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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)D3 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)D3 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.