **chapter 7** focuses on the rate and predictors of failure of NOM in grade IV and V blunt liver injuries. Our multi-institutional study group analyzed 393 patients admitted between 2000 and 2010 across eleven trauma centers. Thirty-three percent (131 patients) were operated on immediately, in most causes due to hemodynamic instability. Of the 262 patients that were managed without an operation, this failed in 23 of them (9%). In 17 out of those 23 patients (6% of total NOM group) non-operative management failed due to liver related reasons. In a multivariate logistic regression model we identified 2 independent predictors of f-NOM; systolic blood pressure on admission ≤ 100 mmHg and other abdominal organ injury. Failure of treatment was observed in 23% of patients when both predictors were present. In patients who were managed successfully without an operation, liver-specific complications developed in 10% and were all managed without major sequelae.

As mentioned above, due to a very low incidence of severe pancreatoduodenal injuries, the NTDB was utilized in **chapter 8** to compare outcomes between patients who were managed with a pancreatoduodenectomy (PDT) for their traumatic injuries versus similarly injured patients (grade IV and V combined pancreatoduodenal injuries) who did not undergo a PDT. Patients who either died almost immediately (in the Emer-

gency Department), or received a PDT > 4 days after admission, or did not undergo a laparotomy at all (in non-PDT group) were excluded. We found that there were no significant differences in outcomes such as mortality, length of stay in ICU and hospital, and ventilator days, between the PDT group (n=39) and non-PDT group (n=38). SBP and GCS at baseline were significantly lower in the non-PDT group, indicating a worse clinical status at baseline. With regard to injury severity, we found that patients in the PDT-group did not always meet the 'standard' indication for a PDT, namely grade IV and V combined pancreatoduodenal injuries; 21% did not have a grade IV or V pancreatic or duodenal injury at all. Injury Severity Score (ISS) was found to be the only independent predictor of mortality in both the PDT group alone (OR: 1.09; 95% CI: 1.01 – 1.18) and in the entire cohort (OR: 1.06; 95% CI: 1.01 – 1.12), while the type of operation did not influence the outcomes. In conclusion, although patients who underwent a PDT had a lower physiologic burden, they were not associated with improved outcomes. Future studies should focus on whether implementation of more conservative procedures in these high-grade injuries of the pancreatoduodenal complex is appropriate.

Finally, in the general discussion in **chapter 9** I conclude that regarding fCDC, optimization of treatment is closely related to logistics of patient care. Identifying patients who are at risk of developing the fulminant disease and assuring that the surgical service is involved early on, may improve outcomes. When designing possible future treatments, prevention is definitely one of the key words; modulation of the causal pathway from 'simple' CDI to fCDC, and defining the optimal balance of the intestinal microbiota. Regarding severe abdominal trauma, optimization of treatment also refers to improved logistics: focusing on more conservative management where possible, and early identification of those patients in need of surgical intervention will result in better outcomes.

Appendices



SUMMARY IN DUTCH (NEDERLANDSE SAMENVATTING)

De studies die deel uitmaken van dit proefschrift zijn gericht op abdominale spoedgevallen; de gecompliceerde, fulminante, *Clostridium difficile* colitis (**Deel 1**) en ernstig buiktrauma (**Deel 2**). Diverse aspecten met betrekking tot het optimaliseren van de behandeling van deze ernstige aandoeningen worden beschreven in dit proefschrift. Een algemene introductie van de onderwerpen is te vinden in **hoofdstuk 1**.

I. *Clostridium difficile* colitis

De darminfectie veroorzaakt door de bacterie *Clostridium difficile* (CDI) is heden ten dage de meest voorkomende oorzaak van diarree tijdens ziekenhuisopname in zowel Noord-Amerika als Europa. De infectie kan variëren van asymptomatische kolonisatie van de darmen tot zware colitis en vormt een ernstig probleem voor de gezondheidszorg, met lange ziekenhuisverblijven, hoge ziektekosten en verhoogde morbiditeit en mortaliteit. Het in dit proefschrift beschreven onderzoek focust zich op de fulminante colitis (fCDC), die voorkomt bij ongeveer 3-8% van alle patiënten met een CDI. In **hoofdstuk 2** wordt beschreven hoe een model tot stand is gekomen dat helpt te voorspellen welke patiënten het hoogste risico hebben om een ernstige colitis te ontwikkelen; een risico scoringssysteem (RSS). Een expert panel koos vier risicofactoren, met behulp van een aangepaste Delphi methode, die in de RSS gebruikt werden. Op basis van de log (odds ratio) van elke factor, werden de volgende factoren meegenomen in de RSS en kregen de volgende punten toegewezen: leeftijd > 70 jaar (2 punten), leukocyten aantal ≥ 20.000/µL of ≤2.000/µL (1 punt), cardiorespiratoir falen (7 punten) en verspreide abdominale gevoeligheid ten tijde van het lichamelijk onderzoek (6 punten). De discriminerende waarde van het MGH RSS (AUC) was 0.98 (95% betrouwbaarheidsinterval [BI]: 0.96 – 1). Daarnaast liet de Hosmer en Lemeshow goodness-of-fit test een p-waarde van 0.78 zien, terwijl de Brier score 0.019 was. Een waarde van 6 punten werd uiteindelijk gekozen als de grens om te kunnen onderscheiden tussen laag (<6) en hoog risico (≥6) patiënten. Concluderend, het MGH RSS is een geldig en betrouwbaar systeem om patiënten die het risico lopen om fCDC te ontwikkelen, tijdig te identificeren. Externe validatie is nog wel nodig voordat dit systeem dagelijks gebruikt kan gaan worden.

De mogelijkheid van vroege interventie is één van de redenen om patiënten met een verhoogd risico op het ontwikkelen van fCDC te identificeren. Met behulp van een gestandaardiseerd, ziekenhuis-breed protocol voor chirurgische consultatie, dat wordt beschreven in **hoofdstuk 3**, laten we zien dat het verrichten van een chirurgisch consult op een eerder moment, met als gevolg vroege identificatie van patiënten die voordeel zouden kunnen hebben van een chirurgische behandeling, leidt tot daling van de mortaliteit. Criteria, ontwikkeld door een multidisciplinair team, zijn gebruikt om een chirurgisch consult te initiëren en de naleving van het protocol is getest gedurende

twee jaar. Het protocol werd nageleefd bij 63% van de CDI patiënten. Alle patiënten die fCDC ontwikkelden ontvingen een chirurgisch consult, met een mediane tijd tot consultatie van 3 uur. Van de 46 patiënten die na implementatie van het protocol werden geïncludeerd, bleek het mortaliteitscijfer na correctie van de comorbiditeits-index significant lager te liggen dan de historische controle groep (18.3% vs. 34.8%, p=0.031). De mortaliteit was 14.7% indien patiënten die palliatieve zorg kregen en patiënten die waren overgeplaatst uit andere ziekenhuizen werden uitgesloten. Bovendien werden patiënten onder het nieuwe protocol significant sneller opgenomen op de intensive care en werd de totale duur van ziekenhuisopname tot chirurgische interventie (indien nodig) significant bekort.

In het geval van chirurgische behandeling voor fCDC, wordt in de meeste gevallen een totale abdominale colectomie (TAC) verricht, waarna een ileostoma wordt aangelegd. Deze operatie, die dankzij verwijdering van de bron van infectie levensreddend kan zijn, resulteert dikwijls in verhoogde morbiditeit en gecompliceerd postoperatief beloop. In **hoofdstuk 4** wordt dit postoperatieve beloop besproken, met speciale aandacht voor postoperatief antibiotica gebruik. In totaal werden, verdeeld over vijf ziekenhuizen, 100 fCDC patiënten geïncludeerd die een TAC ondergingen. Vier verschillende postoperatieve antibioticabehandelingen werden vergeleken; A (metronidazol intraveneus [IV] + vancomycine oraal [PO]), B (metronidazol IV), C (metronidazol IV + vancomycine PO en rectaal [PR]) en D (metronidazol IV + vancomycine PR). Daarnaast werd ook de behandelingsduur geanalyseerd (≤ 7 en ≥ 8 dagen). De resultaten lieten zien dat geen enkele combinatie superieur was. Op basis hiervan bevelen wij aan dat patiënten dan wel met Metronidazol intraveneus, dan wel met Vancomycine oraal behandeld moeten worden, afhankelijk van het regionale ziekenhuisprotocol. Er werd geen bewijs gevonden dat behandeling langer dan zeven dagen ondersteunt. Aangezien antibiotica gebruik één van de voornaamste risicofactoren is voor het ontwikkelen van een CDI, is het van groot belang dat de duur van de antibiotica behandeling zo kort mogelijk wordt gehouden. Tot slot lieten de resultaten zien dat het gebruik van een bloeddruk verhogend medicijn preoperatief (Odds Ratio [OR]: 6.46; 95% BI: 1.96 - 21.24) en het totale aantal gegeven units fresh frozen plasma (FFP) tijdens de ziekenhuisopname (per extra unit, OR: 1.17; 95% BI: 1.06 - 1.3) geassocieerd zijn met een hogere mortaliteit.

In **hoofdstuk 5** is gekeken naar de mogelijke associatie tussen serum-25-hydroxyvitamine D [25(OH)D] spiegels en ernst van de CDI, om verder inzicht te vergaren in de etiologie van CDI. Eerdere studies hebben laten zien dat vitamine D op verschillende manieren invloed heeft op het immuun systeem en in deze studie hebben we de hypothese getest dat een lagere 25(OH)D spiegel geassocieerd is met een ernstigere versie van CDI. In een prospectieve studie werden patiënten, gediagnosticeerd met CDI, geïncludeerd en vervolgens verdeeld in twee groepen, afhankelijk van de ernst van de CDI: groep A (positief voor toxines A/B op basis van ELISA techniek) en groep B (positief voor

toxines A/B op basis van ELISA techniek, met daarbij een abdominale CT-scan positief voor colitis). De serum 25(OH)D spiegels werden gemeten in 100 patiënten en lieten zien dat de gemiddelde 25(OH)D_3 spiegel significant hoger was in groep A (n=71) dan in groep B (n=29): 21 ± 1 ng/mL versus 15 ± 2 ng/mL, respectievelijk (p=0.005). Na correctie voor klinisch relevante variabelen, bleven hogere 25(OH)D_3 spiegels geassocieerd met minder ernstige CDI (gecorrigeerde OR: 0.92; 95% BI: 0.87-0.98). Concluderend laat deze studie zien dat er een associatie bestaat tussen vitamine D en de ernst van CDI. Aanvullende studies zijn nodig om de exacte functie van vitamine D te bepalen binnen de pathofysiologie van CDI.

II. Abdominaal trauma

Deel II is gericht op nieuwe inzichten in de behandeling van ernstig (stomp) buiktrauma. De laatste decennia is deze behandeling veranderd van nagenoeg uitsluitend operatief ingrijpen naar een meer conservatieve behandeling. De eerste twee studies tonen resultaten van twee grote, multicenter studies waar het merendeel van de traumacentra in New England (Noordoosten van de Verenigde Staten) aan meededen. Voor de laatste studie is gebruik gemaakt van de grootste database op het gebied van trauma binnen de Verenigde Staten; de Nationale Trauma Data Bank (NTDB).

In **hoofdstuk 6** ligt de nadruk op het non-operatief behandelen (NOM) van graad IV en V stomp niertrauma. Wij hebben ons in het bijzonder gericht op de oorzaken, voorspellers en consequenties van het falen van een conservatieve behandeling (f-NOM; gedefinieerd als de noodzaak tot verlate operatie of mortaliteit ten gevolge van aan niertrauma gerelateerde complicaties). In totaal werden tussen 2000 en 2011 206 patiënten geïncludeerd in 12 centra. Een vierde van de patiënten werd direct naar de operatie kamer gebracht (IO), terwijl de resterende 75% (154 patiënten) behandeld werd zonder operatie (met angio-embolisatie in 25 patiënten). In totaal faalde de conservatieve behandeling in 7.8% van de NOM populatie (12 van 154 patiënten); bij 10 patiënten was schade aan de nier de oorzaak. Onafhankelijke voorspellers van falen waren: leeftijd > 55 jaar en een verkeersongeluk als trauma mechanisme. Bij aanwezigheid van beide voorspellers was het percentage falen van NOM 27.3%. 10-15% van alle patiënten met stomp nier trauma ontwikkelden een complicatie, met aanhoudende hematurie en de ontwikkeling van een urinoom als belangrijkste complicaties. De meerderheid van deze complicaties behoefde geen operatieve behandeling. Concluderend kon 76.2% van de patiënten (IO + NOM) niersparend behandeld worden en 90.3% van de patiënten die initieel voor NOM geselecteerd waren. Deze resultaten konden wellicht worden verwacht gebaseerd op de regeneratieve kracht van de nieren, maar er waren tot op heden geen overtuigende studieresultaten beschikbaar om dit aan te tonen. Ditzelfde geldt voor stomp levertrauma; er bestond tot op heden geen studie die, met voldoende power, heeft bewezen dat NOM veilig en effectief is bij graad IV en V levertrauma. De focus van

hoofdstuk 7 ligt daarom op het falen van een conservatieve behandeling voor graad IV en V stomp levertrauma, en de risicofactoren hiervoor. Met de multi-institutionele groep, ditmaal bestaand uit 11 centra, werden 393 patiënten geïncludeerd tussen 2000 en 2010. 131 patiënten (33%) werden direct operatief behandeld, voornamelijk vanwege hemodynamische instabiliteit. Van de 262 patiënten die non-operatief behandeld werden, faalde dit beleid bij 23 patiënten (9%). In 17 van de 23 patiënten (6% van de totale NOM groep) lagen lever-gerelateerde oorzaken hieraan ten grondslag. Middels multivariabele logistische regressie werden twee onafhankelijke voorspellers voor het falen van conservatief beleid gevonden: een bloeddruk bij opname van ≤ 100 mmHg en de aanwezigheid van ander abdominaal orgaan letsel. Als beide voorspellers present waren, faalde de non-operatieve behandeling in 23% van de gevallen. Van de patiënten die succesvol behandeld werden zonder operatie, kreeg 10% een lever-gerelateerde complicatie. Deze complicaties konden in alle gevallen behandeld worden zonder blijvende problemen.

De NTDB werd gebruikt in **hoofdstuk 8** om de uitkomsten van letsel aan het pancreaticoduodenaal complex te vergelijken tussen patiënten die behandeld werden met een pancreaticoduodenectomie (PDT) en patiënten die soortgelijke verwondingen hadden (graad IV en V gecombineerde pancreas- en duodenumletsels), maar geen PDT ondergingen. Patiënten die direct overleden, een PDT > 4 dagen na opname ondergingen, of helemaal geen laparotomie ondergingen (in de non-PDT groep) werden geëxcludeerd. Er werden geen significante verschillen in de uitkomsten gevonden tussen de PDT groep (n=39) en de non-PDT groep (n=38), inclusief mortaliteit, lengte van intensive care opname, lengte van ziekenhuisopname en het aantal dagen aan de mechanische ventilatie. Een interessante bevinding was het verschil in systolische bloeddruk en Glascow Coma Scale bij opname; beide waren significant lager in de non-PDT groep, hetgeen wijst op een slechtere klinische status bij opname. Verder is het opmerkelijk dat de 'standaard' indicatie voor een PDT, namelijk graad IV of V gecombineerd pancreaticoduodenaal letsel, bij 21% van de patiënten in de PDT groep niet aanwezig was. De Injury Severity Score (ISS) bleek de enige onafhankelijke voorspeller van mortaliteit te zijn in de PDT groep (OR: 1.09; 95% BI: 1.01 - 1.18) en in het totale cohort (OR: 1.07; 95% BI: 1.01 - 1.12), terwijl het type operatie niet van invloed was op de resultaten. Concluderend, alhoewel patiënten die een PDT ondergingen een betere uitgangspositie hadden, resulteerde dit niet in verbeterde uitkomsten. Toekomstige studies zullen moeten uitwijzen of het haalbaar is om deze ernstige letsels aan het pancreaticoduodenaal complex met een meer conservatief beleid te behandelen.

Concluderend in de algemene discussie (**hoofdstuk 9)** moet de optimalisatie van behandeling in fCDC patiënten vooral gezocht worden in de logistiek rond de patiëntenzorg. Het identificeren van patiënten die risico lopen om de fulminante ziekte te ontwikkelen en ervoor zorgen dat deze patiënten vroegtijdig door de chirurg gezien

worden, kan de uitkomsten verbeteren. Toekomstige studies naar nieuwe behandelingen zullen zich ook moeten focussen op preventie, zowel door middel van ingrijpen op het causale pad van 'simpele' CDI naar fCDC en definiëren wat de optimale balans is van de intestinale microbiota. Bij ernstig abdominaal trauma kunnen we concluderen dat optimalisatie van behandeling ook refereert naar verbeterde logistiek; focussen op een meer conservatieve behandeling wanneer mogelijk en het vroegtijdig identificeren van patiënten die een chirurgische interventie nodig hebben, zal resulteren in verbeterde uitkomsten.

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ACKNOWLEDGEMENTS (DANKWOORD)

Writing a dissertation can be a lonely job at times, the process around it however is a joint effort and my gratitude goes out to all the people that have contributed to it. Although I'm aware of the fact that I'll probably never be complete in thanking every person by name, I'll do my best.

First of all I would like to express my gratitude to Inger Schipper and George Velmahos, who have supported me unconditionally and without whom all of this would not have been possible.

Dear Dr. Velmahos, I never knew the true meaning of the word 'mentor' until I arrived at MGH. Your guidance through the years has not only taught me the essences of clinical research, it also shaped me to the doctor I hope to be in the near future. I'll always be grateful for all the opportunities you have given me, and hope we can continue working together in the future.

Dear Prof. Schipper, thank you for supporting me from the first moment I walked into your office. Although often with an ocean in between, you guided me through this whole process with an enormous enthusiasm and made the transition to Leiden easy. You're an example to me of how women can be successful within the surgical field.

Members of the PhD committee, thank you for your genuine interest in this thesis and the willingness to take a seat in the committee.

Drs. de Moya, King, Fagenholz, Yeh, Kaafarani, Gervasini, and Alam; you taught me the world. Endless research meetings and discussions allowed me to produce the work I've published so far. Your patience and dedication to the job are an example to me.

The 'Dream Team' (from rock to diamond): Maria, Ali, Antonis, Ayesha, John, Oscar, Catrina, Melanie, and fellows after that, you made the job easy. Working with all of you was a joy, as was learning about each other's culture; I'm looking forward to meeting again.

Maura, Karen, Jamie, Laurie, Thom, Sue, Rosangely, Justin, Mike, Ingrid, Amanda, Konan, Jerome, Chad, George, Eric, Sadik, all the NP's, the Wang Clinic, Ellison 4, and Blake 12: it was a pleasure to work with all of you. I could have never imagined that working around the clock is that much fun. Thank you for all your help, understanding, and friendship.

Al zat ik maar even in het LUMC, het was een onvergetelijke tijd. Dank aan alle promovendi binnen de heelkunde die ervoor hebben gezorgd dat ik me snel thuis voelde; ik kijk uit naar al jullie promoties de komende jaren! Iedereen binnen de afdeling traumachirurgie, dank voor alle hulp. Duveken, Ariënne, Ayoub, Petra, Annemarie, Graziella, Zjir en Colette; dank voor de gezellige tijd op J-10!

Familie en vrienden, ik ben dankbaar jullie allemaal te kennen. Jullie continue interesse, ook toen ik 'even' 2.5 jaar in Boston zat, zal ik niet snel vergeten. In het bijzonder, lieve meiden van Kant, met elkaar gaan we fase per fase door en ik kijk uit naar alles wat nog komen gaat! Emilie, mede door jou was de overgang van Boston naar Den Haag zo makkelijk, dank!

Bo, Marije, Judith, Elke, Barbara en Christine, jullie vriendschap is goud waard. Eveneens jullie bezoeken aan Boston, even lekker Nederlands in Amerika. Judith, naar jouw proefschrift kijk ik al jaren uit, je was en bent nog steeds een bron van inspiratie. Christine, mede door jouw hulp en wijsheden ben ik zover gekomen, een beter voorbeeld had ik niet kunnen hebben.

Boston, what a beautiful city. It was an amazing experience to live there for such a long time. I'm grateful for all the extraordinary people I've met there. A special thanks to Bart and Jolijn, our friendship means the world! Ingrid, so many memorable moments; your everlasting understanding and good mood were a relief at times! Jan-Willem, Arjan, Marlien and Frannie, a.k.a. the 'Dutchies', our time together was priceless. There are many more friends to thank; Marti, Marit, Stéphanie, Natalie, and the rest, you know who you are!

Emily, my true American friend. You and your family have shown me the American culture as no other; I've enjoyed every second of it and I hope that at some point I can return the favor!

Speciale dank gaat uit naar mijn paranimfen, Jolijn en Marije, voor al jullie hulp de laatste tijd. Jolijn, samen lange dagen maken op MGH en daarnaast leuke dingen doen; jij was mijn beste maatje in Boston en ik ben blij dat je inmiddels ook weer in Nederland zit! Marije, jouw enorme drive om hard te werken blijft inspireren. Als club- en nu huisgenoten hebben we al veel meegemaakt samen; ik ben blij dat je vandaag naast me staat!

Valerie en Julie, lieve zusjes! Jullie interesse, maar ook onze eindeloze gesprekken en vaak discussies hielden mij gefocust en met beide benen op de grond. Heerlijk om af en

toe even geen medische termen te horen maar de laatste updates op andere gebieden. Dank jullie wel!

Lieve mam en pap, jullie zijn de eersten die ik wil bedanken. Jullie onvoorwaardelijke support en enthousiasme, niet alleen de laatste drie jaar, maar eigenlijk zolang ik het mij kan herinneren, hebben me gebracht waar ik vandaag ben. Dank voor alles!

CURRICULUM VITAE

Gwendolyn van der Wilden was born in Rotterdam on April 8th 1988, the Netherlands. She graduated from the Erasmiaans Gymnasium in Rotterdam in 2006 and started medical school at Leiden University in September of that same year. During her years in medical school, she worked as a 'Joshua' (intensive care support assistant) at the ICU of both the Leiden University Medical Center and the Haga Hospital, which marked the start of her interest in surgery. In 2010 Gwendolyn left the Netherlands for a research fellowship at the Massachusetts General Hospital (a teaching affiliate of Harvard Medical School) in the Department of Surgery, Division of Trauma, Emergency Surgery and Surgical Critical Care, under the supervision of Prof.Dr. George C. Velmahos. Although initially for the period of 1 year, her stay in Boston was extended to 2.5 years in which she conducted multiple studies, mainly on abdominal trauma and *Clostridium difficile*, which resulted in several publications and this thesis. Her work on *Clostridium difficile* was awarded with the Surgical Infection Society 'Award of Excellence in Preventing Surgical Infections' in Dallas, Texas, 2012. After returning to the Netherlands, Gwendolyn spent five more months at the Leiden University Medical Center, under the supervision of Prof.Dr. Inger B. Schipper, to finish her dissertation. Currently, she is continuing her medical training, and she hopes to graduate in the summer of 2015.