Chapter 1
Introduction and outline of the thesis
INTRODUCTION

Being intensively involved in the treatment of children sustaining blunt abdominal trauma, we once posed the simple question: “What is the evidence for one week bed rest in children with liver injury?” This question eventually led to the research resulting in this thesis. In this introduction we will first outline the incidence of pediatric trauma whereafter we will focus on some of the differences between children and adults. Differences in physiology and anatomy form the background for many of the following chapters. All physicians treating children with possible (abdominal) injury should be aware of these differences. In the present thesis, focus is first on the diagnostic process in children with suspected abdominal injury. After delineating the role of CT scan, several possible alternative diagnostic modalities will be discussed. Subsequently clinical outcome in relation to conceivable treatment modalities in children with blunt trauma sustaining solid organ injuries are evaluated. The introduction will be followed by a brief outline of the thesis.

Pediatric trauma

Epidemiology
Trauma still is worldwide the number one cause of death for children below the age of 18 (between 1 and 18 years) even in well-developed and wealthy countries such as the Netherlands. Roughly two third of these fatalities are caused by traffic injury in the Netherlands. Due to the many preventive precautions that have been implemented in traffic such as mandatory child seats and the technical improvements in motorised vehicles the incidence death rate has dramatically declined. In 1983 the Dutch annual number of fatal paediatric road traffic accidents was 191 (0-16 years), while in the year 2012 it has decreased to 27. Figure 1 depicts annual mortality and causes for the years 1983 and 2012. Injury can be inflicted by blunt force trauma and penetrating trauma. In several parts of the world, penetrating trauma is the most prevalent. However, in Europe, >90% of injuries are caused by blunt trauma. Seriously injured children often suffer from multiple injuries. Head injury is present in the majority of cases and accounts for 75% of deaths. The types of injury mechanisms are age dependent. In infants, non-accidental injury is most prevalent whereas, for toddlers, falls are the predominant injury mechanism. In older children, road traffic accidents and sports injuries predominate. More than 50% of road traffic accidents involve the child as a pedestrian and a further 20% as cyclists. For the Dutch population, bicycle and motorcycle accidents might predominate in older children. Whether this indeed is the case will be investigated in the chapters regarding liver and splenic injury of the present thesis. Pediatric trauma deaths have a trimodal distribution with 50% dying at the scene from either severe head injury or major hemorrhage. A further 30% die within the first few
hours from head injury, hemorrhage, or airway emergencies. Late deaths due to organ failure and sepsis are often due to inadequate initial resuscitation.

Abdominal trauma accounts for about 10% of trauma in children but is the leading cause of initially unrecognized fatal injury. It is second only to airway problems as the most frequent cause of preventable death. Therefore a thorough analysis of injury patterns is important in the care of children with possible intra-abdominal injury.

Differences between children and adults

Physiological differences

Stress responses in children are different from those in adults. As stroke volume is relatively constant in children, tachycardia is the only way to increase heart minute volume. Children are able to maintain hemodynamic stability for a long period of time, with only subtle signs of deterioration (often only a mild tachycardia) before they rapidly develop severe hypovolemic shock. Bradycardia should be considered as a near fatal sign.

As the skin area of children is relatively large, hypothermia will develop relatively rapidly when compared to adults. Hypothermia in combination with acidosis and coagulopathy is – just as in adults – the lethal triad. Hypothermia should therefore be avoided whenever possible, and can often be achieved with relative ease such as by heating of the emergency room.
**Anatomical differences**

Due to the size of the patient, injury patterns differ in children when compared to adults. Children will more often suffer from (concomitant) brain injury due to the relatively large size of their head. It is one of the reasons that brain injury is the cause of death in 75% of the cases.

When compared to adults the abdominal organs are closely packed together. Children have relatively little abdominal muscle or fat mass, which can absorb some of the impact. The ribcage is very elastic, offering less protection to the liver and spleen. Also, the diaphragm is placed more horizontally, thus displacing the liver and spleen downwards, which further increases the vulnerability of the intra-abdominal organs. Children have a relatively small pelvis placing the bladder more intra-abdominally and thus less protected. All these factors contribute to the vulnerability of the abdomen in children.3

Finally, although the principles of acute trauma care do not differ between children and adults, in children even “simple” interventions such as placement of an intravenous catheter can be more difficult because of the smaller size of the vessels, while medication regimes also differ from those in adults. For all these reasons, the child with possible severe trauma can therefore pose a significant challenge for ‘adult’ physicians.

**Diagnosing abdominal injury in children**

**Assessment**

Potentially injured children are assessed through the ATLS/APLS principles: ABC (DEFG) and treat first what kills first.4 After establishing a free airway and an adequate oxygenation/ventilation, circulation is assessed. Vital parameters are age-dependent. Signs of shock will only become apparent after a loss of > 15% of the total circulating volume. Hypotension will occur only after an acute loss of 25% of the total circulating volume. When there are signs of shock 20 ml/kg warm isotonic crystalloid is administered, which can be repeated. This first bolus comprises 25% of the circulating volume, after the second bolus 50% of the circulating volume has been replaced. Signs and symptoms of shock can be very subtle; a mild tachycardia is often the only sign and can be easily mistaken as a sign of pain or discomfort. Systolic pressure can even be increased due to the shock response. In this way, children are different from adults. This is important when considering the presence of hemodynamic (in)stability.

The definition of hemodynamic stability in children is subjective to multiple variable parameters. The assessment of hemodynamic instability is an evolving process, in which the physiological reaction to fluid challenges might be more important than the first read-out
of the monitor. Children who respond to fluid boluses can be considered as ‘responders’, and management is different from those who do not respond. Children who are stabilized after a bolus of 2×25% of the circulating volume are considered hemodynamically stable according to the APLS definition.

In case of severe hypothermia, coagulopathy and acidosis ‘damage control surgery’ might become necessary: in the case of abdominal injury this consists of stopping the bleeding as soon as possible, preventing further fecal spill (e.g. by stapling the bowel), (temporarily) closing of the abdomen followed by further stabilization in the pediatric intensive care. While very important in children, a more detailed discussion of the damage control principle goes well beyond the present chapter.

After stabilisation of vital functions and completion of the primary survey, a complete physical examination is carried out. An initial normal physical examination does not rule out internal injury. Especially in children this is an important point. Small external injuries, e.g. a small bruise due to a handlebar injury, can be a sign of severe intra-abdominal injury. Obvious lesions such as the seatbelt sign are pathognomonic for severe intra-abdominal injury. Preferably, the physical examination is repeated by the same (senior) physician at regular intervals after the accident, as changes in the examination can offer important insights in the presence or absence of injury. Repeated physical examination is therefore essential in the assessment of the abdominally injured child and its importance cannot be overstated.5

In the secondary survey X-rays of the chest, pelvis and cervical spine are obtained, Focussed Assessment with Sonography for Trauma (FAST – aimed at identifying free intra-abdominal fluid) or regular ultrasound imaging of the abdomen is performed and blood samples are obtained.

In the absence of hemodynamic instability, a multi-phase contrast enhanced CT is generally performed when abdominal injury is suspected (e.g. when intra-abdominal fluid is present on FAST). Also in the Netherlands and thus in the University Medical Centre Groningen, (UMCG) a CT scan is considered the investigation of choice for determining the presence and extent of intra-abdominal injury in hemodynamically stable children.3 However, indications for CT scan are rather ambiguous in most centres. They often consist of a high index of suspicion (e.g. a seatbelt sign with abdominal tenderness), laboratory disturbances indicative of intra-abdominal injury (e.g. raised liver function tests or raised amylase) or ultrasound findings such as the presence of free fluid or the suggestion of injury to the parenchymatous organs. Hemodynamic instability, as defined by the APLS, should (in non-responders) be seen as an indication for emergency surgical intervention and is thereby a contra-indication for CT scan of the abdomen.4
Blood analyses
Laboratory testing contributes significantly to the identification of children with intra-abdominal injuries after blunt trauma. Since physical examination and hemodynamic parameters are frequently unreliable for the abdominally injured patients, serum analyses are helpful tools in the diagnostic workup, e.g. to assess (persistent) blood loss or to get an indication of the presence of organ specific injury. While detailed discussion of the subtleties of serum analysis goes beyond the scope of this chapter, a specific serum marker for abdominal injury would be a valuable addition to the diagnostic workup. It could save valuable time, and reduce costs and unwarranted medical examinations.

Imaging techniques
Ultrasonography and FAST are quick and non-invasive investigations, readily available in most hospitals. While FAST aims at a rapid identification of free fluid (in Morrison’s pouch, the perisplenic area, the pelvis and the pericardium), a formal ultrasound can be performed in stable patients. With added Doppler, ultrasonography can even assess flow in essential vascular structures. It has no ionising radiation and sedation is not needed for adequate investigation. In hemodynamically unstable patients with blunt abdominal trauma, bedside ultrasound in the emergency room should be the initial diagnostic modality performed to identify the need for emergent laparotomy. It is also very suitable for follow up of abdominal injury.

However, ultrasound also has its downsides. It is operator dependant and although it is reasonably sensitive to free fluid, it is not very reliable for the assessment of solid organ injury, let alone grading of injuries.

CT imaging is considered the golden standard for imaging of abdominal injury due to its accuracy. It is relatively quick and generally available in most hospitals and with the use of intravenous contrast it can even distinguish and localize active bleeding.

The AAST issued the Organ Injury Scales (OIS) to be able to compare patient groups for research purposes. Concurrently the development of the CT scan made swift and relatively accurate initial analysis of the abdominal injury possible. The CT scan has thus become the gold standard of diagnosing intra-abdominal injury in children and has adapted the use of the OIS for grading injuries. Table 1 depicts the AAST grading system for hepatic injury. For all organ injuries a comparable grading system is available.

CT imaging also has its downsides. It has a risk of contrast reactions, can be relatively time consuming and is a serious ionising radiation hazard for patients. Also, there is an inherent danger in transporting patients to and from the CT suite, which itself poses danger as monitoring and intervention options in the CT suite are suboptimal at best.
While CT and ultrasound remain the imaging tests of choice during the golden hour, the subsequent management of patients after trauma, either post surgical or during a watchful waiting algorithm sometimes requires repeated advanced cross sectional imaging. Given the lack of radiation dose and the multiple tools in the MRI armamentarium (i.e. MR cholangiopancreatography), the use of MRI for post-acute imaging does have a role in the assessment and certainly the follow-up of abdominal injury, particularly in young patients. When the child has been stabilized, MRI can be an important adjunct, e.g. in diagnosing pancreatic injuries.

Using MRI scanners in an emergent fashion is impractical for several reasons. Many emergency departments have CT scanners nearby; many do not have easy access to MRI scanners or MRI technologists waiting on standby for trauma studies. It is often impossible or impractical to perform the necessary safety screening of trauma patients. It is necessary to have the surgical trauma team close at hand, often inside or just outside the scan room, making screening of great importance and the risk of projectiles a major hazard. While rapid MRI protocols of the abdomen could easily be performed with scan times similar to that of the CT, trauma patients often undergo total body scanning for concomitant injuries. For reasons of accessibility, safety, and the need to scan multiple body parts in rapid succession, CT is still considered the golden standard of trauma imaging during initial analysis despite the radiation exposure.9

<table>
<thead>
<tr>
<th>Grade*</th>
<th>Injury type</th>
<th>Description of injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hematoma</td>
<td>Subcapsular, &lt;10% surface area</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Capsular tear, &lt;1 cm parenchymal depth</td>
</tr>
<tr>
<td>II</td>
<td>Hematoma</td>
<td>Subcapsular, 10%-50% surface area intraparenchymal, &lt;5 cm in diameter</td>
</tr>
<tr>
<td></td>
<td>Laceration</td>
<td>Capsular tear, 1-3cm parenchymal depth that does not involve a trabecular vessel</td>
</tr>
<tr>
<td>III</td>
<td>Hematoma</td>
<td>Subcapsular, &gt;50% surface area or expanding; ruptured subcapsular or parenchymal hematoma; intraparenchymal hematoma ≥ 5 cm or expanding</td>
</tr>
<tr>
<td></td>
<td>Laceration</td>
<td>&gt;3 cm parenchymal depth or involving trabecular vessels</td>
</tr>
<tr>
<td>IV</td>
<td>Laceration</td>
<td>Laceration involving segmental or hilar vessels producing major devascularization (&gt;25% of spleen)</td>
</tr>
<tr>
<td>V</td>
<td>Laceration</td>
<td>Completely shattered spleen</td>
</tr>
<tr>
<td></td>
<td>Vascular</td>
<td>Hilar vascular injury with devascularizes spleen</td>
</tr>
</tbody>
</table>

Table 1: 1994 AAST revised Hepatic injury score.8
Management of paediatric abdominal trauma through the years: from non-operative management to aggressive surgery and back

During the last 100 years the management and approach to parenchymatous visceral injuries has fluctuated from surgical caution at the turn of the previous century as advocated by Beckman’s “intelligent conservatism” in the 1920s, followed by aggressive surgical intervention throughout most of the century, and finally a move back towards an initial non-operative approach.

Nowadays the selective, non-operative management (NOM) of blunt abdominal trauma in hemodynamically stable patients is well established and accepted as initial modus of treatment. However, as recently as 30 years ago this was not the case. The management of choice at that time was an aggressive approach of mandatory operative repair based on the concept that a significant injury will not heal spontaneously, and therefore, the earlier the surgical intervention the better. In retrospect, the often unnecessary and sometimes technically difficult surgery led to increased morbidity and mortality.

In the sixties, the recognition of Overwhelming Post Splenectomy Infections (OPSI) resulted in the wish for spleen preserving therapies, specifically for children. After splenectomy the lifetime risk for OPSI is around 5%, with a mortality rate of about 50%, which makes it a substantial risk specifically for children. This prompted pediatric surgeons to be as conservative as possible with injury to the spleen, and set the tone for the development of NOM.

The development of endovascular treatment options over the last decades, such as the Selective Arterial Embolization (SAE), have added a potential treatment modality that favours the outcome of non operative management in abdominal injury.

Since the seventies, a shift from operative to non-operative treatment for injury to the intra-abdominal solid organs has occurred. Pediatric surgeons were among the first to adopt this form of treatment. Even for the higher grades of injury in the various organs, high success rates with this policy of “watchful waiting” are achieved. In this regard it is interesting to note that there is a poor correlation of grades of injury and the need for surgical intervention. The success rate of NOM, when necessary assisted by SAE, can reach up to 95%, even for the higher grades of injury.

Gradually the success rate of NOM rose to the extent that guidelines for non-operative treatment of splenic and hepatic injuries were issued by the American Paediatric Surgical Association (APSA) in the year 2000. (Table 2)

These guidelines provide support to maximize patient safety and assure efficient, cost-effective utilization of resources and are based on injury grades using CT imaging. They
provide an algorithm for treatment, observation on ICU and in hospital, repeat of imaging and the period to minimise physical exercise.

**Challenges in diagnosing and treating blunt abdominal injury in children**

Treatment of abdominal injuries in hemodynamically stable children is supposedly based on grade of injury as diagnosed on CT imaging. Whether this corresponds with the actual clinical course is unknown. The difficulty of NOM is that no one knows exactly what is going on inside the abdomen; CT images are only an approximation of the reality. While we tend to treat children based on interpretation of these images, it is unknown whether there is a good agreement between radiologists and surgeons regarding the severity of injury as observed on CT. Also, while we tend to treat children based on interpretation of these CT images, it is well known that the most sensitive prognostic tool for success of NOM is repeated (abdominal) examination of the child by the same investigator. Another important observation is that intra-operative findings and CT-findings do not always match. Frequently a splenic or hepatic rupture is found on explorative laparotomy for concomitant injuries. Likewise the pancreatic duct can be transected where CT imaging had not even raised suspicion of injury. Sensitivity for perforation of a hollow viscus, which is besides hemodynamical instability the only absolute indication for laparotomy, is low. For duodenal injury e.g., sensitivity does not exceed 50%. The administration of oral contrast does not improve this.

Maybe even more important, CT has several major disadvantages. Besides the fact that CT scanning implies – in most hospitals – a time-consuming and potentially dangerous transport of the child from the safe and controlled environment of the shock room to a “doughnut of death” in which monitoring and acute interventions are much more cumbersome, CT itself carries the risks of radiation induced injury.

Ionising radiation such as in X-ray diagnostics brings on a lifetime risk of developing malignancies induced by the investigation. Specifically in children the radiation is known to possibly bring extra harm. For a given radiation dose, there is a difference in cancer risk from radiation exposure for children compared to adults for several reasons: tissues

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**Table 2: Treatment of liver injuries according to the APSA guidelines**

<table>
<thead>
<tr>
<th>Grade I injury</th>
<th>Grade II injury</th>
<th>Grade III injury</th>
<th>Grade IV injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU stay</td>
<td>none</td>
<td>none</td>
<td>1day</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Pre discharge imaging</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Post discharge imaging</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Activity restriction (weeks)</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
and organs that are growing and developing are more sensitive to radiation effects, an infant has a longer life expectancy in which to manifest the potential oncogenic effects of radiation, and finally the radiation exposure from a fixed set of CT parameters results in a dose that is higher for a child compared to an adult.

It is therefore of the utmost importance to adapt our evaluation algorithm to a safe evaluation as regards to detection of injuries that may need treatment but with minimal radiation exposure. Even while following the ‘As low as reasonably achievable’ (ALARA) principle, it is estimated that 1:1000 children might die as a result of a radiation induced tumor.\textsuperscript{28,29} Best is therefore to avoid radiation exposure completely. For abdominal injury in children, little is known about the diagnostic yield of CT scan in the light of radiation exposure.

To conclude, while non-operative management of children with intra-abdominal injury has proven to be a very effective treatment modality, many questions and challenges remain in the diagnostic workup and treatment of these children. Some of these will be addressed in this thesis.

In the first part of the thesis we will describe the current diagnostic work-up in children with suspected intra-abdominal injury in our center. We will investigate whether CT scan is a reliable tool for diagnosing intra-abdominal injury. Also we will describe the diagnostic yield of CT scan in relation to the risks associated with radiation exposure. In a separate chapter we will perform a similar analysis for repeat CT scans after referral to our center. Subsequently we will study the accuracy of a novel abdominal injury score for children and a novel trauma marker. Both are adjuncts to routine care, which might aid in the decision to obtain a CT scan. In the second part of the thesis we will investigate daily practice in our hospital for children with intra-abdominal injury, and compare our results with the literature. In subsequent chapters injury to the liver, spleen and pancreas will be discussed. In these analyses we will focus on the results of non-operative management and we will try to identify areas for further improvement in clinical management for these patients.
OUTLINE OF THE THESIS

A general introduction to pediatric trauma and a short outline of the thesis is provided in chapter 1.

Subsequently we will focus on the diagnostic process in children with suspected intra-abdominal injury. The American Pediatric Surgery Association has issued guidelines for the treatment of hemodynamically stable children with isolated injury to the liver or the spleen. These guidelines are based on the grading of injury on CT.

In chapter 2 the reliability of a CT based grading system of liver injury in pediatric abdominal trauma is investigated. To this end we determine the inter- and intra observer agreement for liver injury as graded following the Organ Injury Scale from the American Association for the Surgery of Trauma. Several specialists, including radiologists, paediatric surgeons, trauma surgeons and hepatobiliary surgeons all independently and repeatedly grade hepatic injury on a CT scan and inter- and intra-observer variation is computed.

In chapter 3 we investigate the additional radiation risk of abdominal CT and calculate the estimated lifetime risk for malignancy and additional mortality risk in the light of novel diagnostic findings that might or might not alter management. This way we will determine the diagnostic yield of CT scan in children with suspected intra-abdominal injury.

Since progressively more injured children are being referred to specialist centres and subsequently undergo a CT scan in both facilities, we set out to compute the extra radiation dose and associated risks of a repeated abdominal CT after transferral to our center. This is described in chapter 4, again in the light of novel diagnostic findings possibly altering management.

Combining readily available data into an abdominal injury score might also aid in preventing unnecessary diagnostic procedures such as CT scan. To this end we will retrospectively validate the Blunt Abdominal Trauma in Children score (BATiC) in a large cohort of patients in chapter 5.

In chapter 6 we investigate the kinetics of plasma Liver Fatty Acid Binding Protein (L-FABP) as a possible marker for intra-abdominal (hepatic) injury. In a pilot study (comprised of the first 50 patients of a large prospective trial into the development of biomarkers for abdominal injury and the development of the Systemic Inflammatory Response Syndrome and Multiple Organ Failure) we measured L-FABP in plasma obtained at three hour intervals from adult patients who were administered to the Shock Room with (suspicion of) severe trauma.
In the second part of this thesis we will investigate injury to the intra-abdominal parenchymatous organs. As described in chapter 7 we analyse liver injury. Main endpoints are the success rates of non-operative management (NOM) and late complications. Among others, trauma mechanism, age; divided in different age groups, treatment modalities and length of hospital and ICU stay are assessed.

Similar data are analysed for the children with splenic injury in our hospital, as described in chapter 8. This chapter describes the data for all pediatric patients with splenic injury, but also divides them into a multi-trauma and isolated splenic trauma group.

Paediatric pancreatic injury is an entity on its own and described in chapter 9. It is relatively uncommon, easily missed, and hard to diagnose even in the higher injury grades such as transsection of the pancreatic duct that sometimes call for early surgical treatment. Several issues on diagnostics regarding abdominal injury are raised.

Chapter 10 has been written as a discussion paper for Dutch physicians dealing with possible intra-abdominal injury in children. Chapter 11 more profoundly discusses the findings of these thesis and the conclusions we can draw. It also casts an eye on future perspectives. Chapter 12 provides a summary and discussion of the main conclusions in English and Chapter 13 in Dutch.
REFERENCES

Part 2
The diagnostic workup in children with suspected abdominal injury