Management of Benign Biliary Stenosis and Injury

A Comprehensive Guide

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Charles M. Vollmer Jr.
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Foreword

In 1920, about 35 years after the introduction of a new operation called cholecystectomy, William Eisendrath of Chicago in the journal we now call *The Journal of the American College of Surgeons* provided case summaries of every bile duct injury that had been reported in the literature up to that time. Already at that time benign biliary stricture, especially iatrogenic biliary stricture, was recognized as a serious problem and a technically challenging one. Throughout the twentieth century many famous surgical leaders including such illustrious names such as Lahey, Maingot, Couinaud, Bismuth, and Blumgart advanced our understanding of the management of benign biliary strictures. The introduction of laparoscopic surgery resulted in a large increase in biliary injuries and challenged us to understand, prevent, and treat this worsening surgical problem. With the advent of biliary endoscopy and interventional radiologic techniques on the biliary tract, new diagnostic and therapeutic options opened for the patient and greatly assisted the performance of surgical operations on the biliary tree.

As a profession we have come a long way in managing the important problems of the biliary tree discussed in this book, but equally we have a long way to go. Dixon, Vollmer, and May—two HPB surgeons and a biliary endoscopist who are well known for their expertise in this area—have produced an outstanding overview of where we are today. Each chapter on a specific topic is balanced by a counterpoint reflecting controversies that still exist. The elephant in the room is still iatrogenic biliary injury but inflammatory causes of benign biliary strictures such as PSC, cholangitis, and pseudotumors receive excellent coverage.

The reader will recognize that the list of authors reads like an international "who's who" of biliary surgery. Many of the authors have contributed seminal articles to this field in the past decade regarding classification, pathogenesis, diagnosis, and treatment of the various problems. American and Canadian authors are joined by experts from Latin America, Germany, and England. The book is an important contribution to our understanding of this field and will be a resource for all HPB

surgeons and of particular value to HPB fellows. It is hoped that it will need multiple editions due to rapid advances in the treatment of benign disease of the biliary tract. Bon voyage à travers les voies biliaires.

Saint Louis, MO, USA Steven M. Strasberg, F.A.C.S., F.R.C.S(C), F.R.C.S(Ed)

Preface

This book arose following a multidisciplinary session on benign biliary strictures that we co-moderated at a recent Digestive Disease Week/Society for Surgery of the Alimentary Tract (SSAT) meeting. As we discussed the issues surrounding benign biliary strictures and bile duct injuries, we realized that we could not do the topic justice in a short 2-h session—much less a full day event or even a conference. Despite the fact that the biliary system is a cornerstone of the gastrointestinal tract, not to mention a core element of general surgical training, when we tried to come up with a reference list to give to the audience, we were unable to deliver even a few sources that could provide reasonable coverage of this domain in a nuanced way. This book evolved from that inadequacy.

We are very proud to be able to provide you with this compilation, which delivers a diverse group of global thought leaders on these topics. We believe strongly that we have produced a singular text that covers the biliary system in a way that is readable for the novice and, for the expert, highlights areas of controversy. Each chapter is structured in a "point–counterpoint" motif. Each is penned by recognized authorities who offer opposing, sometimes complementary, viewpoints on these often controversial subjects. We believe this allows for a very nuanced discussion of each topic. We hope you enjoy the First Edition of this unique text as much as we have enjoyed crafting it for you.

The first chapter, *Biliary System Anatomy, Physiology, and Embryology,* is expertly written by Cecilia Ethun and Shishir Maithel from Emory University. This offering lays the foundation for the subsequent chapters by providing a comprehensive, but sharp, review of the basics of biliary tract anatomy and function. An important theme the authors emphasize is the biliary tract's tendency for variation. This will be of major importance for subsequent chapters that concentrate on the anatomic basis of biliary injury. The authors emphasize the importance of the embryologic derivation of the biliary system in an understandable style and discuss the salient elements of biliary physiology in refreshingly simple terms. This is content that each of your students should study before they enter the operating room with you. Moreover, we can attest that even the most seasoned of HPB experts has something to gain by reading this chapter.

The next section of the book addresses primary pathologies, mainly inflammatory and infectious, that affect the biliary system by invoking benign strictures. The first of these is *Primary Sclerosing Cholangitis*, and Debashis Haldar and Gideon Hirshfield from Birmingham, UK, offer an excellent overview of this frustrating disease. They note this to be the classic HPB manifestation of inflammatory bowel disease and lament its currently irreversible nature. They take us on a journey through histopathology, clinical presentation, diagnostics, and therapeutics of this condition. Management controversies are nicely summarized in a table. In his counterpoint piece, Keith Lindor of the Arizona State University points out the curiosity of demographic disparities in PSC incidence and then hones in on promising approaches that may improve the prognosis of this disease. Like the primary authors, he emphasizes the fact that the etiology is multifactorial and thus will require new management paradigms, such as concentration on the gut biome.

Biliary Manifestations of Chronic Pancreatitis are addressed beautifully by Olivier Strobel, Pietro Contin, and Markus Büchler from the Heidelberg University surgical group. They share their broad familiarity with this problem and emphasize the myriad therapeutic options, none of which are uniquely satisfying. Nonetheless, they suggest that surgical interventions are superior to endoscopic procedures for providing a durable solution. The biggest dilemma for surgeons is the decision between drainage alone and resection for dominant strictures, and the authors reenforce that the treatment of the biliary stricture needs to take into consideration the total manifestations of the disease (i.e., pain, insufficiencies). They offer the full platter of options available to the surgeon, with emphasis on the duodenum-preserving techniques they have promulgated. Furthermore, they touch upon how to manage recurrent strictures after initial endeavors fail. David Adams from the Medical University of South Carolina pens a masterful commentary on this piece, borne from his extensive personal experience with this problem. In it, he suggests a renaissance for the simplest of biliary bypass procedures—the choledocoduodenostomy. Like the authors, he underscores the value of optimal patient selection when choosing among the various therapeutic options.

We are privileged to have contributions from the most recognized authorities on *Autoimmune Pancreatitis.* Neil Sengupta and Sunil Sheth from Beth Israel Deaconess Medical Center/Harvard University describe the latest knowledge on this relatively modern clinical entity. Over the last 20 years, a sea change has occurred in clinical management of AIP from more aggressive surgical interventions to now primarily medical management with steroids. This evolution has been driven by the realization that biliary strictures in this circumstance are not necessarily malignant in nature, as was largely assumed previously because of clinical mimicry with pancreatic cancer. The authors provide us with the absolute latest understandings in pathogenesis, diagnostics, and clinical management, including the dilemma of refractory disease. In his commentary, Suresh Chari from The Mayo Clinic offers insight into the nuances of the IgG4-related diseases.

Primarily a disease of the Orient, *Recurrent Pyogenic Cholangitis* is also prevalent elsewhere in the world where patients of Asian descent live. One such concentration is Canada, and Jerome Laurence and Paul Greig provide us with an exhaustive

literature review, as well as their wisdom from treating this condition over the last three decades at the University of Toronto. They emphasize how successful management of this disease pivots on multidisciplinary care, where the interventional radiologist provides tremendous value. That being said, surgery is commonly required to treat the structural consequences of this inflammatory process, and surgical resection is often the most expeditious path forward. One of the world's foremost biliary surgeons, Henry Pitt, from Temple University in Philadelphia augments this fine chapter.

While this collection does not concentrate on malignant diseases, cancer of the biliary tree is, of course, a terrible diagnosis. Unfortunately (or is it fortunately?) benign conditions masquerade as cholangiocarcinoma. This conundrum of *Proximal Biliary Strictures Mimicking Hilar Cholangiocarcinoma* is adroitly presented by Kelly Nahum, Joshua Smith, and William Jarnagin from the Memorial Sloan Kettering Cancer Center. They note that a handful of rare, benign conditions contribute to proximal bile duct obstruction up to a quarter of the time, and they review the broad array of possibilities from Mirizzi's syndrome to tuberculosis. David Nagorney from The Mayo Clinic reflects on this vexing clinical problem. He emphasizes a practical approach to these patients and indicates how attention to basic clinical intuition, gleaned from a careful history and physical exam, can drive smart decisions. In the end, he rationalizes how a strategy of surgical resection is the most reasonable and prudent approach to this very challenging presentation.

In the next chapter *Traumatic Biliary Strictures*, Chad Ball from the University of Calgary, Canada, marks a shift in the book's content to iatrogenic injuries to the biliary system. Dr. Ball is uniquely qualified to author this particular piece—being fellowship trained in both Trauma and Critical Care, as well as HPB surgery. He provides a very practical "how-to" approach to a rare (0.5 % of traumatic laparotomies) but extremely challenging clinical event. While offering his complete tool set for these injuries, he emphasizes drainage approaches (particularly for patients in extremis) and dissuades against direct biliary ligation. One of the most seasoned trauma surgeons in the world, William Schwab from the University of Pennsylvania, provides a sage opinion piece. He, too, emphasizes the importance of damage control of the patient's overall condition in that these injuries rarely occur in isolation and usually involve significant, concurrent vascular and hepatic damage. He also advocates complex cases first be temporized, and then consideration for more complex definitive management be deferred, and furthermore endorses the involvement of HPB specialists at that juncture. The reader will enjoy the handful of pearls Dr. Schwab provides, which can only be delivered by someone who "has been there before."

Next, the book moves toward rich content on the problem of bile duct injury (BDI). From the time these problems were first recognized and reported, we have often wondered "How could this happen?" Lygia Stewart from the University of California at San Francisco addresses this in her outstanding chapter, *Perceptual Errors Leading to Bile Duct Injury During Laparoscopic Cholecystectomy.* Dr. Stewart uses abundant illustration to help us understand what our mind sees as we carry out laparoscopic cholecystectomy (LC). She introduces us to the field of

neurocognition and to phrases such as "visual perceptual illusion," "surgical sense making," "haptic perception," "human error analysis," and "framing." Former SAGES President Nathaniel Soper's opinion piece beautifully complements the primary chapter. In it, he offers practical tips to overcome the "error traps" that our mind may set. He emphasizes a systematic approach to safety during LC including developing the "critical view." The principles he preaches in this piece have not wavered in the two decades since he pioneered the operation.

The Heuristics and Psychology of Bile Duct Injuries by Francis Sutherland of the University of Calgary is, quite simply, a must-read. This builds on the more abstract notions offered in the previous chapter by Dr. Stewart to provide a framework of how to interpret the operative field during cholecystectomy. An apropos analogy would be that Dr. Sutherland gives us the insight for "slowing down the game" as many championship athletes are able to do when under pressure. We would encourage you to introduce this chapter to all your trainees who are learning LC. John Hunter from the Oregon Health Sciences University, another past-President of SAGES and the SSAT, urges you to develop a "strategy" to this operation. He also offers tools that might help you emerge when you get lost in the imagery during dissection.

Early in the progression of laparoscopic cholecystectomy (early 1990s), it was alarmingly evident that bile duct injury was on the rise. Once enough case reports had accrued, it became obvious that certain patterns of injury were occurring, and better understanding of the problem would benefit from some standardized nomenclature. Edmund Bartlett and Charles Vollmer from the University of Pennsylvania provide us with *The Classification and Injury Patterns of Iatrogenic Bile Duct Injury During Cholecystectomy.* In this chapter, they describe some of the important initial systems (Strasberg/Way) and review the now dizzying array of extensions. They emphasize the balance sought with these systems between utility and granularity and lament the poor association of these schemes with outcomes. Dirk Gouma, a globally recognized authority on this topic from the Academic Medical Center in Amsterdam, provides an astute commentary based on his experience. In it, he espouses the merits of the most modern, comprehensive, and flexible system—ATOM.

Legal Implications of Biliary Injury is a special contribution to the book. Steven Raper from the University of Pennsylvania is a savvy gastrointestinal surgeon who also holds a degree in law. He is uniquely qualified to provide insight to a very difficult problem that many general surgeons will likely encounter at least once in their career. Bile Duct Injuries are among the most litigious events in surgery, and Steve navigates us through the choppy waters that they bring. Specifically, he focuses on the process of informed consent and also cautions proper documentation habits for our operative reports. Keith Lillemoe, the Chairman of Surgery at the Massachusetts General Hospital, is a widely recognized expert in the management of biliary injury. His plain talk commentary provides practical advice on how one can defend against, or even avoid, malpractice claims. Importantly, he alerts us as to what really goes on in the courtroom. Due to the paucity of literature on this subject, this particular dyad is essential reading that you will be unable to find elsewhere.

The next few chapters focus specifically on the management of bile duct injuries when they occur. We have broken these chapters down into what we believe are the commonest scenarios that occur in the real word. Kicking this off is a chapter written by Jeff Barkun and Prosanto Chaudhury from McGill University. *Intraoperative Management of Bile Duct Injuries by a Non-biliary Surgeon* puts the reader in the operating room during a difficult cholecystectomy and discusses actual scenarios and how these can be best managed by a nonexpert in biliary surgery. It is extremely pragmatic and should be required reading for all general surgeons and trainees. Dr. Mark Callery from Harvard University provides the "counterpoint" to this and continues with a very practical discussion of what is a rare, but extremely anxiety provoking, scenario. This especially resonates in a time when conversion from laparoscopic to open cholecystectomy is not viewed by many new graduates as good option for the difficult cholecystectomy.

There is some debate and some variability in how bile duct injuries are approached when they are not identified at the index operation. To highlight the difference in how these might be approached, we have complied three separate chapters. *Management of Bile Duct Injuries Within the First Forty-Eight Hours* is written by John Christein and countered by Miguel Mercado—both are among the most experienced surgeons in the world with this problem. *Operative Repair of Common Bile Duct Injury* follows and is deftly authored by Dr. OJ Garden from Edinburgh (counterpoint by Dr. Javier Lendoire). These chapters walk the reader through all the different presentations and injury patterns and discuss how best to manage them. There is significant dispute and controversy surrounding these topics, which is nicely highlighted in the counterpoint pieces. The chapter *Non-operative Management of Bile Duct Injury During Laparoscopic Cholecystectomy* presents expert perspectives from both a therapeutic endoscopist (Guido Costamagna), as well as that of an interventional radiologist (Rich Shlansky-Goldberg), emphasizing the truly critical nature of multidisciplinary collaboration in the successful management of the variety of clinical presentations of benign biliary strictures and injuries.

As a result of the relatively common occurrence of isolated right-sided posterior sectoral duct injuries, and the debate about how best to manage this injury, we have a separate chapter on *Management of Isolated Sectoral Duct Injury* written by Dr. Michael House with the counterpoint covered by Dr. Reid Adams. This topic always raises debate: repair, simply ligation, Roux-en-Y hepaticojejunostomy reconstruction, or liver resection? Even for expert biliary surgeons, very few groups have amassed a significant series of these injuries. These experts walk us the through the possibilities and discuss the ideal management algorithm for this injury.

The chapters *Liver Resection for Bile Duct Injury* and *Liver Transplantation for Common Bile Duct Injury* written respectively by Drs. Michael McCall/Elijah Dixon and Alex Bressan/Will Chapman discuss the management of certain patients who progress down the treatment algorithm tree to the most severe and significant injuries. Both chapters provide succinct summaries of the worldwide literature on these topics and offer simple and practical approaches to the scenarios where these procedures potentially come into play in the treatment armamentarium.

The corresponding counterpoints written by Tim Pawlik and Al Hemming highlight how little we truly know about these patients because of the rare need to perform these unconventional procedures.

Finally the last two chapters *Biliary Strictures from Liver Transplantation* written by Shimul Shah (counterpoint by Dr. Kim Olthoff) and *Recurrent Biliary Strictures After Initial Biliary Reconstruction* authored by Eduardo De Santibanes from Argentina both discuss advanced reoperative hepatobiliary and transplantation surgery. These are both relatively rare scenarios—even for the expert HPB or transplant surgeon. Using an evidence-based approach, the authors have highlighted the important principles of management for these patients. These chapters will appeal to the expert biliary surgeon.

In this First Edition, we believe we have crafted a single reference book that covers benign biliary strictures and injury in their entirety, while doing justice to the areas of controversy. Large sections of this book apply to the general surgeon in training, the practicing general surgeon, and even the expert biliary surgeon. We wish to thank the fine authors for all the thought and effort that has gone into each chapter. Hopefully you, the reader, find this to be an invaluable reference over the course of your career.

Calgary, AB, Canada — Elijah Dixon
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Part I
Background

Chapter 1
Biliary System Anatomy, Physiology, and Embryology

Cecilia G. Ethun and Shishir K. Maithel

Overview

The biliary system is equally complex and fascinating. From inception, its development, structure, and function rely heavily on other organ systems, yet it maintains a degree of independence and unique properties found nowhere else in the body. When operating on the biliary tract, thorough knowledge of this organ system is of critical importance. Never is this more apparent than when faced with aberrance and injury. However, by strengthening our understanding of biliary embryology, anatomy, and physiology, we can better prepare and manage when things go awry.

Embryology

Overview

The embryologic development of the biliary tract is closely associated with, and largely dependent upon, that of the liver. To start, both are derived from embryonic endoderm. What follows is a series of intricate signaling pathways within and among these growing cell populations and their environment that, in turn, come to form the hepatobiliary system.

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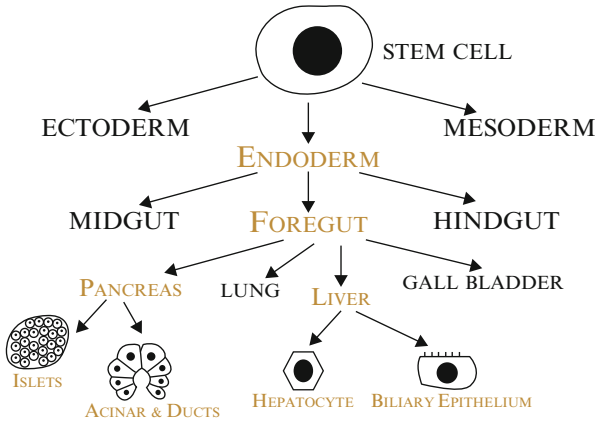

Fig. 1.1 Cell lineage schematic for hepatic, pancreatic, and biliary development from a multipotent progenitor stem cell. El-Gohary Y, Gittes GK. Embryologic development of the liver, biliary tract, and pancreas. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. 1. 5th ed. Philadelphia: Elsevier; 2012. Figure 1A.1. p. 19

Around the middle of the third week of gestation, the liver primordium appears as an endodermal outgrowth at the distal end of the foregut. The liver bud invades the surrounding mesenchyme of the septum transversum cranially and begins a period of rapid proliferation and branching, giving rise to liver parenchyma and the intrahepatic biliary tree. As the liver primordium grows caudally, the connection between the liver and the foregut narrows to form the bile duct. The gallbladder and cystic duct develop from a ventral outgrowth of the bile duct. As the duodenum rotates to the right and becomes C-shaped around the sixth week of gestation, the ventral pancreatic bud that had initially developed at the base of the liver bud swings posteriorly, taking with it the distal segment of the bile duct. The hepatoblasts eventually differentiate into hepatocytes and cholangiocytes, and by the twelfth week, bile produced in the liver begins draining down the newly formed ductal system [1] (Fig. 1.1).

Endodermal Patterning

Derived from the endodermal germ layer, the primitive gut tube is divided into the foregut, midgut, and hindgut. Within each of these domains are specialized regions. The fates of these regions are determined by the expression of specific transcription factors followed by a series of reciprocal interactions between the endoderm and surrounding mesoderm, known as *endodermal patterning*. This complex web of positive and negative signaling appears to be critical for the specialization of the anterior foregut endoderm for organs such as the liver and ventral pancreas, and posterior foregut endoderm for the intestine and dorsal pancreas [2, 3].

Hepatic Competence

Before hepatic specification can occur, the primitive foregut endoderm must first have the potential to adopt its hepatic fate. This inherent ability of the endoderm to begin the process of hepatogenesis, known as *hepatic competence*, is thought to be mediated through transcription factors, such as the HNF-3/fork head and GATA-4 transcription factor families. It is proposed that HNF-3 binding to DNA modulates the chromatin structure in such a way that allows for other binding regions essential for liver bud initiation to become available [4, 5]. One such region within the albumin enhancer is bound by the GATA-4 transcription factor, and is essential for its enhancer activity [6]. Through en vivo footprinting, it has been suggested that HNF-3 and GATA-4 function cooperatively to prime the foregut endoderm to move toward hepatic gene expression, thus making it competent for *hepatic specification* [5, 7].

Liver Specification

Although little is known about the in vivo pathways, several in vitro signaling pathways have been implicated in hepatic specification of the foregut. Hematopoietically expressed homeobox gene (*HHEX*) is one of the earliest foregut markers and is essential for normal liver development in mice [8, 9]. However, expression of *HHEX* alone does not ensure proper liver bud initiation. β-catenin is normally expressed in posterior endoderm and is integral in hindgut development. When activated in the anterior endoderm, β-catenin directly targets and downregulates *HHEX* expression, leading to inhibition of liver formation. Thus, both the expression of *HHEX* and the specific inhibition of β-catenin are necessary to facilitate liver bud development [10]. *FGF4* and *WNT* similarly promote hindgut formation in the posterior endoderm and are inhibited in the anterior endoderm to allow liver development [10]. *FGF2* and bone morphogenetic proteins (BMPs) from the cardiogenic mesoderm and septum transversum mesenchyme, respectively, have also been implicated in liver specification and development, though their exact function and interaction with the endoderm is not entirely understood [11, 12].

Hepatic Bud Morphogenesis and Growth

Once hepatic specification is complete, the anterior endoderm starts the process of hepatic bud morphogenesis (Fig. 1.2a). Mediated by the transcription factor HHEX, growth begins with the transformation of hepatoblasts from simple columnar cells to pseudostratified epithelium, resulting in thickening of the hepatic endoderm region [13]. The laminin- and collagen IV-rich basal membrane layer surrounding the hepatic endoderm then degrades, allowing hepatoblasts organized in cords to begin their invasion of the septum transversum mesenchyme (Fig. 1.2b). This degradation of the basal lamina and subsequent migration of hepatoblasts is thought to

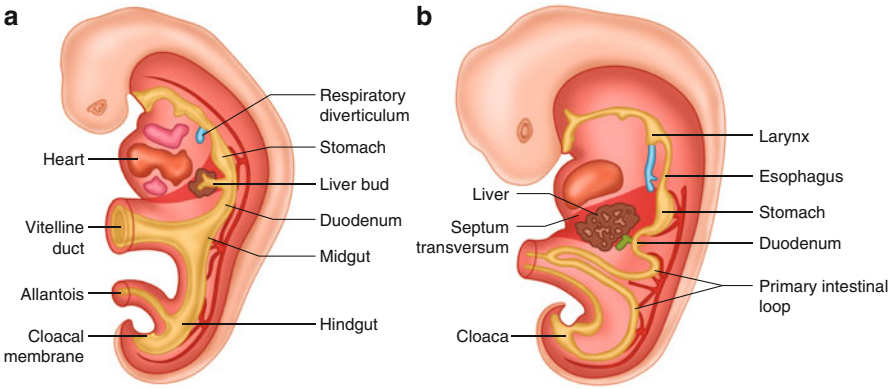

Fig. 1.2 (**a**) A 3-mm embryo (~25 days) showing the primitive gastrointestinal tract and formation of the liver bud. The bud is formed by endoderm lining the foregut. (**b**) A 5-mm embryo (~32 days). Epithelial liver cords penetrate the mesenchyme of the septum transversum. Sadler TW. Langman's Medical Embryology. 11th ed. Philadelphia: Lippincott, Williams & Wilkins; 2010. Figure 14.14. p. 217

be controlled by the transcription factors PROX1 (prospero-related homeobox) and ONECUT1 and -2 [14, 15]. In addition to transcription factors, the extracellular matrix environment and its interaction with hepatoblasts have also been shown to play an important role in this process. These include extracellular matrix remodeling enzymes (matrix metalloproteinases) as well as extracellular matrix protein receptors (β1-integrins) [16, 17].

As liver development within the septum transversum continues, epithelial-mesenchymal interactions, regulated by several growth factors and signals, remain critical for proper organogenesis. One such factor is hepatocyte growth factor (Hgf), which is produced by the mesenchymal cells lining the sinusoids and interacts with hepatocytes via the c-Met tyrosine kinase receptor. Mutations in Hgf have been shown to cause hepatocyte apoptosis, leading to severe liver hypoplasia [18]. Mutations in *HLX* homeobox gene and *BMP4*, which are expressed in septum transversum mesenchyme, and SMAD2 and -3 proteins of the TGF-β signaling pathway similarly result in severe liver hypoplasia [11, 19, 20].

Biliary Morphogenesis

Around the fifth week of gestation, morphogenesis of the biliary tract begins. This process can be broken down into five distinct steps based on observed histology and immunohistochemistry. First, hepatoblasts near the portal mesenchyme express an overabundance of biliary-specific genes, signaling their fate as biliary epithelium.

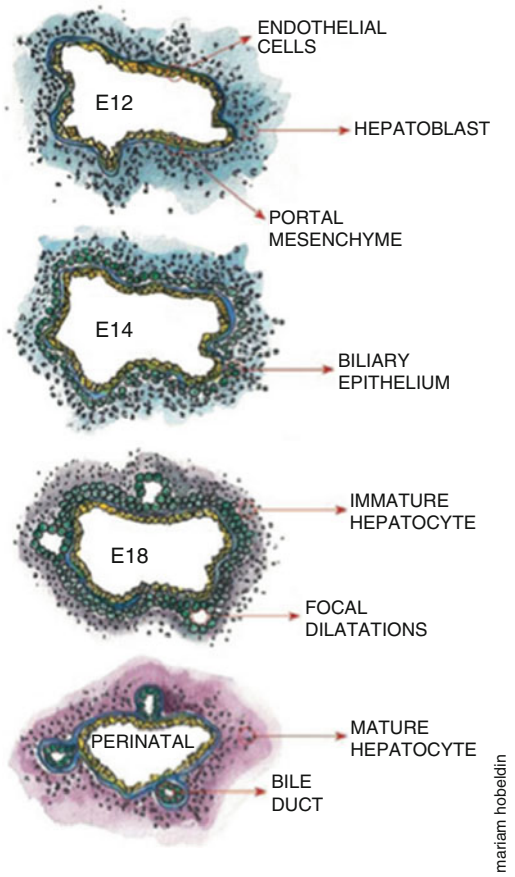

Fig. 1.3 Overview of intrahepatic bile duct formation around the portal vein. Hepatoblasts in the portal mesenchyme vicinity begin to acquire the biliary epithelial cell marker (KRT19) and downregulate hepatic genes, first forming a single layer, then a bilayer with focal dilations that eventually form the intrahepatic bile ducts. The rest of the bilayer regresses. El-Gohary Y, Gittes GK. Embryologic development of the liver, biliary tract, and pancreas. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. 1. 5th ed. Philadelphia: Elsevier; 2012. Figure 1A.5. p. 24

In the second step, these biliary precursor cells form a single layer around the portal mesenchyme, known as the ductal plate, followed by the formation of a second layer in the third step. The fourth step is marked by significant remodeling of the ductal plate, in which focal dilatations form between the two cell layers giving rise to the bile ducts, while those cells not involved in duct formation regress. The final step begins after birth and involves the incorporation of the bile ducts into the portal mesenchyme [21] (Fig. 1.3).

Hepatoblast Differentiation

While the origin of the biliary ductal system has been subject to much debate, the prevailing theory is that biliary epithelium stems from biopotential hepatoblasts capable of developing into either hepatocytes or cholangiocytes [22] (Fig. 1.1). This is supported largely by the observation that nearly all early hepatoblasts express markers for both hepatocytes (*ALB*) and biliary epithelial cells (*KRT19*) [23]. Thus,

as hepatoblasts differentiate, their expression of these genes varies depending on their fate, such that biliary epithelial cells upregulate biliary-specific *KRT19* while downregulating liver-specific genes. This theory of biopotential progenitor cells is further supported by transplantation studies, in which fetal liver fragments transplanted before the development of intrahepatic bile ducts into the testes of syngeneic animals still gave rise to both hepatocytes and normal bile ducts [24].

Biliary Epithelial Cells and Formation of the Ductal Plate

The exact mechanisms by which hepatoblasts differentiate into biliary epithelial cells are not well understood, though several factors have been implicated. The ONECUT protein hepatocyte nuclear factor (HNF)-6 has been identified as the first transcription factor required for the initiation of biliary epithelial cell differentiation and is additionally thought to confine biliary differentiation to the areas surrounding the portal mesenchyme and restrict the number of cells involved [21, 25]. Normally expressed in the biliary epithelial cells of the intrahepatic bile ducts, primordial gallbladder, extrahepatic bile ducts, and in hepatoblasts, *HNF6*−/− embryo develops severe biliary anomalies, characterized by an absent gallbladder, an enlarged structure connecting the liver with the gallbladder in place of the extrahepatic bile duct, and cholestasis due to large intrahepatic cystic formations. These abnormal cysts are similar to those seen in Caroli disease, though no direct correlation has been identified [25].

Interactions between cells and the surrounding mesenchyme are also thought to be important for biliary epithelial cell differentiation [21]. This role of the mesenchyme can be demonstrated by examining FOXF1, a transcription factor found in gallbladder mesenchyme. *FOXF1*+/− mice were found to have significant structural abnormalities of the gallbladder, a reduced mesenchyme, an absent biliary epithelial cell layer, and deficient external smooth muscle. Interestingly, because it is not found in intrahepatic biliary duct mesenchyme, *FOXF1*+/− mice were spared from intrahepatic ductal abnormalities [26]. Components of the extracellular matrix of the portal mesenchyme, namely laminin, fibronectin, and collagen I and IV, are also implicated in biliary cell differentiation, as are specialized laminin receptors composed of biliary-specific integrin heterodimers found exclusively on ductal plate cells [27–31].

Ductal Plate Remodeling

Remodeling of the ductal plate occurs through the formation of focal dilatations in the ductal bilayer surrounding the portal vein (Fig. 1.3). Those cells not involved in bile duct formation regress through apoptosis [32]. Though this process of remodeling is not entirely understood, cell-cell and cell-matrix interactions, as well as soluble factors, are thought to play a role. The balance between β-catenin, whose expression increases during remodeling, and E-cadherin, whose expression decreases, is one example of a cell-cell interaction that may be necessary to control

the remodeling phase of the ductal plate [33]. Tenascin, a component of the extracellular matrix found specifically at the interface between the mesenchyme and the ductal plate cells of migrating tubules and hilar ducts, but not peripheral ones, is thought to contribute to duct morphogenesis through time- and site-specific cell-matrix interactions [21, 29].

Biliary Tubulogenesis

Once ductal plate remodeling is underway, biliary tubulogenesis begins via cholangiocyte proliferation. There is some evidence in in vitro studies that suggests soluble factors may drive biliary tubule formation, as demonstrated when co-cultured biliary epithelial cells and hepatocytes induced duct morphogenesis, leading to well-formed, luminal bile ducts. This phenomenon was then reproduced when new biliary epithelial cells were grown in the conditioned, previously co-cultured medium [34]. Furthermore, studies focusing on biliary inflammatory processes and oncogenesis have shown that certain factors, such as insulin-like growth factor-1 (IGF-1), interleukin-6 (IL-6), and vascular endothelial growth factor (VEGF), may stimulate cholangiocyte proliferation [35, 36]. Their role in normal human fetal tubulogenesis, however, is unclear.

Extrahepatic Biliary Tract

Little is known about the morphogenesis of the extrahepatic biliary tract. It is believed that prior to expansion, the liver primordium develops into two portions: the cranial, which will invade the septum transversum mesenchyme to become the liver parenchyma and intrahepatic bile ducts, and the caudal portion, which will become the extrahepatic bile duct [22]. However, neither the distinction between the cranial and caudal portions nor their degree of interaction or overlap is well understood. Still, observational studies have shown that mice deficient in pancreatic and duodenal homeobox-1 (*PDX1*), *HNF6*, *HNF1β*, or *FOXF1*, demonstrate significant gallbladder and common bile duct malformations, suggesting their role in the development of the extrahepatic biliary system [25, 26, 37, 38].

Anatomy

Overview

The biliary tract and its supporting cast of arteries, veins, lymphatics, and nerves are highly anatomically variable, with aberrant biliary anatomy seen in roughly 30–40 % of patients and in up to two-thirds when vascular variations are considered [39–41]. Surgery involving the biliary tract requires good exposure and meticulous

dissection, and injury to the tract and its surrounding structures can be devastating. Thus, detailed knowledge of biliary anatomy, including the common variants and anomalies, is essential to operate safely and successfully on this organ system.

Intrahepatic Biliary Anatomy

The anatomy of the intrahepatic bile ducts is closely associated with that of the liver. The segmental anatomy of the liver is determined by the portal venous system, as it bifurcates at the hilum and branches within the liver parenchyma. Based on Couinaud's classification, this includes segment I, which is the caudate lobe, segments II, III, and IV, which comprise the left hemiliver, and segments V, VI, VII, and VIII, which comprise the right hemiliver [42, 43]. Running roughly parallel with the portal veins are the corresponding hepatic arteries and bile ducts, which together form the portal triads. Smaller intrahepatic duct tributaries drain the hepatic segments and converge to create the left and right hepatic ducts within their respective hemilivers.

The left hepatic duct drains the left liver, and is composed of ducts draining segments II, III, and IV. The duct draining segment III is relatively large and is joined by a smaller segment II duct, whose course runs obliquely toward the porta hepatis. In the vast majority of patients, their union is found behind the left portal vein at, or slightly left of, the umbilical fissure, although in 16 % it may be found to the right [44]. The segment IV duct, comprised of tributaries from IVa (superior) and IVb (inferior), then joins to form the left hepatic duct, as it courses at the base of segment IV just superior and posterior to the left branch of the portal vein (Fig. 1.4). This classic distribution of the left intrahepatic biliary ductal system, however, exists in only 60–67 % of patients, with variations characterized by the insertion of the segment IV duct [44, 45]. The most common variant is the insertion of the segment IV duct into segment III, prior to its union with the duct from segment II, which is seen in roughly 25 % of patients. In 3–10 %, the tributaries from segments IVa and IVb insert independently, and in 2 % the duct from segment IV joins the common hepatic duct [44] (Fig. 1.5d).

The right hepatic duct drains the right liver and arises from the union of two main sectoral ducts—the right anterior and right posterior—each accompanied by their corresponding portal venous pedicles. Taking a nearly horizontal course, the right posterior sectoral duct is formed by the confluence of the ducts draining segments VI and VII. The shorter and more vertical right anterior sectoral duct is formed by the ducts of segments V and VIII. Variations in segmental drainage of the right intrahepatic ductal system are more common than in the left and primarily involve aberrant ducts from segments VIII (20 %), VI (14 %), and V (9 %) (Fig. 1.5a–c). As it approaches the hilum, the right posterior sectoral duct wraps around superiorly to the right anterior pedicle and drains into the right anterior sectoral duct just above the right branch of the portal vein [44]. However, roughly 20 % of individuals have a right posterior duct that drains inferiorly to the right anterior pedicle, and up to 43 % have entirely independent drainage of the right anterior and right posterior sec-

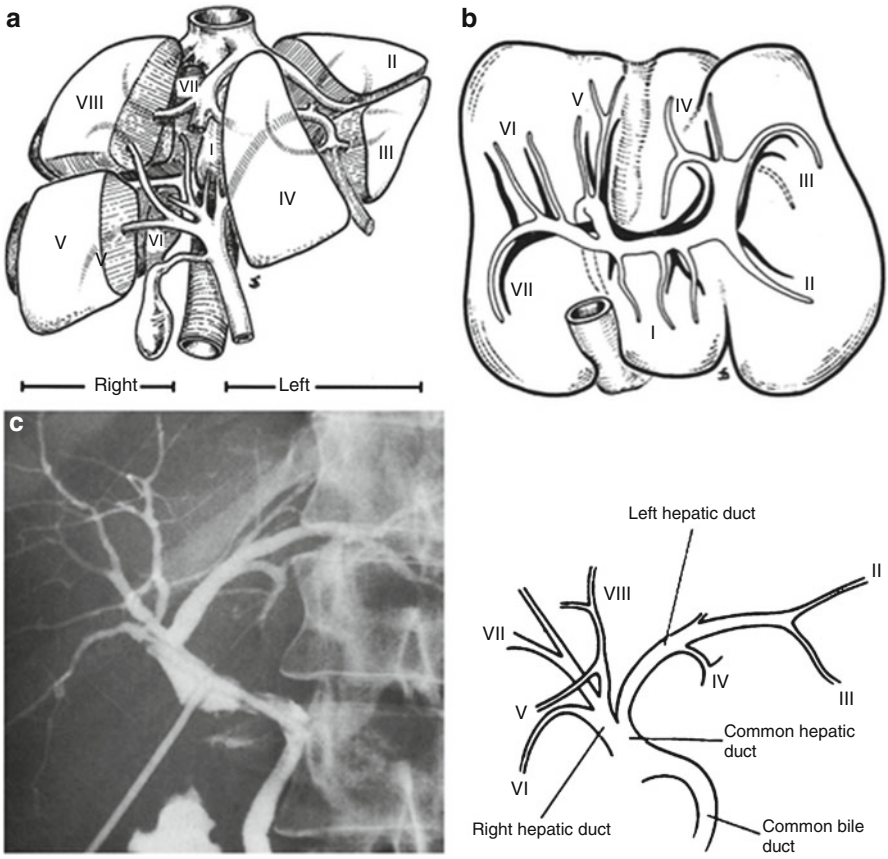

Fig. 1.4 (**a**) Biliary drainage of the two functional hemilivers. Note the position of the right anterior and right posterior sectors. The caudate lobe drains into the right and left ductal system. (**b**) Inferior aspect of the liver. The biliary tract is represented in *black*, and the portal branches are represented in *white*. Note the biliary drainage of segment IV (segment VIII is not represented because of its cephalad location). (**c**) T-tube cholangiogram shows the most common arrangement of hepatic ducts. Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver, biliary tract, and pancreas. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. 1. 5th ed. Philadelphia: Elsevier; 2012. Figure 1B.15. p. 39

toral ducts, which are seen in a variety of extrahepatic configurations, without a common right hepatic duct [45, 46].

The caudate lobe (segment I) has its own biliary drainage and can be divided into three parts—right and left portions, and a caudate process. In 44 % of cases, three separate ducts drain these three parts, while in 26 % the right portion and caudate process share a common duct. In the vast majority of individuals (78 %), the ductal tributaries from the caudate lobe drain into both the left and right hepatic ducts, although exclusive drainage into either the left (15 %) or the right (7 %) hepatic ductal system does occur [45].

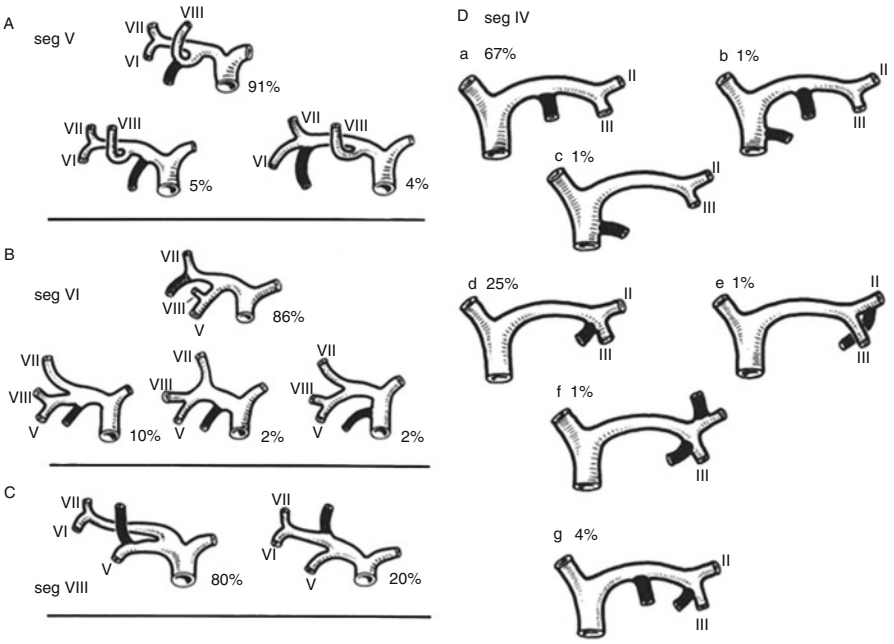

Fig. 1.5 Sketch shows the main variations of the intrahepatic ductal system. (**a**) Variations of segment V. (**b**). Variations of segment VI. (**c**) Variations of segment VIII. (**d**) Variations of segment IV. There is no variation of drainage of segments II, III, and VII. Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver, biliary tract, and pancreas. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. 1. 5th ed. Philadelphia: Elsevier; 2012. Figure 1B.26. p. 45

Extrahepatic Biliary Anatomy

The extrahepatic biliary system is represented by the extrahepatic segments of the left and right hepatic ducts, the biliary confluence, the common hepatic duct, the gallbladder and cystic duct, and the common bile duct.

Biliary Confluence

The right hepatic duct is characteristically short, measuring 0.9 cm, on average. In contrast, the left hepatic duct is typically 2.5 cm, though ranges from 2 to 5 cm [46]. Crossing anteriorly to their respective portal veins, the extrahepatic left and right ducts join at the hepatic ductal confluence anterior to the origin of the right branch of the portal vein within the liver hilum. Variations of the ductal confluence are common and are reported in nearly half of individuals (Fig. 1.6). Apart from the typical biliary confluence, the next most frequent configuration is a right anterior sectoral duct inserting directly into the common hepatic duct, as reported in 16 % of

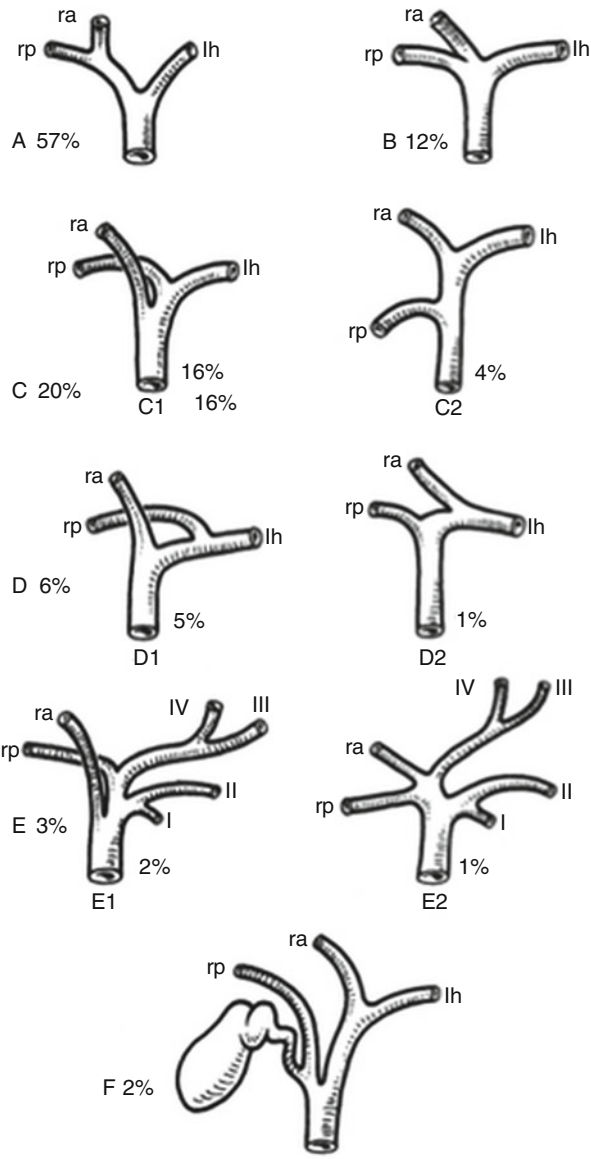

Fig. 1.6 Main variations of the hepatic duct confluence. (**a**) Typical anatomy of the confluence. (**b**) Triple confluence. (**c**) Ectopic drainage of a right sectoral duct into the common hepatic duct. (**d**) Ectopic drainage of a right sectoral duct into the left hepatic ductal system. (**e**) Absence of the hepatic duct confluence. (**f**) Absence of right hepatic duct and ectopic drainage of the right posterior duct into the cystic duct. *ra* right anterior, *rp* right posterior, *lh* left hepatic. Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver, biliary tract, and pancreas. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. 1. 5th ed. Philadelphia: Elsevier; 2012. Figure 1B.25. p. 44

cases. In 12 %, a trifurcation involving the right anterior, right posterior, and left hepatic ducts is seen [43, 44]. In these cases, the right posterior sectoral duct is three times more likely to be superior to the right anterior duct [44]. Ectopic drainage of the right posterior sectoral duct is seen in 11 % of individuals, with 5 % draining into the left hepatic duct, 4 % into the common hepatic duct, and 2 % into the cystic duct, a potentially dangerous anatomical variation should it not be properly identified during surgery of the gallbladder [43].

The ductal confluence and its corresponding vascular elements are enclosed in a sheath of connective tissue, known as the *hilar plate*, which is continuous with the hepatoduodenal ligament and fuses with Glisson's capsule on the posterior aspect of the quadrate lobe (segment IVb). By lifting up the quadrate lobe and incising the glissonian capsule at its junction with the hilar plate, good exposure of the hilar structures can be achieved, a technique known as *lowering of the hilar plate*. This is of particular importance when access to the left hepatic duct is required and, because the plane is largely devoid of vascular interpositions, it is relatively safe [42].

Common Bile Duct, Sphincter of Oddi, and Ampulla of Vater

The extrahepatic bile ducts contain columnar epithelium surrounded by a lamina propria rich in collagen and elastin fibers, and a layer of connective tissue. Muscle fibers are sparse and scattered, though a more developed muscle layer is seen distally as the bile duct enters the pancreas. The *common hepatic* duct begins at the biliary confluence and courses downward, anterior to the portal vein, at the free edge of the lesser omentum. After 2–3 cm, it is met by the cystic duct, at which point it becomes the *common bile* duct.

Approximately 8 cm in length with a normal diameter ranging from 4 to 9 mm, the common bile duct can be divided into three anatomic segments—supraduodenal, retroduodenal, and intrapancreatic. Like the common hepatic duct, the supraduodenal segment of the common bile duct runs at the free edge of the lesser omentum in the hepatoduodenal ligament, anterior to the portal vein and lateral to the hepatic artery. The retroduodenal segment passes posterior to the first portion of the duodenum and sits anterior to the inferior vena cava and lateral to the portal vein. The intrapancreatic portion lies on the posterior aspect of the pancreas within a tunnel or groove, where it is joined inferiorly by the pancreatic duct. Together they enter the second portion of the duodenum at an oblique angle, pass through the sphincter of Oddi, and finally terminate at the ampulla of Vater within the duodenal lumen [46].

The relationship between the common bile duct, the pancreatic duct, and their opening at the duodenal papilla is variable and occurs in three ways. Most often (60 %), the bile duct and the pancreatic duct together form a common duct, 1–8 mm in length. In 38 % of cases, however, a "double-barreled" opening is seen at the apex of the papilla. In these instances, the opening of the pancreatic duct is always inferior and anterior to that of the bile duct. Rarely (2 %), the two ducts have two separate openings in the duodenum [47, 48]. In the 5–10 % of individuals who have pancreas divisum (nonunion of the ventral and dorsal pancreatic buds), the ventral pancreatic duct joins the common bile duct and empties through the major papilla; the dorsal pancreatic duct empties through an accessory tract, the minor papilla [1]. In 75 % of individuals, the papilla is found on the posterior-medial aspect of the proximal to mid second portion of the duodenum. In 25 %, however, it is found lower, occasionally implanting in the third portion of the duodenum just right of the superior mesenteric artery [47].

The sphincter of Oddi is approximately 6 mm in length and is composed of thick bundles of circular, semicircular, and longitudinal muscle fibers, with numerous glands interspersed throughout. It exists separately from the surrounding muscle of the duodenum, from which it is distinguished by a plane known as the *duodenal window* [49]. Muscle fibers from the duodenum traverse the duodenal window and tether the sphincter of Oddi to the wall of the duodenum. Weak points in these fibers, particularly at the inferior aspect of the duodenal window, are susceptible to mucosal hernias. These diverticula may lead to sphincter of Oddi dysfunction and are suggested to play a role in some obstructive, inflammatory, and infectious processes of the pancreaticobiliary system [50, 51].

Gallbladder and Cystic Duct

The gallbladder is a pear-shaped reservoir that lies within the cystic fossa on the undersurface of the liver at the junction of segment V and IVb. An extension of the hilar plate, the *cystic plate* is a sheath of connective tissue fused with the underlying glissonian capsule that separates the gallbladder from the liver parenchyma. The gallbladder is typically 7–10 cm in length and 2.5–3.5 cm in width, although its size may vary considerably in fasting and post-prandial states, and in certain pathologic conditions. The gallbladder consists of a fundus, body, infundibulum, and neck, though these divisions are relatively arbitrary and imprecise. The tip of the fundus usually extends up to, or beyond, the free edge of the liver and is closely adherent to the cystic plate. The body of the gallbladder rests on the first and second portion of the duodenum and occupies the majority of the gallbladder fossa within the liver. The angled portion of the inferior body as it enters the neck is called the infundibulum, though this term is omitted in many classifications. When this portion is dilated, either as a normal anatomic variant or as sequela of chronic inflammation, the infundibulum produces an asymmetric bulge, known as a *Hartmann pouch* (Fig. 1.7b). It is important to note that the presence of this pouch may obscure the common hepatic duct, posing a real danger during cholecystectomy. If the pouch is large enough, the cystic duct may actually appear to enter the gallbladder mid-body, rather than at its apex, as is traditionally seen [52].

The cystic duct arises from the neck of the gallbladder and, coursing downward, joins the common hepatic duct at an acute angle to form the common bile duct. Its mucosa is arranged in spiral folds, referred to as the *valves of Heister*, although they have no known function. The length of the cystic duct depends on its point of union with the common hepatic duct, averaging 2–4 cm. Its luminal diameter usually measures 1–3 mm [42].

Many anomalies of the gallbladder and cystic duct have been described and vary in their incidence and clinical significance. In general, anomalies of the gallbladder can be divided into three groups based on formation, number, and position. Though of no pathological significance, a phrygian cap deformity is the most common anomaly of the gallbladder, seen in up to 18 % of individuals, and is formed by an

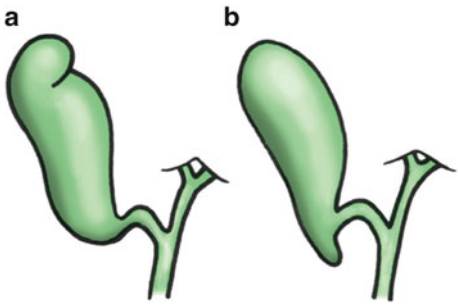

Fig. 1.7 (**a**) Phrygian cap deformity. (**b**) Hartmann pouch of the infundibulum. Gray SW, Skandalakis JE: Embryology for surgeons. Philadelphia: Saunders, 1972. p. 254

infolding or cleft at the base of the fundus [53] (Fig. 1.7a). Bilobar, hourglass, diverticular, and septated gallbladders have also been described [54–56] (Fig. 1.8b, c).

In approximately 1 in 4000 persons, a duplicated gallbladder may be seen (Fig. 1.8a). Existing and functioning as two separate cavities, each gallbladder may either have its own cystic duct that empties independently into the extrahepatic biliary tree, or they may merge into a common cystic duct before emptying into the common bile duct [57]. Although rare, agenesis of the gallbladder is also described, and may be seen in isolation or less frequently with other, often fatal, congenital anomalies. Despite an absent gallbladder, up to 50 % of these patients develop symptoms similar to biliary colic, though the cause is unclear [58].

Finally, anomalies of the position of the gallbladder can be seen, which most often include an intrahepatic, floating, or left-sided gallbladder. Intrahepatic gallbladders may be either partially or completely embedded within the liver parenchyma and should be suspected if ultrasound or cholecystogram reveals an unusually high gallbladder. Associated with gallstones in approximately 60 % of adults, these gallbladders may be challenging to remove during cholecystectomy. A floating gallbladder is a rare finding in which the gallbladder is completely surrounded by peritoneum and, rather than being tightly adherent, is freely suspended from the cystic fossa on the undersurface of the liver by a pedicle. This attachment may course the entire length of the gallbladder or involve only the cystic duct, leaving the gallbladder at risk for torsion and infarct [59]. Most commonly found on the undersurface of the left liver, left-sided gallbladders may be seen in isolation or in association with situs inversus [60].

Several anomalies of the cystic duct exist and primarily involve variations in length, course, and insertion into the common hepatic duct (Fig. 1.8d, e). An angular union between the cystic duct and common hepatic duct is most common, found in 75 % of individuals. In 15–20 %, the cystic duct may run parallel to the common hepatic duct for a variable distance before joining. In these cases, both ducts are encased in a sheath of connective tissue and care must be taken during dissection to avoid damage to either structure. In approximately 8 % of individuals, the cystic duct may spiral around the common hepatic duct, forming a left-sided union.

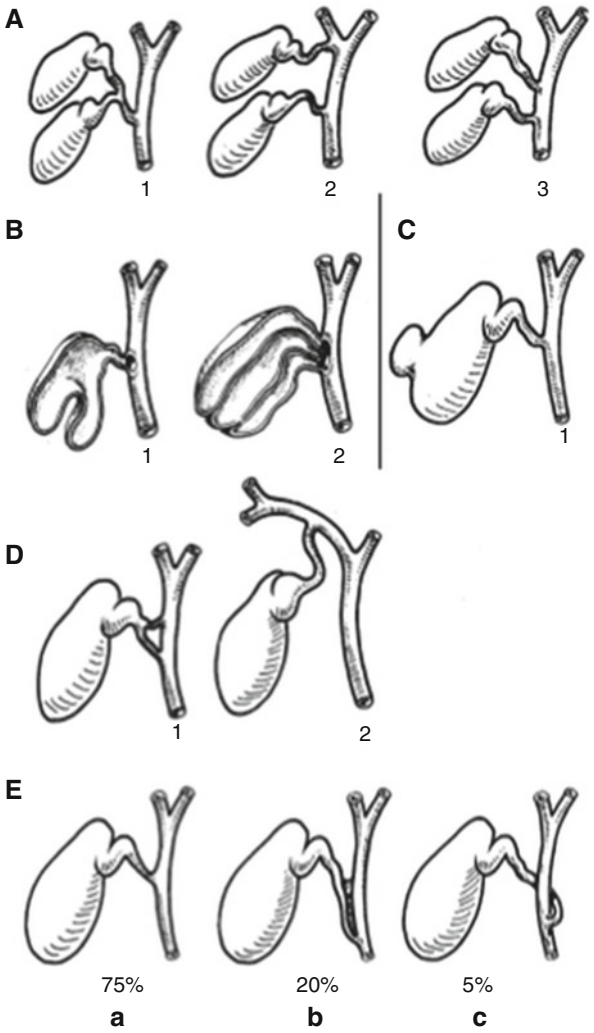

Fig. 1.8 Main variations in gallbladder and cystic duct anatomy: (**a**) Duplicated gallbladder. (**b**) Septum of the gallbladder. (**c**) Diverticulum of the gallbladder. (**d**) Variations in cystic ductal anatomy. (**e**) Different types of union of the cystic duct and common hepatic duct: angular union (*a*), parallel union (*b*), spiral union (*c*). Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver, biliary tract, and pancreas. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. 1. 5th ed. Philadelphia: Elsevier; 2012. Figure 1B.28. p. 46

Rarely, the cystic duct may insert into the right hepatic duct or form a trifurcation with the right and left hepatic ducts. In these situations, the right hepatic duct may easily be mistaken for the cystic duct and inadvertently ligated or divided, thus, underscoring the importance of adequate understanding and identification of these structures [61, 62].

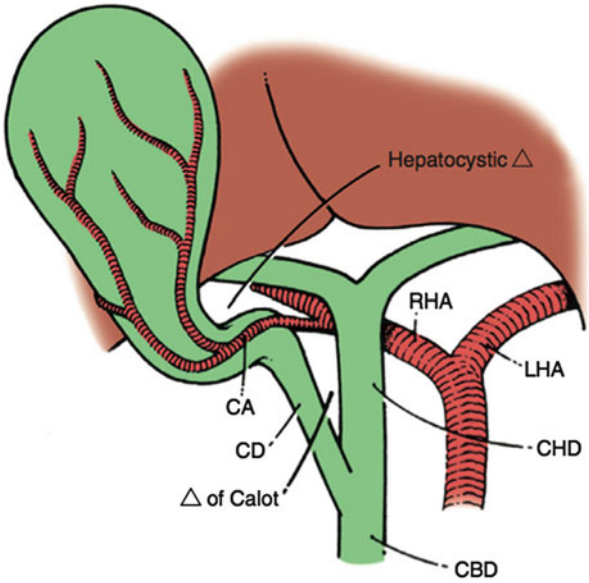

Fig. 1.9 The triangle (Δ) of Calot and the hepatocystic triangle. The upper boundary of the triangle of Calot is the cystic artery (CA), while that of the hepatocystic triangle is the inferior margin of the liver. *CBD* common bile duct, *CD* cystic duct, *CHD* common hepatic duct, *LHA* left hepatic artery, *RHA* right hepatic artery. Skandalakis JE, Gray SW, Rowe JS Jr: Biliary tract. In Skandalakis JE, Gray SW, editors: Anatomical complications in general surgery. New York, McGraw-Hill; 1983. p. 31

Triangle of Calot

The *triangle of Calot* was originally described in 1891 as a triangular anatomic region formed by the cystic artery superiorly, the cystic duct laterally, and the common hepatic duct medially. In the commonly accepted definition of this triangle, also known as the *hepatocystic triangle*, the inferior surface of the right lobe of the liver constitutes the upper border, rather than the cystic artery [63] (Fig. 1.9). Thorough anatomical knowledge of the triangle is of key significance, as several important structures pass through the area and must be identified when dissecting this region during cholecystectomy. The cystic artery is nearly always found within the triangle of Calot (96 %), and in 80 % of individuals its origin from either a normal or aberrant right hepatic artery is found within the triangle. The right hepatic artery passes posterior to the common hepatic duct in 85 % of individuals, as it ascends to the liver through the triangle of Calot; in 15 % it passes anterior to the common hepatic duct. When originating from the superior mesenteric artery (15 %), a replaced or accessory right hepatic artery may be found within the medial aspect of Calot's triangle. Aberrant hepatic ducts may also be found within the triangle, before joining the cystic or common hepatic duct [64].

Vasculature of the Biliary System

Bile Duct Blood Supply

The arterial blood supply to the right and left hepatic ducts, the biliary confluence, and the upper portion of the common hepatic duct comes from the surrounding left and right hepatic arteries and the cystic artery, forming a rich network on the surface of the ducts. The blood supply to the supraduodenal bile duct is mostly axial and is made up of an average of eight small arteries, with the majority arising from the superior pancreaticoduodenal artery, the right hepatic artery, the cystic artery, the gastroduodenal artery, and the retroduodenal artery. The most important of these ductal arteries run parallel along the lateral borders of the duct and are known as the *3 o'clock* and *9 o'clock arteries* (Fig. 1.10). Roughly 60 % of the blood supply to the supraduodenal bile duct originates inferiorly from the gastroduodenal, retroduodenal, and superior pancreaticoduodenal arteries. Conversely, 38 % of the blood supply originates superiorly from the right hepatic and cystic arteries. Only 2 % of the blood supply to the supraduodenal bile duct is nonaxial, arising directly from the proper hepatic artery as it courses within the hepatoduodenal ligament, parallel and

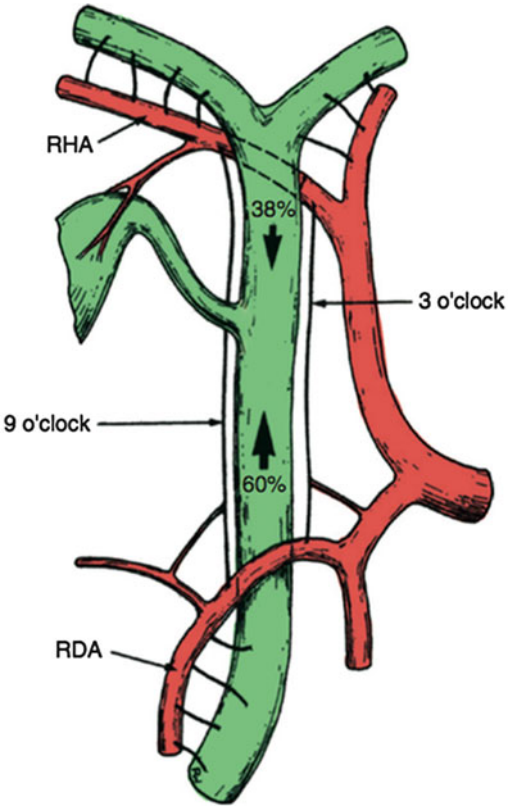

Fig. 1.10 Distribution of arterial blood supply to the extrahepatic biliary tree. *RDA* retroduodenal artery, *RHA* right hepatic artery. Terblanche J, Allison HF, Northover JMA. An ischemic basis for biliary strictures. Surgery. 1983; 94(1):56

to the left of the common bile duct. The retroduodenal and intrapancreatic portions of the common bile duct are supplied by the retroduodenal and pancreaticoduodenal arteries [65].

The venous drainage of the hilar hepatic ducts and the hepatic surface of the gallbladder occurs through small vessels that empty directly into branches of the surrounding hepatic veins within the liver. The veins draining the main bile duct run on either side of the duct as satellites of their corresponding arteries and drain into the liver separate from the portal vein, while venous drainage of the lower part of the bile duct runs directly into the portal vein [42].

Cystic Artery

The cystic artery usually arises as a solitary branch from the right hepatic artery within the triangle of Calot. The lymph node of Calot often lies just superficial to the cystic artery within the triangle and may serve as a guide to easily identify the artery. Running parallel and just medial to the cystic duct, the cystic artery supplies the duct with one or more small arterial branches. As it approaches the gallbladder, the cystic artery divides into a superficial branch, which runs along the anterior surface of the gallbladder, and a deep branch, which passes behind the gallbladder in the cystic fossa.

Occasionally, the cystic artery may arise from the common hepatic, left hepatic, gastroduodenal, or superior mesenteric arteries (Fig. 1.11). If the cystic artery arises from the proximal right hepatic artery or from the common hepatic artery, it often lies in close proximity to the hepatic duct, putting the latter at risk for injury during dissection [61, 66]. In the 20 % of patients whose cystic artery originates outside the triangle of Calot, the majority enter the triangle posterior to the common hepatic or common bile ducts. If the cystic artery crosses anterior to these ducts, it is often the first structure encountered during dissection, rather than the cystic duct, and usually requires early ligation and division to provide adequate exposure to the remaining structures [66]. In 15–20 % of individuals, a double or accessory cystic artery is seen. Rarely, a triple cystic artery may be seen [61, 67].

In approximately 10 % of individuals, the right hepatic artery runs across the triangle of Calot adjacent to the cystic duct before sharply turning upward toward the liver, giving it a tortuous or humped appearance. This is of particular importance in the 15 % of patients whose right hepatic artery runs anterior to the common hepatic duct. In these cases, the cystic artery often arises from the angled portion, also known as the *caterpillar hump*, of the right hepatic artery as it changes course. During cholecystectomy, this caterpillar hump may easily be mistaken for the cystic artery and inadvertently ligated. In addition, cystic arteries that arise from a caterpillar hump are often short and at risk for avulsion if excessive traction is applied to the gallbladder [61].

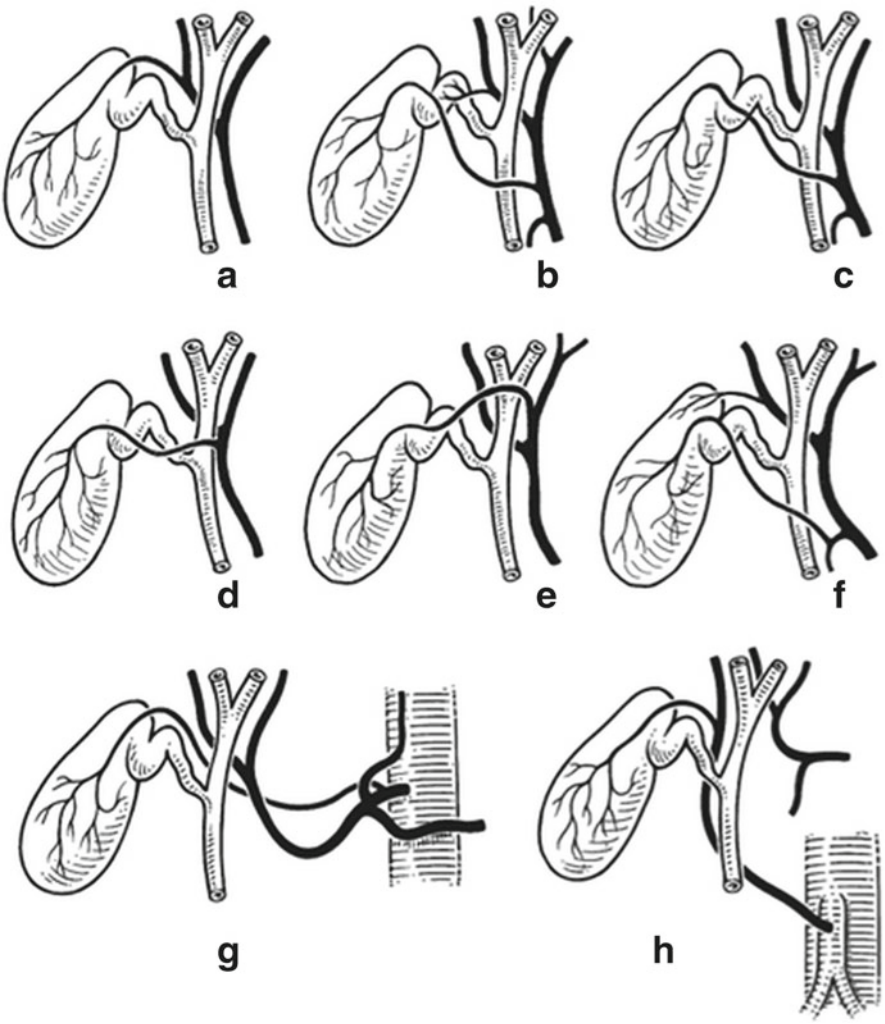

Fig. 1.11 The main variations of the cystic artery: (**a**) Typical course double. (**b**) Cystic artery. (**c**) Cystic artery crossing anterior to main bile duct. (**d**) Cystic artery originating from the right branch of the hepatic artery and crossing the common hepatic duct anteriorly. (**e**) Cystic artery originating from the left branch of the hepatic artery. (**f**) Cystic artery originating from the gastroduodenal artery. (**g**) Cystic artery arising from the celiac axis. (**h**) Cystic artery originating from a replaced right hepatic artery. Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver, biliary tract, and pancreas. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. 1. 5th ed. Philadelphia: Elsevier; 2012. Figure 1B.22. p. 43

Lymphatic Drainage

The lymphatic drainage from the hepatic ducts and common bile duct is primarily to the hepatic lymph nodes within the hepatoduodenal ligament and along the hepatic artery. The lymphatics of the gallbladder partially drain into the liver, but also drain through the cystic duct node, located at the junction of the cystic duct and the common hepatic duct, before joining the hepatic lymph node chain. The lower portion of the bile duct drains via the superior pancreatic lymph nodes [42].

Neural Innervation

The nerve supply to the gallbladder and biliary tree comes from both sympathetic and parasympathetic nerve fibers derived from the celiac plexus that run along the hepatic artery [42].

Physiology

Overview

Bile secretion is one of the major functions of the liver and biliary tree and serves two major roles: the excretion of hepatic metabolites and organic solutes, and the facilitation of intestinal absorption of lipids and fat-soluble vitamins. Hepatocytes within the liver continuously synthesize and secrete bile, which collects in the intrahepatic canaliculi, flows out the liver through the bile ducts, and fills the gallbladder, where bile is concentrated and stored. When chyme reaches the small intestine, cholecystokinin (CCK) is secreted and stimulates contraction of the gallbladder and relaxation of the sphincter of Oddi. This allows stored bile to flow from the gallbladder into the lumen of the duodenum, where bile salts emulsify and solubilize dietary lipids. Once these lipids are absorbed, the bile salts are recirculated through the portal system to the liver via the enterohepatic circulation. Alterations in bile secretion and obstruction of flow due to various pathologic conditions and iatrogenic complications may contribute to the derailment of multiple organ systems and lead to significant patient morbidity and mortality [68].

Bile Composition

Bile is composed of several organic constituents secreted by hepatocytes, including bilirubin, bile salts, phospholipids, and cholesterol, in addition to electrolytes and water.

Bile Salts

Bile salts, which are steroid molecules synthesized by hepatocytes and include bile acids, constitute 50 % of the components of bile and are the major osmotic force behind bile flow. Formed at a rate of 500–600 mg per day, the total bile salt pool is approximately 2.5 g, with the bulk of the bile salts found in the gallbladder, followed by the liver, the small intestine, and the extrahepatic bile ducts.

Four bile acids are present in humans: two primary and two secondary bile acids. The two primary bile acids are synthesized from cholesterol by hepatocytes via two main pathways. The *classic pathway*, the primary mode of bile acid synthesis, leads to the formation of cholic acid, which constitutes the vast majority of the bile acid pool. The *alternate pathway* leads to the formation of chenodeoxycholic acid. Once secreted into the lumen of the intestine, a small percentage of the cholic and chenodeoxycholic acids are dehydroxylated by intestinal bacteria, producing the two secondary bile acids: deoxycholic acid and lithocholic acid, respectively [68, 69].

The liver conjugates the four bile acids with one of two amino acids, glycine or taurine, to form a total of eight bile salts, each named for the composing bile and amino acids. This conjugation is a critical step in bile function, as it changes the bile acids, which are insoluble in the acidic environment of the duodenum, into the much more water-soluble bile salts. Bile salts are amphipathic, meaning they have both hydrophilic and hydrophobic portions, a property critical to solubilize lipids. The first role of bile salts is to emulsify lipids in order to maximize surface area for digestion. This occurs when the negatively charged bile salts surround the lipids, creating small lipid droplets dispersed within the intestinal lumen. Next, bile salts form micelles, which contain a core of lipid breakdown products, including monoglycerides, lysolecithin, and fatty acids, and a surface lined with bile salts. The hydrophobic portion of the bile salts dissolves in the lipid core, while the outward pointing hydrophilic portion dissolves in the aqueous duodenal environment.

Phospholipids and Cholesterol

Phospholipids and cholesterol are primarily synthesized in the liver from low-density lipoproteins circulating in plasma and from de novo pathways, with only a small percentage of cholesterol coming from dietary sources. The primary phospholipid in human bile is lecithin, representing 95 % of its total. Though their role in bile secretion is largely secondary compared to bile salts, biliary lipids play an important role in cholesterol excretion, intestinal absorption of lipids, and protection of biliary epithelial cells against bile acid-induced injury [70].

Phospholipids and cholesterol are secreted into bile by hepatocytes and are included in micelle formation, with hydrophobic cholesterol joining the lipid degradation products within the core and the amphipathic phospholipids providing structural support. This bile salt-phospholipid-cholesterol complex, however, is not the only carrier of biliary cholesterol. Unilamellar vesicles made up of a phospholipid

and cholesterol bilayer can be seen in various concentrations in human bile (Fig. 1.12). In states of excess cholesterol, these vesicles can aggregate, forming large, multilamellar vesicles. When the bile concentration of cholesterol becomes supersaturated and exceeds the transport capacity of these vesicles, liquid crystals of cholesterol monohydrate can form, known as *cholesterol nucleation*, a precursor condition in cholesterol gallstone formation [71].

Bilirubin

Bilirubin serves as the major bile pigment, giving it its characteristic yellow color. A by-product of senescent erythrocyte degradation by the reticuloendothelial system, heme is the source of 80–85 % of the daily bilirubin production, with the remaining percentage derived from breakdown products of hepatic hemoproteins. Found in high concentrations in the liver, spleen, and bone marrow, the enzyme heme oxygenase plays a major role in the initial conversion of heme to biliverdin, though both enzymatic and nonenzymatic pathways have been proposed. Biliverdin is then reduced to bilirubin in a nicotinamide adenine dinucleotide (NADH)-dependent reaction by biliverdin reductase prior to being released into the circulation. In this form, bilirubin is "unconjugated" and poorly soluble, requiring that it be bound to plasma proteins, primarily albumin, as it is transported through the circulation for further processing by the liver.

Once extracted from the blood, bilirubin binds to a driver of glutathione-S-transferase within the hepatocyte and is catalyzed by bilirubin uridine-5-diphosphate (UDP)-glycosyltransferase to form bilirubin glucuronide, the water-soluble, "conjugated" form of bilirubin. Mutations in the bilirubin UDP-glycosyltransferase gene have been implicated in the Crigler-Najjar and Gilbert syndromes, both characterized by unconjugated hyperbilirubinemia [72]. Conjugated bilirubin is secreted as a component of bile into the intestine, where it is converted back to unconjugated bilirubin, then to urobilinogen by intestinal bacteria. A portion of the urobilinogen produced is then recirculated to the liver, a portion excreted in the urine, and the remainder is oxidized to urobilin and stercobilin within the intestine, giving stool its characteristic dark brown color [68].

Water and Electrolytes

The final components of bile are electrolytes and water, which are secreted by the epithelial cells lining the bile ducts in response to stimulation by numerous gastrointestinal hormones. Water constitutes 85 % of the volume of bile leaving the liver.

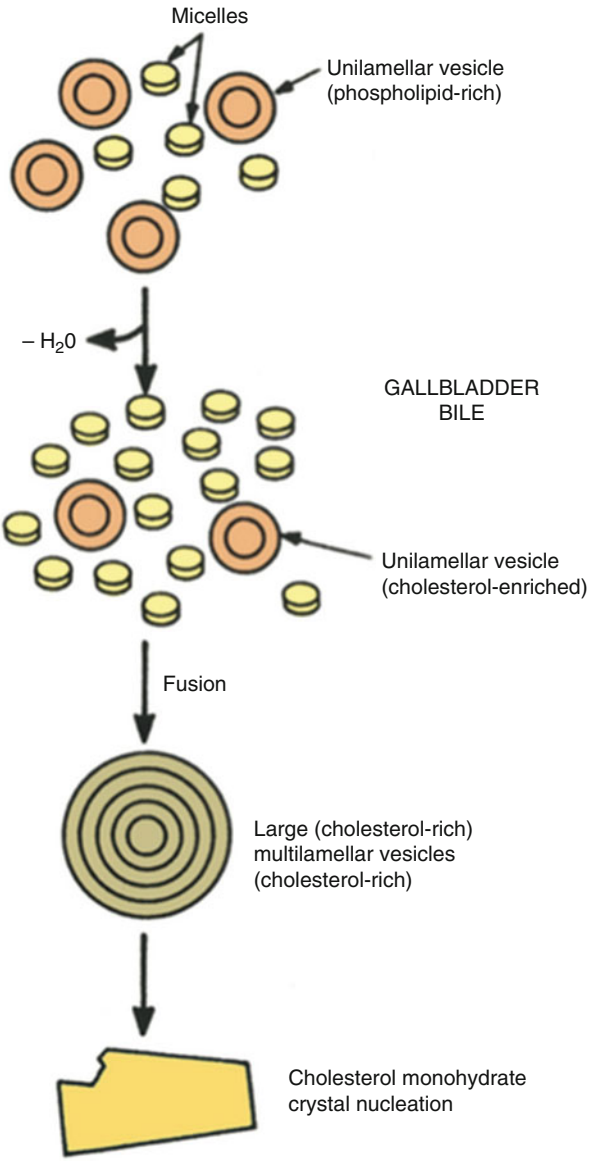

Fig. 1.12 Concentration of bile leads to net transfer of phospholipids and cholesterol from vesicles to micelles. Phospholipids are transferred more efficiently than cholesterol, leading to cholesterol enrichment of the remaining (remodeled) vesicles. Aggregation of these cholesterol-rich vesicles forms multilamellar liquid crystals of cholesterol monohydrate. Pitt HA, Nakeeb A, Espat NJ. Bile secretion and pathophysiology of biliary tract obstruction. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. Vol. 1. 5th ed. Philadelphia: Elsevier; 2012. Figure 7.2. p. 115

Bile Secretion

Hepatocytes are arranged in plates along vascular network connecting the portal to the central venous system. The small apical domains of adjacent hepatocytes within these plates form tubular lumen, known as canaliculi. Normally in a low-pressure system (5–10 cm H_2O), bile is secreted into the canalicular network by the active transport of solutes followed by the passive flow of water. Roughly 750–1000 mL of bile is secreted by the liver daily, which depends on neurogenic, humoral, and chemical control. Bile secretion is increased by vagal stimulation, while hepatic vasoconstriction, seen during splanchnic stimulation, results in decreased bile secretion. Various gastrointestinal hormones, including secretin, CCK, and gastrin, play a role in increasing bile flow. The most important factor in the regulation of bile flow, however, is the rate of hepatocyte bile salt synthesis, which is largely dictated by the recycling of bile salts via the enterohepatic circulation.

Bile Salt Secretion

In plasma, bile acids are bound to either albumin or lipoproteins. Their uptake from the space of Disse within the liver into hepatocytes is mediated by sodium-dependent and sodium-independent mechanisms. Several transport proteins have been identified as playing key roles in this process. The *sodium-taurocholate cotransporting polypeptide* (NTCP) is a bile salt transporter found exclusively on the basolateral membrane of hepatocytes and is responsible for 80 % of taurocholate uptake. In contrast, the *organic anion transporting polypeptides* (OATPs) are a family of sodium-independent transporters that mediate the uptake of a broad variety of organic anions, of which bile acids are only one of their many substrates [73, 74].

Two primary mechanisms have been suggested to control bile acid intracellular transport: one involves the transport of bile acids from the basolateral to the canalicular membrane through bile acid-binding proteins, while the other depends on the vesicular transport of bile acids [75]. Regardless of the method of intracellular transport, the transport of bile salts across the hepatocyte canalicular membrane represents the rate-limiting step in the overall secretion of bile salts.

The concentration of bile salts within the canaliculi is 1000 times greater than in the hepatocytes, necessitating an ATP-dependent, active transport of solutes. This is largely mediated by the bile salt export pump (BSEP), which is closely related to the proteins of the multidrug resistant (MDR) gene family of ATP binding cassette (ABC) transporters, and serves as the major transporter of monovalent bile salts into the canaliculi [73]. MDR-related protein-2 (MRP2) has also been shown to transport certain bile salts into the canaliculi, along with the export of other organic solutes, including conjugated bilirubin, chemotherapeutic agents, antibiotics, toxins, and heavy metals [76, 77].

Biliary Lipid and Cholesterol Secretion

The secretion of phospholipids involves the translocation of phosphatidylcholine from the inner to the outer leaflet of the canalicular plasma membrane, which is mediated by the MDR3 transporter. Defects in MDR3 expression are thought to cause progressive familial intrahepatic cholestasis type 3, a rare autosomal recessive disorder marked by progressive liver disease. Because these patients lack phosphatidylcholine in their bile, which normally protects biliary epithelium from the toxic injury of bile salts, early childhood cholestasis, cholestasis of pregnancy, and progressive liver failure can occur [78]. In addition, some genetic variations of *MDR3* have been associated with increased susceptibility to drug-induced liver injury and primary biliary cirrhosis [79, 80].

Less is known about cholesterol secretion, although several studies have shown that the ABC transporters, ABCG5 and ABCG8, may play an important role. Mutations in these transporters are seen in patients with sitosterolemia, a rare autosomal recessive disorder characterized by intestinal hyperabsorption of all sterols, including cholesterol, coupled with the impaired ability to excrete these sterols in bile [81]. In more recent years, the cholesterol-lowering drug, ezetimibe, has been suggested to target ABCG5 and ABCG8 by indirectly upregulating their expression in the liver [82].

Bilirubin Secretion

The liver is the only organ in the body capable of removing the bilirubin-albumin complex from the circulation. On the basolateral membrane of hepatocytes, both conjugated and unconjugated bilirubin are taken up by the membrane transporters OATP1B1 and OATP1B3, both members of the OATP transporter family mentioned previously [83]. Because of its lipid soluble properties, unconjugated bilirubin can additionally cross the sinusoidal membrane by passive diffusion. Once conjugated, bilirubin glucuronides are excreted into the biliary canaliculi via the ATP-dependent MRP2 transporter. As previously mentioned, MRP2 has a broad substrate affinity and is responsible for the transport of a wide spectrum of organic ions [76, 77]. Interestingly, a substantial percentage of conjugated bilirubin is returned to the sinusoidal membrane and secreted back into plasma by MRP3, where it is taken up by downstream hepatocytes via their OATP1B1/3 transporters. This observed phenomenon is thought to prevent the saturation of the biliary secretory capacity of the hepatocytes surrounding the portal tracts by shifting some of the substrate burden toward those hepatocytes downstream near the central vein [84].

Bile Flow

Although bile salt secretion by hepatocytes is the principle driver of bile flow, it is regulated in part by other external factors. As bile passes through the biliary ductal network, its concentration is altered by the absorption and secretion of water and

electrolytes by cholangiocytes. Transcellular movement of water across cholangiocyte membranes is mediated by the uniquely co-expressed aquaporin channels, AQP1 and AQP4 [85]. Bicarbonate secreted by the Cl^-/HCO_3^- exchanger (AE2) and chloride secreted by cystic fibrosis transmembrane conductance regulator (CFTR) are also thought to play an important role in ductal bile flow, independent of bile salt secretion. In addition, the gastrointestinal hormone secretin has been shown to stimulate the exocytic insertion of vesicles containing AQP1, AE2, and CFTR, thus demonstrating its role in increasing ductal bile flow [86].

Gallbladder Function

The gallbladder's primary function is to store bile, concentrate bile, and when stimulated to contract in response to a meal, in a coordinated manner, eject bile. To accomplish this, the gallbladder has unique absorptive, secretory, and motility capabilities.

Absorption

The normal storage capacity of the human gallbladder is 40–50 mL. This seemingly minute fraction of the total bile produced by the liver per day is overcome by the gallbladder's remarkable absorptive ability, concentrating bile as high as tenfold. Indeed, the gallbladder epithelium has one of the highest rates and capacities to absorb water and electrolytes in the body [87]. The transport of water by gallbladder epithelia occurs through AQP1 and AQP8, and is a passive process secondary to the active transport of solutes, namely via Na^+/H^+ and Cl^-/HCO_3^- exchangers [88]. In this way, water is absorbed in an isosmotic fashion, meaning that an osmotic equilibrium is maintained across the absorbed and luminal solutions. However, because the net transport of water is always coupled in the same direction with sodium and chloride transport, water absorption in the gallbladder occurs against its chemical gradient (i.e., from the concentrated lumen into the dilute intracellular environment of the gallbladder epithelia) [89, 90].

As the gallbladder mucosa readily absorbs water, the concentration of biliary lipids, bile salts, bilirubin, and cholesterol increases, making the environment ripe for solute precipitation and gallstone formation. Although some calcium (Ca^{2+}) is absorbed by the gallbladder epithelium, its absorption is not as efficient as that of water, leading to a relative increase in luminal Ca^{2+} concentration. Elevations in gallbladder Ca^{2+} coupled with increased concentrations of unconjugated bilirubin, as may be seen in patients with hemolysis, alcoholism, ileal disease, and TPN dependence, lead to the precipitation of calcium bilirubinate crystals and pigmented gallstones [91].

The increased concentration of bile within the gallbladder also has effects on the solubility of cholesterol. Although the solubility within micelles increases, the stability of phospholipid-cholesterol vesicles decreases with increasing cholesterol

concentrations, and as a result, there is an increased tendency to form aggregate vesicles and cholesterol crystals [69]. Furthermore, increased concentrations of luminal Ca^{2+} ions have been shown to disrupt the structural integrity of the phospholipid-cholesterol vesicles, facilitating cholesterol nucleation and stone formation [92]. In addition, it has also been suggested that the presence of calcium bilirubinate crystals may further promote cholesterol precipitation by serving as a nidus to which it adheres [93].

Secretion

Though initially thought to only have absorptive capabilities, the gallbladder mucosa is responsible for the secretion of two important products: mucin and hydrogen ions (H^+). Synthesized and secreted by the surface mucous and submucosal glandular cells primarily lining the gallbladder neck and cystic duct, mucin serves as a lubricant and an important protective barrier against the detergent effect of highly concentrated bile acids on the gallbladder mucosa. However, numerous animal and human studies have demonstrated the pronucleating effects of mucin in gallstone disease [94–96]. Furthermore, bile from patients with gallstones has been shown to contain higher concentrations of mucin than from controls. Though the exact mechanism by which mucin promotes gallstone formation is unknown, it is thought that the plentiful hydrophobic binding sites within mucin's polypeptide core create a favorable environment for phospholipid-cholesterol vesicle aggregation and cholesterol nucleation [97]. Prostaglandins, the caustic effects of bile salts, and local inflammation have all been shown to stimulate gallbladder mucin secretion and are thought to play a role in mucin hypersecretion and gallstone formation [98, 99].

The intraluminal transport of hydrogen ions via the Na^+/H^+ exchanger coupled with the reabsorption of HCO_3^- via luminal membrane carbonic anhydrases leads to a decrease in bile pH from 7.5 to 7.8 down to 7.1 to 7.3 [100, 101]. This acidification of bile within the gallbladder promotes calcium solubility and thus is crucial in preventing calcium precipitation and gallstone formation.

Motility

Gallbladder filling and emptying is a dynamic process in response to a complex web of neural, hormonal, and mechanical interactions. Motor activity of the gallbladder occurs in response to, as well as in the absence of, food. During fasting states, known as the *interdigestive phase,* gallbladder motility is characterized by periods of filling, facilitated by gallbladder wall relaxation coupled with the tonic contraction of the sphincter of Oddi, followed by periods of partial emptying, controlled largely by the hormone motilin. Coordinated with the cyclic contractile activity of phase III of the intestinal migrating motor complex (MMC), these brief spurts of gallbladder contraction result in the emptying of 20–30 % of its volume every 1–2 h and are thought to play an important "housekeeping" role [102, 103]. First, the

delivery of small amounts of bile into the duodenum is thought to assist the MMC in cleansing the small intestine of residual food after digestion. It has also been suggested that partial gallbladder emptying and refilling results in the vigorous mixing of concentrated gallbladder bile with fresh, dilute hepatic bile, thereby preventing supersaturation and accumulation of cholesterol crystals and debris. In the instance that cholesterol crystals do form, these periodic contractions may allow for their ejection, thus preventing their further compaction and stone formation [102]. In several animal studies, vasoactive intestinal peptide (VIP) and nitric oxide (NO) have also been hypothesized to play a role in gallbladder motility during the filling portion of the interdigestive phase, primarily through smooth muscle relaxation of the gallbladder wall [102].

Following a meal, the gallbladder contracts in response to the potent stimulating effects of CCK, emptying 70–80 % of its contents over 30–40 min. CCK is also responsible for the coordinated relaxation of the sphincter of Oddi during this period. Receiving both sympathetic and parasympathetic nerve fibers, gallbladder motility is also under neural influence. During post-prandial and fasting states, gallbladder contractility is controlled by cholinergic vagal pathways via muscarinic receptors [104].

Impaired gallbladder motility is thought to play an important role in gallstone formation, as prolonged residence of bile within the gallbladder increases the opportunity for cholesterol nucleation and crystal formation. In addition, the loss of periodic gallbladder emptying results in fewer crystals being released into the duodenum [105]. Various conditions and medications have been implicated in gallbladder dysmotility. Patients with celiac disease, growth hormone deficiency, irritable bowel syndrome, chronic pancreatitis, hypertriglyceridemia, and somatostatinoma are thought to have decreased gallbladder motility through the inhibited release of or impaired response to endogenous CCK. This has also been demonstrated in patients receiving chronic TPN and octreotide therapy. In patients with autonomic neuropathy, as seen in diabetes and β-thalassemia, and in those who have had total or partial gastric resections, the disruption in vagal stimulation is thought to cause impaired gallbladder motility [106]. Medications affecting smooth muscle tone, such as calcium channel blockers, progesterone, loperamide, and spasmolytics, have all been suggested to decrease gallbladder contractility [107].

Just as gallbladder motor function can influence bile composition, so too can the components in bile affect gallbladder motility. Cholesterol hypersaturation is thought to induce excess accumulation of bile within the cell walls of gallbladder smooth muscle, resulting in decreased membrane fluidity and both impaired smooth muscle contractility and relaxation [106]. Increased mucin production may accelerate this process by increasing cholesterol absorption by the gallbladder wall [108]. Interestingly, the proliferative effects of cholesterol on arterial myocytes during atherogenesis are similar to those seen on gallbladder smooth muscle, suggesting a form of gallbladder hypertrophic leiomyopathy [109]. In animal models, bile acids, particularly the more hydrophobic ones, have been shown to cause muscle cell dysfunction through the production of free radicals, suggesting their potential role in gallbladder dysmotility in humans [110].

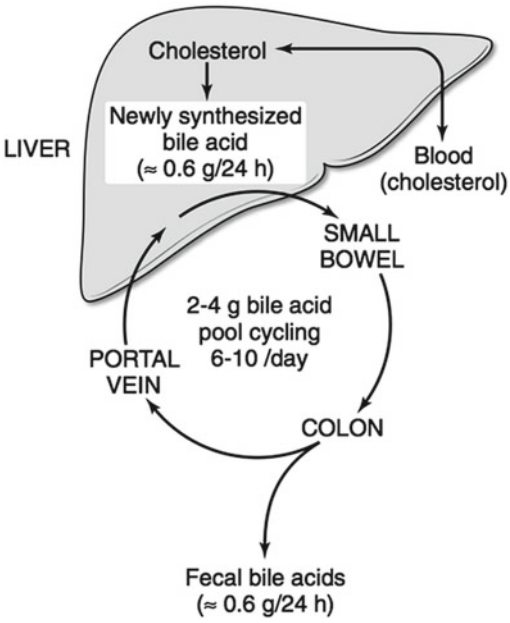

Fig. 1.13 Enterohepatic circulation of bile salts. Cholesterol is taken up from plasma by the liver. Bile acids are synthesized at a rate of 0.6 g/24 h and are excreted through the biliary system into the small bowel. Most of the bile salts are reabsorbed in the terminal ileum and are returned to the liver to be extracted and reextracted. Pitt HA, Nakeeb A, Espat NJ. Bile secretion and pathophysiology of biliary tract obstruction. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. Vol. 1. 5th ed. Philadelphia: Elsevier; 2012. Figure 7.3 p. 116

Enterohepatic Circulation

Bile salts are synthesized and conjugated in the liver, secreted in bile, stored in the gallbladder, ejected into the duodenum, reabsorbed by the small intestine (primarily the ileum), and returned to the liver via the portal venous system. This liver-intestinal cycling of bile, known as the *enterohepatic circulation*, completes 6–10 times daily and is responsible for the intestinal reabsorption of nearly 95 % of bile acids. The total amount of bile salt involved in the enterohepatic circulation is called the *circulating bile pool*, which equals roughly 2–4 g in normal human adults (Fig. 1.13). Nearly 90 % of the bile salt pool is sequestered in the gallbladder during periods of fasting.

In cases where there is an excess loss of bile salt, such as in ileal Crohn's disease, through biliary fistula, or with bile-binding products, an increase in bile salt production is seen. In this way, the enterohepatic circulation serves an important negative feedback role, maintaining a constant bile salt pool size [69].

Biliary Obstruction and the Pathophysiology of Jaundice

Obstruction of the biliary tract is a common and often challenging problem faced by general and hepatobiliary-trained surgeons. The causes of biliary obstruction are many and may be broken down into four categories: those conditions causing complete obstruction, such as common bile duct ligation or injury; intermittent

Table 1.1 Conditions commonly associated with biliary tract obstruction

Complete obstruction
Pancreatic head tumors
Common bile duct ligation or transection
Cholangiocarcinoma
Parenchymal liver tumors
Intermittent obstruction
Choledocholithiasis
Periampullary tumors
Duodenal diverticula
Choledochal cysts
Polycystic liver disease
Biliary parasites
Hemobilia
Chronic incomplete obstruction
Common bile duct strictures
Congenital
Traumatic/Iatrogenic
Primary sclerosing cholangitis
Post radiation therapy
Stenosis of biliary-enteric anastomosis
Chronic pancreatitis
Cystic fibrosis
Sphincter of Oddi stenosis
Segmental obstruction
Traumatic/Iatrogenic
Intrahepatic stones
Cholangiocarcinoma

Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver, biliary tract, and pancreas. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. 1. 5th ed. Philadelphia: Elsevier; 2012. Table 7.3 p. 117

obstruction, such as choledocholithiasis and choledochal cysts; chronic incomplete obstruction, such as biliary strictures, sclerosing cholangitis, and chronic pancreatitis; and segmental obstruction, such as an isolated sectoral duct injury (Table 1.1). Regardless of etiology, all patients with biliary obstruction are at risk for developing hyperbilirubinemia, whose manifestations may range from symptomatic (fevers, pain, pruritis) to clinical jaundice. If prolonged, fibrosis of the liver and biliary tract, cirrhosis, and eventual liver failure may develop. In addition to derangements in liver and biliary function, jaundiced patients are at increased risk of cardiovascular compromise, renal failure, coagulopathies, malnutrition, inadequate wound healing, and immune dysfunction, and carry a higher risk of perioperative mortality (Table 1.2) [101].

Table 1.2 Potential multisystem effects of biliary obstruction and jaundice

Hepatobiliary
Dilated bile canaliculi, distortion and swelling of microvilli
Hepatic ductule proliferation (chronic obstruction)
Inflammatory infiltration and fibrosis
Mucosal atrophy and squamous metaplasia of extrahepatic bile ducts
Impaired micro- and macrovascular perfusion to liver
Decreased bile secretion
Impaired excretion of drugs and toxins (antibiotics, endotoxin)
Decreased liver metabolism (inhibition of cytochrome P450 enzymes)
Hepatocyte apoptosis
Decreased hepatocyte synthetic function (albumin, clotting factors, IgA)
Impaired Kupffer cell function
Increased systemic proinflammatory cytokines (TNF-α, IL-6)
Cardiovascular
Decreased cardiac output
Impaired cardiac contractility
Blunted response to β-agonist drugs
Decreased peripheral vascular resistance
Renal
Decreased renal perfusion
Inappropriate diuresis
Endotoxin-mediated tubular and cortical necrosis
Coagulation
Decreased production of vitamin K-dependent clotting factors
Endotoxin-mediated platelet dysfunction
Immune
Impaired delayed-type hypersensitivity
Impaired T-cell proliferation
Decreased neutrophil chemotaxis
Defective phagocytosis
Bacterial intestinal translocation
Wound healing
Decreased collagen synthesis

Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver, biliary tract, and pancreas. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. 1. 5th ed. Philadelphia: Elsevier; 2012

Summary

Over the last century, studies of the biliary tract—how it's formed, how it's arranged, and what functions it serves—on micro- and macroscopic levels have improved our understanding of normal biliary embryology, anatomy, and physiology tremendously. Perhaps more importantly, though, it has broadened our appreciation for the abnormal and given us a foundation from which we may begin to anticipate, mitigate, and manage biliary pathology and injury.

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Part II
Inflammatory and Infectious

Chapter 2
Primary Sclerosing Cholangitis

Debashis Haldar and Gideon M. Hirschfield

Introduction

Primary sclerosing cholangitis (PSC) is a chronic, progressive and destructive cholangiopathy that results in fibrotic strictures and dilations of the intra- and extrahepatic biliary tree. The natural history of disease results in clinical cholangitis, secondary biliary cirrhosis, and a risk of hepatobiliary malignancy. In the current era where effective medical therapy remains absent, more than half of the patients ultimately become in need of a liver transplant, although increasingly it is recognised that there is a degree of heterogeneity in the natural history and progression of disease [1].

Unlike the autoimmune lymphocytic cholangitis of primary biliary cirrhosis (PBC), the large bile duct lymphocytic sclerosing cholangiopathy of PSC has a male bias (1.7:1), a pan-age presentation (median age of diagnosis 40) and a notable increased risk of hepatobiliary malignancy. A systematic review investigating the epidemiology of PSC suggested that the incidence rate is 1 per 100,000 person-years [2]. The available data proposes this value to be true for Europe and North America, with little knowledge of the epidemiology in the developing world. Seemingly however, there is a distinction in incidence between Northern and Southern hemispheres, and PSC appears infrequent in Asia.

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Patients are usually non-smokers, which contrasts with PBC [3], and there is an archetypal association with inflammatory bowel disease (IBD), particularly for Northern European Caucasian subjects, wherein one expects a 60–80 % coincidence of PSC and IBD. This compares to a lower rate of PSC-IBD (30–50 %) in southern European and Asian populations. Conversely, the quoted prevalence of PSC in colitis is variably reported, but it seems less than 5–10 % of patients develop clinically significant disease; the rate of so called "occult" cholangiopathy may be higher, and certainly some sensitive MRI studies would support that. Of note gender distinctions are also relevant with women less likely to have IBD.

Ulcerative colitis (UC) is three times more common than Crohn's disease in the setting of PSC, and it is commonly extensive—a large Dutch observational study found that 83 % had pancolitis. The same study noted that 95 % of the Crohn's Disease with PSC patients had (ileo)colitis [4]. An earlier study from Rochester published in 2005 [5] was the first to suggest a distinct "PSC-IBD" phenotype, characterised by a preponderance for colitis with rectal sparing (52 %) and backwash ileitis (51 %), though this was not replicated in the aforementioned Dutch study. Nevertheless, our experience supports the distinctive IBD pattern in PSC, and highlights the increasing frequency with which PSC is diagnosed first, and asymptomatic colitis confirmed through screening colonoscopy and biopsy [6]. A pathologic explanation for this correlation is lacking, and it is worth noting that despite the extent of colitis being associated with a risk of PSC, there is as of yet no evidence to suggest that the activity of the colitis correlates to risk of liver disease. A "Crohn's phenotype" of IBD is however reportedly associated with a milder PSC disease course. What has proved interesting has been the evaluation of genetic risk across UC and PSC-IBD, wherein both shared and distinct risk hallmarks are seen.

Nevertheless, PSC has been shown to be an independent risk factor for colorectal carcinoma (CRC), with a fivefold increased risk compared to the general population, and a tenfold increased risk in the setting of UC with PSC, compared to UC alone [1]. Moreover, CRC is diagnosed considerably earlier compared to UC controls (median age 39 years vs. 59 years) [1].

Pathogenesis

Cholangiography is capable of identifying a sclerosing cholangiopathy, as is histopathology, but the visual appearance of bile duct injury by imaging or histology is insufficient to distinguish primary and secondary etiologies, albeit radiologic or immunohistochemical clues may be present (Table 2.1 and Fig. 2.1). Histologic changes can occur in isolation (so-called small-duct disease) and this raises questions about the course of disease. It is recognised that some small-duct PSC patients, but not the majority, progress to large-duct disease, and cholangiocarcinoma is rarely seen in patients with small-duct disease, unless it has progressed to more classic PSC.

Table 2.1 Differential diagnosis for sclerosing cholangitis

Varying etiologies for sclerosing cholangitis clinically
Cholangitis and chronic biliary infection Acquired immune deficiency syndrome (probably infective from cytomegalovirus or cryptosporidium)
Choledocolithiasis Biliary tract surgery/trauma
Biliary toxin exposure
Biliary strictures (inflammatory/malignant) Cholangiocarcinoma Papillary tumour Choledochal cyst disease
Ischaemic biliopathy Portal biliopathy (portal vein thrombosis)
Graft-versus-host disease
IgG4-associated cholangiopathy

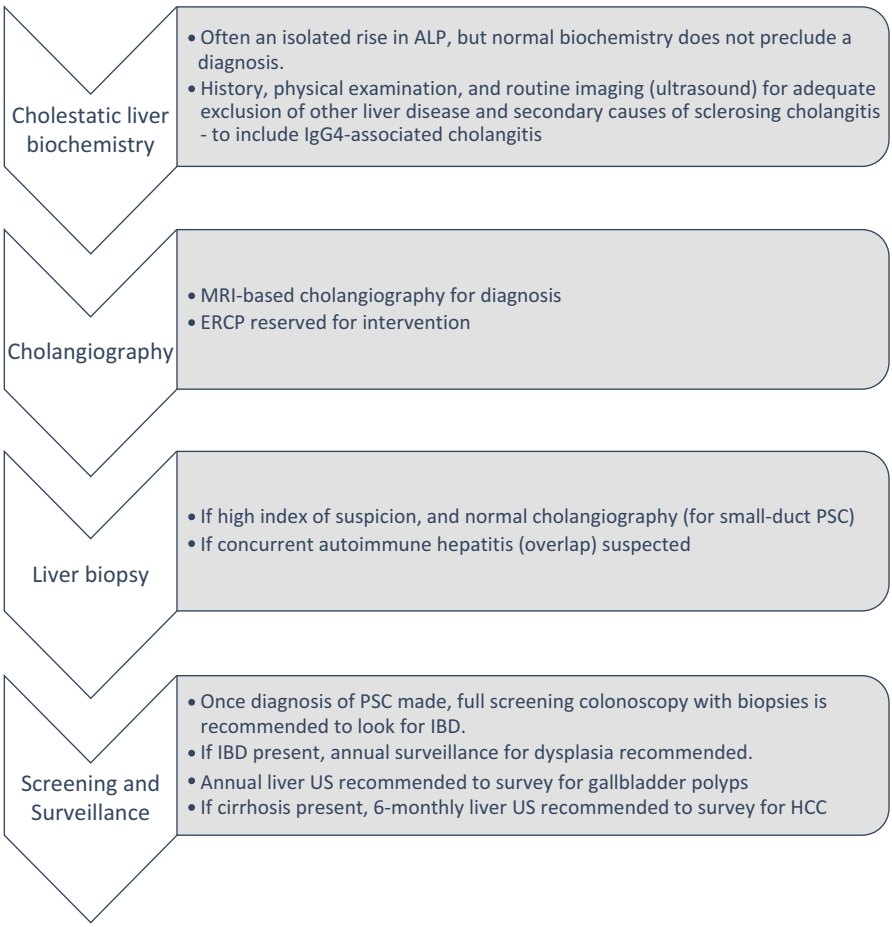

Fig. 2.1 Diagnostic pathway for patients with primary sclerosing cholangitis

Common pathways to biliary injury become apparent when one recognises the myriad of secondary etiologies for sclerosing cholangitis that span vascular, immunologic, septic, toxic and inherited insults. Additionally the co-existence at such a high rate of IBD is important to appreciate and rationalise. The biliary and gut epithelium is a continuum, and the blood supplies are intimately linked, with the healthy liver receiving 70 % of its blood from the gut via the portal vein. This inevitably means the liver is a continued barrier to gut derived toxins and an organ that has evolved to be inherently immunotolerant.

Histology points towards a progressive and chronic injury to predominantly the medium to large bile ducts, that culminates in an obliterative and inflammatory concentric periductal fibrosis, giving the recognisable term "onion-skinning" [7]. On a cholangiogram this manifests as an alternating series of strictures and dilatations—resulting in a beaded appearance. The initial periportal (primarily periductal) infiltrate is predominantly a mixed inflammatory concentrate of lymphocytes, plasma cells and neutrophils. Central to this is the inherently immunologically innocent cholangiocyte, which, in response to injury, becomes a key recruiter and homing destination for the inflammatory mediators. There is an increase in the expression of adhesion molecules and profibrogenic cytokines. The consequence of inflammation is progressive fibrosis, ductopenia, and disorganised ductal proliferation. Immune injury, impaired vascular supply, retention of bile acid, biliary obstruction and altered secretion all seemingly contribute to disease. Clearly biliary homeostasis is undoubtedly interrupted in sclerosing cholangitis, and it is increasingly recognised that the gut-liver bile acid axis/signalling pathways are very active biologic pathways. Normal biliary epithelium is resistant to inherently toxic bile, likely because of a bicarbonate enriched protective "umbrella": human cholangiocytes are continuously exposed to millimolar levels of hydrophobic bile salts; a co-ordinated apical biliary bicarbonate secretion process likely prevents protonation of biliary glycine-conjugated bile salts and uncontrolled, potentially toxic, cell entry of corresponding bile acids. Disease modifies biliary flow and function, and future choleretic therapies are set to focus on ameliorating damage secondary to the consequences of biliary damage. Exposure to bacteria and/or their cellular products, whether it be in the biliary tree, or as a consequence of toxic agents penetrating through a leaky and inflamed colon is likely to also play a role, and may even explain the reactivity patterns of perinuclear antineutrophil cytoplasmic antibodies.

Finally, whilst it is semantic to discuss whether PSC is autoimmune or autoinflammatory, manifestly immunological mechanisms are central to the pathophysiology of disease; the tight genetic HLA association identified strongly points to the importance of immune mediated mechanisms of disease initiation. Genome-wide association studies confirm HLA associations and moreover implicate a battery of susceptibility and modifier genes, with a varied likely biological impact [8]. This is further supported by evaluation of biliary infiltrates that are mainly activated effector or memory T cells, but also include B-cells and players from the innate immune system. Finally there is evidence to suggest that effector lymphocytes in colitis home, via a common adhesion molecule signal, between the colon and liver [9], and

blocking this enterohepatic immune "circuit" is the focus of some proposed targeted monoclonal antibody therapy.

Clinical Presentation and Diagnostic Considerations

Although natural history studies give the impression that the typical PSC presentation is that of a non-smoking 40-year-old man with colitis presenting with abnormal liver biochemistry, it is increasingly recognised to be a stereotype that is challenged by patients presenting with early and milder disease, and in both genders. Thus, the challenge has become not only the natural history of severe disease, but the need to stratify risk and treatment across heterogeneous populations, some of whom are likely to have very benign outcomes, whilst others are either very inflammatory and rapidly progressive, or pre-malignant.

Natural history studies do suggest that the prevalence of asymptomatic PSC may be as high as 40 % of all patients with PSC [10]. Non-specific fatigue and pruritus may similarly provoke a search for a cause of cholestasis. A presentation with decompensated liver disease and portal hypertension can still occur across all ages, and the extremes of age do not infer either overt good or bad prognosis.

Cholangiography: The diagnosis of sclerosing cholangitis requires anatomic evaluation of the biliary tree, and thus, cholangiography (Fig. 2.2). Typical and characteristic findings include multifocal biliary strictures, which may be diffusely

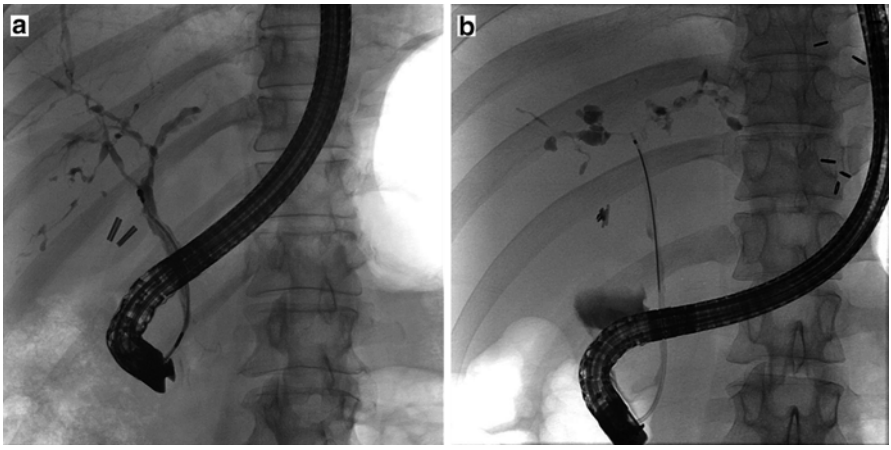

Fig. 2.2 Cholangiographic changes in primary sclerosing cholangitis. Cholangiographic appearances of PSC obtained at time of interventional endoscopy: (**a**) diffuse appearance of marked intrahepatic PSC in a patient with progressive jaundice and pruritus, illustrating the challenge of delivering effective therapy to widespread biliary disease; (**b**) malignant bile duct stricture identified in a patient with PSC, and subsequently evaluated for suitability for liver transplantation according to "Mayo" protocol. Images kindly provided by Dr G May, Head Division of Gastroenterology, St Michaels Hospital, Toronto

distributed to involve both intra- and extrahepatic biliary system. The disease is rarely (5 %) limited to the extrahepatic ducts. Strictures are short, and annular, and alternate with dilated areas to give a "beaded appearance". Biliary diverticula and pruning are also common. Endoscopic retrograde cholangiopancreatography (ERCP) has long been considered the "gold standard" for diagnosis. However, it is an invasive procedure that carries a risk of cholangitis, bleeding, pancreatitis and very rarely death. A recent prospective risk analysis of ERCP in PSC patients by the Dutch PSC Study Group reported a 2 and 14 % complication rate at 1 week in asymptomatic and symptomatic patients, respectively [11]. A retrospective cohort-study highlighted that operator-volume and experience is an independent predictor of uncomplicated ERCP [12], which is reflected in conclusions drawn from data extracted from the Swedish nationwide quality register (comprising 51 ERCP centres), which demonstrated a complication rate of 18 % in those with PSC (compared to 7 % in those without) [13]. Thus, advances in non-invasive imaging such as magnetic resonance cholangiopancreatography (MRCP), have made it the primary diagnostic tool; an added value being the additional insights gained from extra-hepatic imaging of the abdomen. A meta-analysis of the diagnostic performance of MRCP concluded that the overall sensitivity and specificity for PSC detection were 0.86 and 0.94 respectively. The positive and negative likelihood ratios were 15.3 and 0.1, respectively, and even in the worst case scenario (pre-test probability of 50 %) post-test probabilities were 94 % for a positive, and 13 % for a negative MRCP result [14]. Nevertheless, MRCP has its limitations. One case–control study highlighted the risk of false positive results in cirrhotic patients [15]. Furthermore, there is a perceived high interobserver variability in reporting (which is no different from ERCP), which may be particularly relevant in patients with early subtle disease [16]. Moreover, it does not allow for therapy. Nevertheless, two cost-effectiveness studies also support the use of MRCP first, with the selective use of ERCP following [17, 18]. This approach has been estimated to involve 11.7 % lower costs compared with ERCP when sedation and supply costs are included [18].

Histology: In the event of a high pretest probability for PSC, a normal cholangiogram, and no other explanation for persistent cholestasis (in particular negative immunology for PBC), a liver biopsy may be required to allow a diagnosis of small-duct PSC. Histologic evaluation also has value when an "overlap syndrome" with autoimmune hepatitis is suspected, and can be equally relevant if there are other potential confounding diagnoses such as steatohepatitis.

Excluding Known Secondary Etiologies

A diagnosis of PSC requires the exclusion of often clinically apparent potential secondary causes. These include biliary calculi, cholangiocarcinoma, biliary tract surgery, choledochal cyst disease, biliary toxin exposure, chronic biliary infection, portal vein thrombosis/portal biliopathy, ischaemic biliopathy and graft-versus-host disease, to name the more prevalent causes (Table 2.1). For the most part, a good history, physical examination and routine imaging can identify secondary causes.

One specific etiology to proactively exclude is IgG4-associated cholangiopathy (IAC), because of its ability to mimic PSC, yet be highly sensitive to glucocorticoids. IAC is a component of an autoimmune multi-system disease encompassing the spectrum of autoimmune pancreatitis, IgG4 cholangiopathy and extra-hepatobiliary manifestations (e.g. retroperitoneal fibrosis, interstitial nephritis, pulmonary infiltrates, parotitis) [19]. It has an incidence and prevalence of 0.9 and 2.2 per 100,000 population, respectively [20]. It preferentially presents in men (8:1), has a median age of presentation older (60–70) than classic PSC, and is associated with "blue-collar" work, suggesting a potential allied environmental trigger [21]. Diagnosis requires correlation of historical, biochemical, serological, imaging and histopathological markers, and this is reflected in validated diagnostic systems [22, 23].

The laboratory biochemistry results will not be discriminatory, but if IgG4 disease is suspected, then serology can be helpful, and it is recommended that IgG4 levels are measured at least once in all patients at the point of considering PSC as a diagnosis. Cholangiographic changes are not defining, and may resemble cholangiocarcinoma, pancreatic cancer or PSC [24], but associated changes in the pancreas may be more telling. Histopathology is potentially helpful in the diagnosis, with hallmark features of type 1 autoimmune pancreatitis being described as a tumefactive mass with a dense lymphoplasmacytic infiltrate that is organised in a storiform pattern, a moderate eosinophil infiltrate, and a very characteristic obliterative phlebitis; increased immunostaining for IgG4 is also characteristic.

Variant Presentations

The main variant presentations to recognise are small-duct PSC, "overlap" syndrome with autoimmune hepatitis and childhood "autoimmune sclerosing cholangitis".

Small-duct PSC: This is phenotypically a milder version of its medium and large duct counterpart. The diagnosis is made in patients with chronic cholestatic liver disease who have histological changes suggestive of PSC, in the presence of a normal cholangiogram, and in whom other liver and biliary disease has been excluded using standard laboratory and imaging techniques. Natural history studies suggest that small-duct PSC has a better long-term prognosis (13-year median transplant-free survival), and is not associated with cholangiocarcinoma in the absence of large-duct disease. Approximately a quarter will transform to large-duct PSC within 10 years, and progression to end-stage liver disease can occur in the absence of large-duct disease [25]. The two entities are assumed to have a shared etiology. However, a recent study demonstrated that small-duct PSC without IBD had a distinct HLA signature to that with IBD or large duct PSC [26].

Overlap: When coexistent, PSC and autoimmune hepatitis can occur simultaneously, or sequentially. An "overlap syndrome" may be a true representation of two distinct pathologies occurring simultaneously, or a description of a phenotype in which biopsy-proven hepatitis and cholangiographic changes are part of the natural history of a single disease.

Autoimmune sclerosing cholangitis: Overlap presentations seem commoner in younger adults, and a prospective study described 50 % of children with autoimmune hepatitis having cholangiographic changes—this has been termed autoimmune sclerosing cholangitis [27], and it may be more sensitive to immunosuppression.

Prognostic Models

Attempts to mathematically model and predict outcomes in PSC are borne out of datasets from referral programmes, with the Mayo PSC model being well established and of some value in late disease. However, no good model exists for patients at early stages of their disease, reflecting a heterogeneous disease course that can be unpredictable. Dominant strictures, cholangitis and malignancy can portend an accelerated trajectory, but are difficult to risk-stratify for in themselves. Alkaline phosphatase levels do seemingly allow stratification of risk, with those failing to normalise/lower their alkaline phosphatase being at greater risk of adverse events, regardless of intervention with ursodeoxycholic acid (UDCA), or the presence of dominant strictures [28]; this mirrors the experience of using alkaline phosphatase as a stratifier of risk in PBC patients. An unmet need therefore is for better surrogates of disease and its prognosis, and there are efforts to apply markers such as transient elastography readings or the serum of the enhanced liver fibrosis test to patients with PSC over time.

Therapy

UDCA is a hydrophilic bile acid that has a proven beneficial role in cholestatic liver disease. The mechanisms by which UDCA exerts its positive effects are multiple. At doses >10 mg/kg/day it constitutes 50–60 % of the bile acid pool, whereas in normal physiology it accounts for 2–3 %. It exerts a cytoprotective effect by displacing toxic endogenous hydrophilic bile acids, and blocks the dissolution of membrane-bound lipids. A choleretic effect is exerted by the increase in the secretion of bile acids and phospholipids that manifests as an increase in bile flow and decreased acidity of the bile. It solubilises cholesterol in bile, thereby theoretically decreasing the risk of sludge build up behind stenoses. It has also been demonstrated to have an in vitro immunomodulatory effect [29]. Despite its proven efficacy in delaying the need for transplantation in PBC, the evidence in PSC is less convincing, to the point where current guidelines do not support its use. The controversies surrounding the use of UDCA are summarised in Box 2.1.

Modulation of cholestasis and bile flow by the use of bile acid treatment remains an attractive therapeutic avenue to study. 24-Norursodeoxycholic acid is a novel treatment currently being explored in phase 2 clinical trials. It is a derivative of UDCA, which has been shown to stimulate a bicarbonate-rich hypercholeresis (due

Box 2.1 Controversies in the management of patients with PSC

Controversial areas of clinical care

Ursodeoxycholic acid

- Early studies suggested a biochemical and cholangiographic improvement from UDCA, and indicated a possible chemopreventative role against cholangiocarcinoma and CRC at 13–15 mg/kg/day.
- In contrast, contemporary studies suggest no benefit in biochemistry, symptoms, quality of life, cholangiocarcinoma or transplant free survival with doses at 17–23 mg/kg/day; higher doses (28–30 mg/kg/day) carried a greater risk of decompensated liver disease, transplantation, cholangiocarcinoma, CRC and death despite improved liver biochemistry.
- The deleterious effects of high-dose UDCA may be, in part, attributable to a direct toxic effect of UDCA or more likely the colonic accumulation of toxic metabolites of UDCA—namely lithocholic acid, a tertiary and hydrophobic bile salt.
- No substantive recommendation can be given for normal doses, but high-dose regimes should be avoided.

Antibiotics

- Frequently used for cholangitis and occasionally used continuously for recurrent cholangitis, although evidence for efficacy is limited.
- There is no data to support the use of antibiotics as prophylaxis against cholangitis in PSC, but antibiotics peri-ERCP is sensible.
- Thus far, three clinical trials have been completed to investigate the role of antibiotics in disease modification—they all demonstrate an improvement in biochemistry, without an effect on harder end points.

Balloon dilatation versus stentplacementfor dominant strictures

- Dominant strictures are associated with reduced transplant-free survival, and increased risk of carcinoma.
- Endoscopic relief of a dominant stricture has a suggested benefit in extending transplant-free survival—yet no clear guidance exists on the best way to do this.
- Endoscopic balloon dilatation may portend a lower risk of complications despite the need for repeat procedures, compared to sent placement.
- Further studies to compare the two treatment modalities are under way.
- In the absence of data, the benefit of endoscopic intervention in the setting of cirrhosis and jaundice should be weighed up against the high-perceived risk in this cohort.

Colorectal Cancer surveillance

- The risk of CRC is markedly higher in those with PSC-IBD.

(continued)

Box 2.1 (continued)

- Annual surveillance colonoscopies are advocated, although this recommendation would benefit from more supporting data.

Prognostication

- Prognostic scoring models are lacking for early PSC. The Mayo PSC model is of established value in late disease.
- There are no established surrogate markers to predict treatment response, though stratification of future risk by alkaline phosphatase values is effective. Elevated IgG4 values in the absence of overt IgG4 disease are also seemingly stratifying, as are measures of liver elastography.
- The disease is often unpredictable meaning risk stratification and the timing of liver transplantation are challenging.

to its notable chole-hepatic cycling) that protects the liver from cholestatic injury in mouse models of sclerosing cholangitis (Mdr2$^{-/-}$mice) [30].

Nuclear hormone receptors provide another attractive therapeutic avenue. They are critical in co-ordinating and regulating genes involved in bile synthesis and secretion, and small intestinal and hepatic detoxification of bile acids. Farsenoid X receptor agonists (e.g. obeticholic acid) have been explored in PBC, and early-phase PSC trials are planned. However, an important distinction between PSC and PBC is the presence of strictures and relative obstruction to biliary flow in PSC, which raises the concern that a FXR agonist may, through enhanced bile flow, precipitate obstruction; the further concern is the complex interplay that FXR signalling has in oncogenesis. However, only carefully controlled clinical trials can bridge these concerns, which remain theoretical only. Peroxisome proliferator-activated receptor agonists may also have yet unexplored value in PSC [31].

Other Treatment Attempts

Antibiotics offer a mechanistically attractive treatment—to combat the possible contributory effects of the gut microbiota and biliary infection to the pathogenesis and progression of sclerosing cholangitis. A randomised trial comparing UDCA and metronidazole vs. UDCA monotherapy demonstrated improved liver biochemistry in the trial arm, but no effect on disease progression [32]. Vancomycin has been shown to similarly improve liver biochemistry in a paediatric population of PSC [33]. Other published data on the use of other antibiotics are limited to case reports and pilot studies.

Disappointingly steroids, tacrolimus and anti-TNF agents have to date had no meaningful impact on disease. This however, has not reduced the optimism for new strategies. These include anti-fibrosis monoclonal antibody therapies (e.g. against LOXL2—an extracellular matrix protein or anti-VAP1 antibodies) and biologic therapy (Vedolizumab) targeting potential gut-primed lymphocytes, which home to the biliary tree.

Cholangitis and Dominant Strictures

Cholangitis contributes to disease progression [34]. Charcot's triad of fever, jaundice and right upper quadrant pain may not occur, and patients may experience a more insidious onset of non-specific symptoms, or even an asymptomatic worsening of liver biochemical markers. Nevertheless, cholangitis may present as a medical emergency requiring appropriate resuscitative management. The role of endoscopic therapy is not straightforward. ERCP has an overall complication rate of around 10 %, which increases in the presence of newly symptomatic disease and the length of procedure [11, 35]. Biliary sphincterotomy may protect against post-ERCP pancreatitis [11], and whilst the evidence is lacking, it is common practice that all PSC patients have antibiotic prophylaxis peri-ERCP [34, 35].

ERCP has a suggested benefit in potentially extending transplant-free survival in the setting of a dominant stricture; the challenge however is that there is such a wide variability in therapeutic decisions and rates of diagnosing dominant strictures. One definition of a dominant stricture is that of a biliary stenosis of >1.5 mm in the common bile duct, or >1 mm in the main hepatic duct; by this definition they are reported to occur in up to 50 % of patients with PSC, although this does not mirror clinical practice more broadly. True, clinically meaningful, dominant strictures appear associated with a reduced transplant-free survival, and an increased risk of carcinoma, especially in the setting of concomitant IBD, or fungal biliary infection [36, 37]. Relief of dominant strictures may improve transplant free survival, though there remains no clear guidance as to the best way to do this (Box 2.1). The safety of endoscopic biliary stent placement was established early, but retrospective long-term follow-up data suggests that the complication risk is lower in balloon dilatation, even accounting for the increased need for repeat procedures [38]. The longest follow up study described 171 patients who were followed up for 21 years. 500 balloon dilatations were performed which yielded an overall 52 % 10-year transplant-free survival rate; a subset analysis of the jaundiced cohort revealed a 10-year transplant-free survival rate of 44 % [39]. Further study to compare the two modalities is currently underway.

The Risk of Malignancy

PSC is associated with hepatobiliary and colonic malignancy. The lifetime risk of cholangiocarcinoma is 10–15 %, with a third being diagnosed at, or within 1 year of, diagnosis of PSC. Thereafter, the annual incidence is around 1 %. Cholangiocarcinomas are difficult to diagnose and differentiate from benign disease. As things stand, surveillance for cholangiocarcinoma has no firm, evidence-based guidance. They can occur as a biliary stricture, hilar mass or intrahepatic tumour. Unlike hepatocellular carcinoma, it does not have a readily reproducible and specific radiologic signature. Traditional serum markers such as heightened concentrations of carbohydrate antigen 19–9 have a poor sensitivity and specificity, with increased concentrations also resulting from cholangitis, biliary dilatation and endoscopic intervention [40]. Routine cytology from endoscopic aspirates and brushings are close to 100 % specific, but has a poor sensitivity (7–33 %), though endoscopic ultrasound and final-needle aspiration may be more fruitful for distal lesions [41]. Fluorescent in situ hybridisation and digital image analysis allow for the detection and quantification of chromosomal abnormalities and aneuploidy. These techniques have been shown to increase the diagnostic yield of cytology [41, 42]. Early data suggests that transpapillary intraductal ultrasonography may have a significant role in differentiating malignant and benign strictures, and when combined with fluorescent in situ hybridisation and digital-image analysis, the sensitivity and specificity may be >90 % [41, 43]. Other endoscopic techniques such as per-oral cholangioscopy, narrow-band imaging and confocal laser endomicroscopy are still in their infancy, and it is too early to foresee what role they will have.

Cholangiocarcinoma-specific peptide markers can be identified in urine and bile using capillary electrophoresis mass spectrometry. Pilot studies demonstrate they are effective in differentiating PSC from cholangiocarcinoma. This technology is also in its infancy, but if established, may provide a non-invasive tool for surveillance and diagnosis [44].

Hepatocellular carcinoma can arise in those with cirrhosis or advanced fibrosis, and local surveillance strategies should be employed—with 6-monthly ultrasonography. This will also allow for the recognition of gallbladder polyps and screening for gallbladder cancer. In the non-cirrhotic PSC patient this is done by annual ultrasound imaging. In some reports 50 % of gallbladder polyps could be malignant, and the incidence of gallbladder cancer in PSC is approximately 2 % [45].

As already described, the inflammatory bowel phenotype in the setting of PSC is a distinct entity, and the risk of associated CRC is amplified [5]. The risk of CRC in PSC-UC is tenfold higher than that of UC alone [1]. Furthermore, carcinoma generally occurs at an earlier age [1]. For this reason it is recommended to screen for colitis at the onset of disease, and then undertake surveillance annually, if diagnosed. Care should be taken to ensure adequate bowel preparation, and appropriate views of the right-sided colon are obtained, as this is the site of the majority of

dysplastic lesions in this setting. However, it worth bearing in mind, the impact of well-established surveillance and treatments (5-aminosalicylic acid, thiopurines) on this malignant transformation risk remains unclear.

The Management of Symptoms and Complications of Cholestasis

Pruritus of cholestasis is a common affliction in those suffering from PSC. It can be severe enough to be the predominant concern and significantly reduce a patient's quality of life. It is often associated with depression, anxiety, disturbed sleep and can even induce suicidal ideation. In its classic form, the pruritus of cholestasis has a diurnal variation with it being at its most intense in the late evenings, preferentially affecting the soles of the feet and the palms of the hands. Bile salt sequestrants (cholestyramine) and other non-specific agents such as μ-opioid receptor antagonists (naltrexone and nalmefene), serotonin antagonists (sertraline), and pregnane X receptor agonists (rifampicin) have moderate antipruritic action, and have been adopted in treatment algorithms [46]. Intractable pruritus may be amenable to Molecular Adsorbents Recirculating System, and may require consideration towards liver transplantation, irrespective of hepatic function. The discovery of new putative pruritogens (lysophosphatidic acid/autotaxin) and ongoing clinical trials (using apical sodium dependent bile acid transporter inhibitors) may further therapy in this field.

Hepatic osteodystrophy describes the bone disease that occurs as a result of liver disease. In PSC, the osteopathy is multifactorial. Cirrhosis, imbalanced bone turnover, osteomalacia, acquired vitamin D deficiency, reduced physical activity, reduced body mass index and hypogonadism all play a role. PSC patients can have the added burden of cholestasis-induced vitamin K deficiency, which is an essential cofactor for osteocalcin production. Furthermore, the encumbrance of coexistent IBD, its cytokine load, and associated glucocorticoid therapy has a cumulative effect on bone mineral density. A recent 10-year cohort study demonstrated that osteoporosis was found in 15 % of patients and occurred 23.8-fold more frequently in PSC than expected from a matched population [47]. Management algorithms should be individualised to consider both liver and non-liver-related risk (which may be estimated by the World Health Organisation Fracture Risk Assessment Tool), and be guided by objective measures of bone mass. Those with cirrhosis or persistent cholestasis may benefit from calcium and vitamin D replacement, though the benefit of this approach is unproven. Specific therapy may be offered when a secondary treatable contributor is identified (i.e. hormone replacement in secondary hypogonadism). Oral bisphosphonates, when taken appropriately, are safe, and have clinically proven benefit in preventing corticosteroid-induced osteoporosis in liver disease. One must not also forget basic lifestyle measures that have proven benefit in alleviating fracture risk—smoking cessation and regular weight-bearing exercise.

The management of cholestasis- and cirrhosis-associated fatigue (seen in 65–75% of patients) requires the physician to source and treat any contributory factors such as allied thyroid disease, anaemia, depression, adrenal insufficiency and drug side effects (beta-blockers are a common culprit). There is however laboratory data to suggest that the fatigue of cholestasis is biologically driven, and therefore in the future may have specific therapy.

Transplantation

In the absence of reliable and easily applicable disease-specific prognostic models, a suitable patient with PSC is listed for transplantation on similar grounds to those with parenchymal diseases of other aetiologies. In the UK, a UK end-stage liver disease score of 49 or more is deemed to be minimal listing criteria in the presence of a specific indication. The score is calculated by the use of a formula involving the following prognostic variables: bilirubin, sodium, creatinine and international normalised ratio. Other countries apply the similar model for end-stage liver disease score, comprising bilirubin, creatinine and international normalised ratio. Whereas hepatocellular carcinoma is an indication for transplantation, cholangiocarcinoma remains a contraindication in most centres despite optimism from facilities undertaking transplantation for small hilar cholangiocarcinomas after neo-adjuvant chemo- and brachytherapy [48]. Very occasionally, intractable and debilitating symptoms in the absence of significant synthetic failure may warrant assessment of the patient for transplantation.

Sclerosing cholangitis is not uncommon post transplantation, and may be due to secondary causes such as ABO blood group mismatch, ischaemic vascular insults and chronic rejection. Nevertheless PSC can reoccur in as many as 20% of patients within 5 years of transplantation. Male sex and an intact colon at the time of transplantation, acute-cellular rejection and the need for maintenance steroids for UC are independent risk factors [49].

Conclusions

PSC remains a very difficult disease to have and to manage. Fundamentally it is a rare hepatobiliary manifestation of IBD that is frequently progressive can prove pre-malignant, and currently devoid of medical therapy. Better understanding of disease is however driving new hope for novel drug treatments and opportunities are being seized to overcome roadblocks to implementing new therapies, such as the development of better surrogate end points of outcome.

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Chapter 3
Commentary: Primary Sclerosing Cholangitis

Keith D. Lindor

This chapter provides a nice overview of primary sclerosing cholangitis (PSC). It brings the reader up to date on current state of knowledge; however it also points out a number of areas in which further work is necessary to answer currently unresolved questions.

In the epidemiology of the disease it remains uncertain why the disease seems to be one of northern climates. There are very few studies from southern Europe, the southern USA, and even less from countries nearer the equator. Furthermore, there are very few studies from the southern hemisphere. The reason for this is unknown, but certainly it may provide some clues as to potential etiologies or may be a reflection of awareness of the disease and rigor of case finding efforts. This question remains unresolved [1].

Similarly the geographic differences in the association of inflammatory bowel disease with PSC remain unexplained. Studies from the more northern parts of the world, including Scandinavia and the upper Midwest of the USA, suggest an association of colitis in about 70 % of the patients with PSC. However, in other studies from the warmer parts of the world the association is found in fewer than 50 % of PSC patients.

One of the other unexplained findings that relates to the association of colitis and primary sclerosing cholangitis is the increased risk of developing colorectal cancers in patients with inflammatory bowel disease who have coexisting PSC. In patients with colitis this risk increases over time as it does in patients with PSC; however in patients with PSC, this risk is usually five times greater than at any point in time than if a patient simply has colitis. The reason for this is unexplained, but it is certainly worthy of further evaluation in the hope that there may be intervention to prevent this high risk of colon cancer.

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In the discussion regarding pathogenesis, the authors introduce the concept that the etiology may not be due to simply one cause but may be multifactorial. Perhaps recognition of this will help further our understanding of the causes of the disease and eventual treatment strategies. Currently the approaches to treatment have considered the disease to be of a single cause and have not explored the possibility that agents with different mechanisms of action may have efficacy for diseases of varying causes. One area that the authors allude to and is ripe for much further study has to do with the role of the gut microbiome. This is an important and increasingly recognized area in gastroenterology and hepatology. Clearly the relationship of the gut microbiome and the etiology of PSC is important to explore particularly given the association of inflammatory bowel disease in many PSC patients.

Diagnosis of PSC has become simpler with MR cholangiography which avoids the morbidity associated with endoscopic retrograde cholangiopancreatography. However as the authors point out MR cholangiography is also subject to interobserver variability, which can impair the diagnostic utility of this cost-effective test. [2]

One of the variants of PSC recently described is IgG4-associated disease. Autoimmune pancreatitis which is also an IgG4 associated disease has a number of diagnostic schema that have been proposed; whereas IgG4 associated cholangitis does not have clear diagnostic criteria established, some have used elevations of serum IgG4 levels above normal, others have used serum IgG4 levels above certain multiples of the upper limit of normal, whereas others have required histology. Histologic sampling of the biliary tract is problematic and is rarely diagnostic, and so we are left with a need for standardized criteria to establish a diagnosis of IgG4-associated disease. Once these criteria are established this will help us to better define the disease and then make treatment trials more feasible. At present, the diagnosis is uncertain, hampering development of adequate treatment trials beyond empiric immunosuppressive based therapy [3].

One of the other important questions related to therapy has to do with value of ursodeoxycholic acid, which the authors discuss. Randomized control trials have failed to disclose the benefit of a dose of 13–15 mg/kg/day. There is biochemical improvement, but not clinical improvement, whereas a dose of double that led to clinical worsening and increased risk of colorectal neoplasia. Intermediate doses have not yet been adequately studied. Recently, data suggests that patients on ursodeoxycholic acid with PSC who had the drug withdrawn underwent clinical deterioration. Several other studies have recently shown the patients who achieved biochemical normalization, whether spontaneously or with ursodeoxycholic acid have a better outlook of their disease course. This opens the door for strategies in which ursodeoxycholic acid is administered for a predefined period of time of 6–12 months to see if biochemical normalization can be achieved, and if so the drug would be continued. However, there are no controlled data supporting this approach [4].

Other therapies that are being evaluated include other derivatives of bile acids such as obeticholic acid which is 6-ethyl-chenodeoxycholic acid, an FXR inhibitor as well as well as norursodeoxycholic acid. Results are not yet available from these drugs. Anti-fibrotic drugs such as lysyl oxidase-like 2 cross-linking inhibitor studies are underway with the results expected shortly. Finally, antibiotics such as

vancomycin have been explored particularly in children and hold some promise but much more work is needed before this approach can be considered as recommended therapy.

The authors introduce the concept of the management of dominant strictures. Like IgG4 associated disease, we do not yet have agreed-upon criteria to define what a dominant stricture is. This is because these are difficult to define and therefore reports of attempted therapy are difficult to place into context.

Also, an important area that is not often times given adequate attention is cancer surveillance for patients with PSC who are at a substantially increased risk for developing cholangiocarcinoma. Some data suggests that regular cross-sectional imaging with ultrasound or MR along with measure of serum levels of CA19-9 might identify patients early enough to find patients eligible for liver transplantation. However, liver transplantation is not always used for patients with primary sclerosing cholangitis. Programs using neo-adjuvant radiation therapy have achieved excellent results. Hopefully, this approach will begin to spread and become more widely available. In institutions in which this approach is available, earlier detection with surveillance does appear to lead to improved overall patient survival.

Finally, liver transplantation is extremely successful in patients with PSC but it is estimated that 20–40 % of patients with PSC will develop recurrent disease after liver transplantation. Clearly, therapy to prevent the reoccurrence of disease is necessary. Perhaps in the absence of effective therapy for the disease itself, it is not surprising that recurrence cannot be prevented also [5].

Primary sclerosing cholangitis is an important disease with many remaining questions and much need for further research as nicely outlined in this chapter.

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Chapter 4
Biliary Manifestations of Chronic Pancreatitis

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Epidemiology and Etiology of Biliary Stenosis in Chronic Pancreatitis

Common bile duct stricture (CBDS) is a common and clinical relevant local complication of chronic pancreatitis (CP). The reported incidence of CBDS in CP varies widely due to differences in the precise definition, the diagnostic vigor, and demographics of different series [1]. Many patients with CBDS in CP do not present with jaundice but with chemical cholestasis. In the majority of patients with CP the disease involves mainly the pancreatic head [2, 3]. Most of these patients will eventually develop CBDS in the natural history of CP. As many patients with CP are referred to surgery (too) late in the course of their disease the incidence of CBDS in surgical series is higher than in nonsurgical series and is reported up to 46 % [3–5]. In series from Europe and especially from Germany, the vast majority of patients present with a large inflammatory mass in the head of the pancreas and frequently present with CBDS, while in the USA the inflammatory mass is less pronounced, resulting in a lower incidence of CBDS [3, 4, 6]. In a comparative study of a US and a German center specialized in pancreatic surgery, CBDS was radiologically proven in 26 % and 40 % of patients while chemical cholestasis was reported in 4 % and 46 %, respectively [4]. These obvious but unexplained differences in pathologic anatomy have led to different strategies and preferences in the surgical management of CP as described in detail below.

Restriction and compression of the intrapancreatic common bile duct by dense fibrotic tissue and calcifications is the common etiology of CBDS in CP

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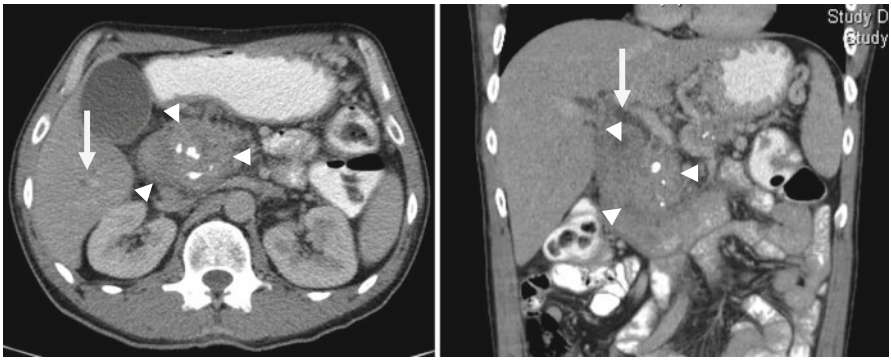

Fig. 4.1 Typical radiological findings in a patient with CBDS in CP. Preoperative CT scan in axial (*left*) and coronal (*right*) orientation showing an inflammatory mass in the head of the pancreas (*arrowheads*) with parenchymal calcifications and extra- and intrahepatic bile duct dilation (*arrows*) as sign of a biliary stricture

(Figs. 4.1 and 4.2a), is usually progressive, and does not spontaneously resolve. In contrast, compression of the common bile duct by pseudocysts is less frequently observed and may resolve with spontaneous regression or successful treatment of the pseudocyst.

Autoimmune pancreatitis with common bile duct compression or direct involvement of the biliary tract is a rare but important differential diagnosis and can usually be ruled out by the typical medical history and the typical morphological changes (calcification) in patients with CP. The management of biliary manifestations of autoimmune pancreatitis is described in detail in the following chapter XXX, p. XXX.

Management of Biliary Stenosis in Chronic Pancreatitis

If a CBDS presents as a manifestation of CP, it should not be considered as an isolated problem but in the context of the underlying disease. The management has to address both the CBDS and all other concomitant symptoms and complications of CP.

Conservative Therapy of Chronic Pancreatitis

Conservative treatment is the basis of any adequate management of CP and includes (1) reduction of etiologic risk factors, including abstinence from alcohol and nicotine consumption; (2) substitution for exocrine and endocrine insufficiency and nutritional supplements; as well as (3) effective pain therapy according to the WHO

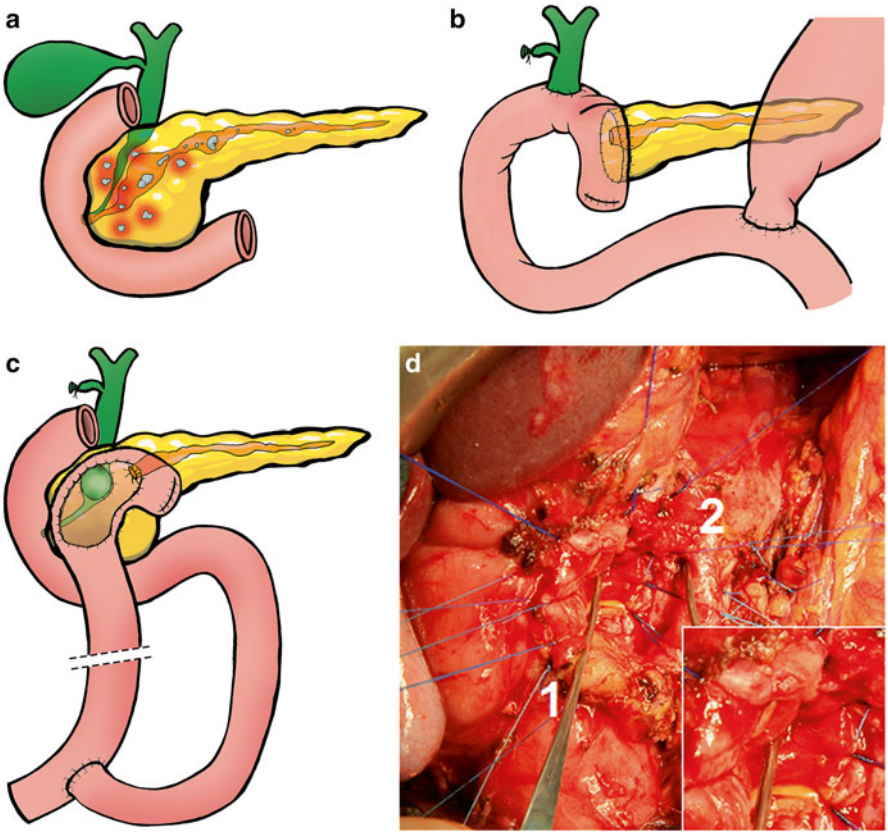

Fig. 4.2 Preferred techniques of pancreatic head resection for the management of CP with common bile duct stricture. (**a**) Preoperative finding of CBDS due to calcifying CP. (**b**) Pancreatoduodenectomy for the management of CBDS in CP. Biliary drainage is performed by hepaticojejunostomy. (**c**) Duodenum-preserving pancreatic head resection (DPPHR, Berne modification) with internal biliary anastomosis for CBDS in CP: By excavation of the pancreatic head, the intrapancreatic portion of the CBD is decompressed. Biliary drainage is secured by an internal biliary anastomosis to the resection cavity. Drainage of the resection cavity by Roux-en-Y pancreatojejunostomy. (**d**) Operative situs of DPPHR (Berne-modification) with internal biliary anastomosis before reconstruction. *Probe 1* marks the bile duct. The bile duct wall has been anastomosed to the resection cavity (*inset*). *Probe 2* marks the main pancreatic duct towards the tail

scheme (Table 4.1) [7, 8]. Management of intermittent chemical cholestasis may include ursodeoxycholic acid. However, in case of prolonged chemical cholestasis, presence of morphological CBDS, and manifest jaundice further treatment is warranted. Prolonged conservative treatment without adequate drainage harbors the danger of secondary biliary cirrhosis while early adequate biliary drainage in CP can result in regression of liver fibrosis [9, 10].

Table 4.1 Management options of biliary stenosis in chronic pancreatitis

Conservative	
– Quit smoking and alcohol	*Basis of any therapy in CP*
– Substitution for exocrine and endocrine insufficiency	
– Effective analgesia	
– Ursodeoxycholic acid	Short-term management
– Antibiotics	Short-term management in case of cholangitis
Endoscopic	*Indication: primary management*
– ERC + ePT + stenting	– Effective in the short term
	– Only 30 % long-term success
	– Poor results if treatment >12 months
	– Poor results in patients with calcifications
– Endoscopic cystogastrostomy/ cystoduodenostomy	– CBDS due to compression by pseudocysts
	– Less invasive than surgery
	– Problems with dislocation and recurrence
Radiologic intervention	
– Percutaneous transhepatic cholangio drainage (PTCD)	Only rarely indicated if neither surgery nor ERC are possible
– External drainage of pseudocysts	
Surgical	
Drainage procedures	
– Hepaticojejunostomy (Roux-en-Y)	– In patients without pancreatic duct obstruction (rare)
	– If exposure of the pancreatic head is not possible
	– In patients with recurrence after other procedure
– Choledochoduodenostomy	Similar indications but inferior to hepaticojejunostomy due to higher risk of ascending cholangitis
– Surgical cystogastrostomy/ cystoduodenostomy	For pseudocysts in the absence of inflammatory mass
Resections	
– Duodenum preserving pancreatic head resection *with internal bile duct anastomosis* (DPPHR)	Safe and effective. Berne technique is an equally effective but technically easier technique compared to the Beger procedure and PD

(continued)

Table 4.1 (continued)

– Pancreatoduodenectomy (PD)	– Equally effective but more invasive and technically more difficult compared to DPPHR
	– Procedure of choice if malignancy is suspected
– Total pancreatectomy (TP)	– Rarely performed
	– Can be performed with islet autotransplantation
	– Favorable outcome reported in selected cases

ERC endoscopic retrograde cholangiography, *ePT* endoscopic papillotomy, *PTCD* percutaneous transhepatic cholangio drainage, *DPPHR* duodenum-preserving pancreatic head resection, *PD* pancreatoduodenectomy, *TP* total pancreatectomy

Endoscopic Treatment Options vs. Surgery

Many patients with CP will require additional therapy for effective pain relief or for treatment of local complications such as CBDS. As most of these patients are primarily referred to gastroenterologists they first undergo endoscopic treatment. Endoscopic treatment options and their indications are summarized in Table 4.1. In patients with CP most endoscopic interventions are performed for pancreatic ductal obstruction. However, with disease progression, patients frequently develop chemical cholestasis or manifest CBDS and will undergo bile duct stenting as well. In almost all patients endoscopic treatments, such as stone extraction, dilations, and stenting have to be repeated on a regularly basis. Common complications such as stent occlusion with subsequent cholestasis and cholangitis result in frequent rehospitalizations. Endoscopic retrograde cholangiography (ERC) with papillotomy and bile duct stenting is certainly effective for short term relief and, therefore, indicated in the acute situation and especially in patients with severe cholangitis. In contrast, the long-term outcome of endoscopic treatment for CBDS is poor. A large retrospective multicenter study in 1018 patients reported a success rate of endoscopic therapy (multiple sessions) in 65 % and necessity of surgery in 24 % of patients [11]. However, if endoscopic treatment for 12 months does not result in resolution of the CBDS further endoscopic treatment is ineffective [12]. In a prospective observational study the success rate of ERC and stenting (every 3 months) was 59.1 % in patients without calcifications but as low as 7.7 % in patients with calcifications [13].

In contrast, in patients with CBDS due to compression by pseudocysts, endoscopic drainage procedures may be equally safe and effective as surgical drainage and superior to external drainage, as reported in a retrospective study [14].

Two randomized controlled trails demonstrated the superiority of surgical versus endoscopic therapy for obstructive CP in general with respect to primary success

rate, pain relief, and quality of life in patients with proximal pancreatic duct obstruction [15, 16]. However, there are so far no randomized controlled trials comparing endoscopic and surgical therapy specifically for patients with CBDS in CP. A small non-controlled study comparing endoscopic and surgical management of CBDS in CP in 39 patients found a low success rate of endoscopy if more than three interventions are needed and clearly favors surgery in these patients [17].

The current evidence allows for the following recommendations concerning endoscopic vs. surgical treatment of CBDS in CP:

- Prolonged chemical cholestasis, radiologic proof of bile duct stenosis, and cholangitis are indications for endoscopic or surgical management.
- In patients with jaundice and acute cholangitis ERC with stenting is an effective procedure with good short-term results.
- Endoscopic management is only effective in one-third of patients. Long-term results of endoscopic treatment are poor if the CBDS is not resolved after 12 months and in the presence of parenchymal calcifications.
- Cholestasis due to pancreatic pseudocysts may resolve spontaneously and can be treated endoscopically. If endoscopic treatment fails, a surgical drainage procedure should be performed.

If endoscopic treatment did not effectively resolve CBDS (and other concomitant symptoms and complications of CP) after 12 months, patients should undergo surgical therapy. Prolonged endoscopic management of CP is associated with poor long-term outcome.

Surgical Management Options for Chronic Pancreatitis with a Focus on Biliary Stenosis

The surgical options for CP in general and for biliary stenosis can be divided in drainage procedures and resections (Table 4.1).

Drainage Procedures

As mentioned above any surgical procedure for CP has to address the entire disease and not one single complication such as CBDS. Most patients who develop CBDS in the setting of CP have extensive changes in the pancreatic head and also present with a pancreatic ductal obstruction (Fig. 4.2a). An isolated biliodigestive anastomosis is an effective therapy for the CBDS, but does not adequately address pancreatic ductal obstruction, consecutive pain, and disease progression. Isolated biliodigestive anastomosis should, therefore, be reserved for the following rare situations: (1) patients with isolated CBDS *without* pancreatic ductal obstruction, (2)

patients with extensive peripancreatic inflammation or extensive venous collaterals that prevent a safe exposure of the pancreatic head, (3) patients who need a redo-procedure due to recurrent biliary obstruction after surgical therapy. For biliodigestive anastomosis hepaticojejunostomy with Roux-en-Y reconstruction should be preferred whenever possible, because of the lower risk of ascending cholangitis compared to choledochoduodenostomy.

Some authors describe the combination of biliodigestive anastomosis with pure drainage procedures for the pancreatic ductal system or with the Frey procedure [9, 18]. The resection procedures described below effectively address both problems at once.

Resection Procedures

In patients with CP and CBDS the main problem is located in the pancreatic head. Therefore, pancreatoduodenectomy (PD) and duodenum preserving pancreatic head resection (DPPHR) are the main alternatives of resection procedures (Table 4.1 and Fig. 4.2). As introduced above, different techniques were developed and are still preferred in the US and Europe as a result of regional differences in the typical pathological anatomy observed in CP [4]. The *partial pancreatoduodenectomy (PD)* or Kausch-Whipple-procedure includes resection of the pancreatic head with duodenum and the lower third of the stomach. PD was initially reserved for malignancies in the pancreatic head [19]. With increasing safety the procedure was also introduced for patients with CP in its classical or pylorus-preserving form (Fig. 4.2b) [20, 21]. In experienced hands PD for CP is a safe procedure (mortality of 2–5 %) that effectively resolves both biliary and pancreatic ductal stenosis and results in long-term pain relief in about 80 % of patients [22–24]. PD is the preferred resection by several centers of pancreatic surgery in the USA and the procedure of choice in cases in which malignancy is suspected.

However, malignancy in CP is rare and for most patients with CP resection of the duodenum is not necessary for oncologic reasons. Moreover, a PD can be technically very demanding and may then be associated with increased morbidity in patients with CP and severe portal hypertension. Taking this into account, Beger et al. introduced the *duodenum-preserving pancreatic head resection* (DPPHR) as a less invasive and organ-sparing procedure designed specifically for patients with CP and an inflammatory mass in the head of the pancreas [2, 25, 26]. Similar to PD the pancreas is divided at the level of the portomesenteric axis. However, in contrast to PD, the pancreatic head is excavated with preservation of the duodenum and a thin layer of pancreatic tissue. The reconstruction is performed by two anastomoses with a jejunal loop to drain the pancreatic tail remnant and to cover and drain the resection cavity in the pancreatic head. During this procedure the common bile duct can be opened and drained with an internal anastomosis to the resection cavity to treat CDBS [3, 27]. In cases with chemical cholestasis or manifest CBDS this internal bile duct compression has to be routinely performed. In the USA Frey et al. developed a hybrid technique combining aspects of the DPPHR as described by Beger

and a laterolateral pancreatojejunostomy (Partington–Rochelle procedure) [28–30]. Compared to the Beger procedure the resection in the pancreatic head in the Frey procedure is less extended and decompression of the bile duct is possible, but may be less effective [18]. Therefore, the Frey procedure is frequently augmented with a biliodigestive anastomosis in cases with CBDS [18]. This procedure is advantageous in patients with a less severe inflammation in the pancreatic head but a pancreatic ductal obstruction that extends towards the tail. The *Berne modification of DPPHR* (Fig. 4.2c) represents a technical simplification of the Beger procedure with equal efficacy [5, 7, 31, 32]. In the Berne modification of DPPHR the pancreatic body is not divided at the level of the portomesenteric axis, a step of the Beger procedure and PD that is often difficult because of inflammatory adhesion and portal hypertension. However, the excavation of the pancreatic head can be performed with identical extent compared to the Berger procedure. The reconstruction can be performed by one single anastomosis between a jejunal loop and the continuous pancreatic resection rim (Fig. 4.2c) [7, 31]. As in the Beger procedure, a CBDS can be effectively decompressed by an internal bile duct anastomosis (Fig. 4.2d). In cases with CBDS thorough decompression and internal anastomosis of the common bile duct is mandatory. We advocate the Berne modification as the procedure of choice in patients with CP and associated CBDS due to an inflammatory mass because it is equally effective but technically easier than PD and the Beger procedure [5, 7, 32]. Independent of the technique of DPPHR, an intraoperative frozen section has to be obtained to rule out pancreatic adenocarcinoma. If the rare event that frozen section is suspicious for malignancy or if a cancer is suspected already preoperatively, PD is the procedure of choice.

If carried out by experienced hands all techniques of pancreatic head resection are safe and effective and associated with good short- and long-term results in patients with CP [3, 6, 28, 32, 33]. In several randomized-controlled trials (RCTs) all techniques of pancreatic head resection were compared and their safety and efficacy was confirmed [5, 32, 34–41]. The RCTs comparing PD and DPPHR [32, 34, 35, 37, 39, 40] as well as a recent meta-analysis [42] demonstrate comparable mortality and efficacy in terms of pain relief as well as endocrine insufficiency. However, the less invasive DPPHR was superior in hospital stay, exocrine insufficiency, weight gain, and quality of life in medium-term follow-up. In follow-up studies reporting long-term outcome these metabolic advantages appear to be lost over time and long-term results of PD and DPPHR are equal in terms of pain management and quality of life as well as endocrine and exocrine function [24]. It should be noted that the resection techniques remain effective in terms of pain relief and quality of life but cannot stop the progress of exocrine and endocrine insufficiency on the long term [24, 40]. While none of the RCTs focused on long-term efficacy of biliary decompression, most re-hospitalizations after pancreatic head resection were necessary for pain attributed to recurrent pancreatic ductal obstruction. Recurrent biliary stenosis was not identified or discussed as a frequent problem even in long-term follow-up.

Total pancreatectomy is controversially discussed but can be an effective alternative to partial pancreatectomy in the management of CP in selected patients

with severe disabling complications of the disease and in individuals with high risk to develop pancreatic cancer [43]. To preserve endocrine function and avoid brittle diabetes total pancreatectomy can be combined with islet autotransplantation [38, 44, 45].

Based on the current literature the following recommendations can be made with respect to surgical management of CBDS in CP:

- With respect to long-term outcome surgery is superior to endoscopic treatment of CBDS in CP.
- Patients with CBDS persisting after 12 months of endoscopic treatment and with parenchymal calcifications should undergo early surgical intervention rather than prolonged endoscopic therapy.
- Most patients with CBDS in CP also have a pancreatic ductal obstruction. The surgical strategy has to address both problems. Therefore, resections procedures should be preferred.
- PD and DPPHR with internal biliary anastomosis are equally effective in the management of CBDS in CP.
- The Berne modification of DPPHR represents an equally effective but technically less demanding technique if compared to PD and the Beger procedure.

Surgical Management for Recurrent Biliary Obstruction in CP

The etiology of recurrent biliary obstruction after surgery for CP depends on which procedure was initially performed. Such redo procedures in CP are often technically demanding and should be performed by an experienced pancreatic surgeon [46].

After isolated biliodigestive anastomosis or PD recurrent biliary obstruction is frequently observed as a late complication of leakage at the biliary anastomosis. Interventional radiology with PTCD and dilation are effective in the initial management of such anastomotic strictures. If the interventional management does not resolve the stricture a surgical redo procedure is indicated. The management of anastomotic strictures is described in detail in Chapter IV b, p. XXX.

After DPPHR with internal biliary anastomoses recurrent biliary obstruction may occur by progressive mass-forming inflammation with subsequent stenosis of the internal anastomosis. If the pancreatic head was thoroughly excavated and the bile duct adequately opened and inserted in the resection cavity such recurrence of biliary obstruction should only very rarely occur. If it occurs, interventional management is rarely effective and redo procedures are usually indicated. In these cases, the decision for Re-DPPHR, conversion to a PD, or additional biliodigestive anastomosis with the loop used for DPPHR or a second Roux-en-Y loop has to be made on a case-by-case basis.

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Chapter 5
Commentary: Biliary Manifestations of Chronic Pancreatitis—Critical Uncertainties, Controversies, and Future Considerations

David B. Adams

Terminal biliary stenosis is commonly a challenging complication of fibrosing chronic pancreatitis. In chronic, severe pancreatitis, patients can develop evidence of stenosis of the distal common bile duct due to ductal compression by the inflammatory process in the head of the pancreas. Similar compression and obstruction of the terminal bile duct may be associated with a pancreatic pseudocyst in the region of the head of the pancreas. Although it may be difficult to differentiate the two processes, pseudocyst-related obstruction is ameliorated with pseudocyst drainage. The fibrotic encasement of the terminal bile duct associated with chronic fibrosis in the head of the pancreas requires surgical bypass in order to prevent the consequences of cholestasis, recurrent cholangitis and biliary cirrhosis. Recently endoscopic therapies have been employed in the management of terminal biliary stenosis with variable success. Questions that are worthy of debate are which patients should be treated endoscopically, which patients should be treated surgically, and which patients should be managed expectantly? It is difficult to quantify and clearly define the risk of terminal biliary stenosis in a patient who has a dilated bile duct with minimal elevation in liver enzymes.

When patients with terminal biliary stenosis develop jaundice, pain, or cholangitis, surgical or endoscopic intervention is indicated. Both open and laparoscopic biliary bypass have been utilized in the management of symptomatic biliary stenosis. Open procedures may be safer when other complicating factors such as portal venous occlusion with cavernous transformation of the portal vein are present. Choledochoduodenostomy has a simplicity that makes it safe and effective in the management of biliary obstruction. When peripancreatic inflammation involves the

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proximal duodenum and renders it fixed and immobile the Roux-en-Y hepaticojejunostomy is preferred. Cholecystectomy is undertaken to prevent future complications with cholelithiasis and cholecystitis. Many patients develop small, pigmented gallbladder stones in association with biliary stenosis. When undertaking surgical management of chronic pancreatitis with resection or drainage procedures, evaluation for terminal biliary stenosis is required so that biliary bypass can be undertaken if stenosis is present, even if asymptomatic. Biliary-enteric bypass with should be part of the Puestow, Berne, Frey, or Beger procedure when biliary stenosis is present.

Advances in endoscopic retrograde cholangiopancreatography (ERCP) and endobiliary stent technology have led to increasing use of endoscopic management of patients with symptomatic biliary obstruction associated with chronic pancreatitis [1]. Endoscopic management avoids surgical morbidity associated with open and laparoscopic procedures. Endoscopic drainage involves a biliary sphincterotomy, dilation of the stricture using graduated catheters or hydrostatic balloons, and placement of multiple plastic stents in parallel. The short-term efficacy of endoscopic drainage is high, but its durability is limited by the degree of peri-ductal pancreatic fibrosis. Endoscopic management requires three to four ERCPs to achieve maximal dilation. Fully covered, self-expanding metallic stents may improve outcomes for endoscopic therapy by providing sustained radial expansion of the stricture with an indwelling stent. Utilization of self-expanding metallic stents for benign disease is controversial because of associated problems with long-term stenting. The decision to proceed with endoscopic or surgical treatment of terminal biliary stenosis is usually based on local expertise and clinical factors. Endoscopic therapies are frequently selected for patients with complicated pancreatic disease and medical comorbidities where surgical complications are expected to be high. Stent therapy may improve the underlying medical disorders and assist in making the patient a better surgical candidate. If comorbid conditions are severe, stent therapy may be highly successful in palliative strategies.

Biliary-enteric bypass has been utilized as a safe and effective treatment of biliary strictures for decades. Robert Hermann at the Cleveland Clinic was a proponent of choledochoduodenostomy (CDD) for biliary strictures associated with periampullary malignancy, and we adopted this technique for the management of biliary strictures associated with chronic pancreatitis. In 79 patients who underwent CDD for terminal biliary stenosis associated with chronic pancreatitis, long-term success was achieved in 77 with an operative morbidity of 19 % [2]. The so-called sump syndrome refers to a clinical diathesis of fever, elevated hepatic chemistries, cholangitis, or hepatic abscess due to biliary stasis in the terminal bile duct and reflux of duodenal contents is a reported complication after CDD. With an adequate anastomotic size sump syndrome is a rare event; more commonly sump syndrome is associated with anastomotic stenosis. Other retrospective series of CDD for chronic pancreatitis have reported long-term success rates of 90–100 %.

Choledochojejunostomy (CDJ) is preferred to CDD by many surgeons [3]. CDJ is useful when a fibrotic duodenum is not suitable for anastomosis and is some surgeons' preference to avoid the sump syndrome. CDJ may have less entero-biliary reflux than CDD. On occasion patients with recurrent bouts of cholangitis with a

patent CDD may be converted to CDJ with resolution of cholangitis. Both CDD and CDJ are associated with a small incidence of recurrent cholangitis that may be an indicator of chronic intrahepatic biliary tract disease.

Laparoscopic management of biliary stenosis associated with chronic pancreatitis has been utilized with both CDD and CDJ. Conversion rates may be high but long-term success is expected. Operative morbidity and mortality are influenced by disease severity and underlying medical comorbidities.

Frequently terminal biliary stenosis is not the primary indication for surgery in chronic pancreatitis. In patients in whom pain is the chief indication for operation who have a dilated pancreatic duct, lateral pancreaticojejunostomy may be combined with a CDD. Patients with biliary obstruction and duodenal stenosis have an indication for pancreatoduodenectomy (PD). In patients with an inflammatory mass in the head of the pancreas, a variety of hybrid procedures have been described and evaluated prospectively in head to head comparisons. The Frey procedure, Beger, procedure, and Berne procedure all have strong proponents. Excellent outcomes are reported for all procedures and when biliary stenosis is present, the pancreatic drainage with a Roux-en-Y pancreaticojejunostomy is combined with a hepaticojejunostomy or choledochojejunostomy.

The basic principal of endoscopic treatment of biliary stricture associated with chronic pancreatitis is to maximally dilate the stricture using graduated catheters or hydrostatic balloons, followed by placement of multiple parallel plastic stents [4, 5]. After 3–4 months, stent occlusion rates rise, and repeat ERCP and stent upsizing is undertaken. Experts advocate maintaining patency of the stricture for up to 12 months after embarking upon endoscopic treatment. Patients can assume an average of three to four ERCPs and up to 1 year of therapy in order to achieve stricture resolution. This long-term investment in stent therapy is undertaken to avoid the high recurrence rates seen with short-term stenting. Fully covered, self-expandable metallic stents (SEMS) have features which may produce better long-term outcomes than plastic stents [6, 7]. Because SEMS radially expand within the duct, a sustainable dilation of the biliary stricture and lower recurrence rates are possible. Drawbacks of SEMS include difficulty with removal and specific complications such as acute pancreatitis due to compression of the pancreatic orifice, cholecystitis due to occlusion of the cystic duct, and secondary bile duct compression injury due to an oversized stent. Although comparative efficacy trials are lacking, there is a growing body of literature favors the safety and efficacy of SEMS in appropriately selected patients.

Therapeutic endoscopy is a controversial primary approach to terminal biliary stenosis associated with chronic pancreatitis. Endoscopy can potentially avoid the high reported surgical morbidity. This recommendation is supported by high initial endoscopic success rates. While the durability of endoscopic therapy is inferior to surgery, substantial number of patients will avoid surgery, and those that don't can be salvaged with operation. Judgment in patient selection and technical expertise and experience are the key to good outcomes with stenting strategies.

Surgery is an effective treatment for biliary strictures associated with chronic pancreatitis. In patients with non-biliary complications of chronic pancreatitis

requiring surgery (pancreatic duct obstruction with pain, pancreatolithiasis, duodenal obstruction) surgery is a reasonable primary approach. Biliary bypass can be included with pancreatic duct drainage. Side-to-side choledochoduodenostomy is my preference. It is safe and durable with minimal morbidity. By separating the biliary and pancreatic anastomoses, the risk of a combined biliary and pancreatic leak is diminished which decreases the morbidity of a leak of pancreatic enzymes activated by biliary enterokinase. "Sump syndrome" is an unusual long-term complication of CDD and can be avoided by an adequate anastomotic diameter.

Chronic pancreatitis is a heterogenous disease with different clinical and morphological presentations that depend on environmental, genetic, and anatomic factors. There is great geographic variation in the presentation of the disease as exemplified by the calcific chronic pancreatitis of Southern India and the inflammatory head mass reported in studies from Germany. Thus it is hard to classify and directly compare different management strategies for biliary obstruction associated with chronic pancreatitis. Also unanswered is the risk of cholangitis and biliary cirrhosis associated with terminal biliary stenosis. Certainly the patient with cholangitis and multiple medical comorbidities would be best managed with minimally invasive endoscopic techniques. But what about the asymptomatic patient with mild elevations in serum alkaline phosphatase and bilirubin with common bile duct dilation? What is the natural history of that disorder? Identification of the non-dilatable stricture is difficult and is the crux of patient selection process. When patients have symptomatic terminal biliary stenosis with fibrosing pancreatitis, repeated endoscopic stenting may be needed indefinitely. Choledochoduodenostomy is an attractive long-term solution and may be performed with minimally invasive laparoscopic techniques. However, chronic peripancreatic and peri-duodenal inflammation may make the operation difficult and hazardous. Normal anatomic landmarks may be hidden and simple identification of the inflamed and dilated common bile duct can be challenging. When duodenal fibrosis is severe, mobilization and anastomosis between a fibrotic duodenum and the bile duct may be difficult. In this situation preoperatively placed transpapillary biliary stents are useful to protect the anastomosis post-operatively. Alternatively, Roux-en-Y hepaticojejunostomy may be more prudent when the duodenum is unfavorable for anastomosis. Patients who have cavernous transformation of the portal vein associated with superior mesenteric and portal vein stenosis can safely undergo CDD though increased operative blood loss is expected, and these patients are frequently directed towards endoscopic therapy. An evidence-based approach to biliary strictures in chronic pancreatitis is problematic and patient selection remains grounded in local experience. As new minimally invasive laparoscopic and endoscopic tools and techniques are developed they can be better tested against traditional open surgical techniques in appropriately classified patient cohorts and evidence will replace experience in clinical practice.

Our current practice is outlined in the following:

1. Poor operative candidates

   Endoscopic therapy, consider indefinite placement of SEMS.

2. Reasonable operative candidates, no other chronic pancreatitis-related morbidity

   Endoscopic therapy as first-line treatment
   Surgical intervention for non-response or recurrence following endoscopic therapy

3. Reasonable operative candidates, concomitant CP-related morbidity

   Surgical therapy as first-line treatment

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Chapter 6
Autoimmune Pancreatitis

Neil Sengupta and Sunil Sheth

Introduction

Autoimmune pancreatitis (AIP) is a chronic, fibro-inflammatory disease of the pancreas that has been recognized as a distinct clinical entity for approximately two decades [1]. Since patients with this rare disorder commonly present with obstructive jaundice mimicking pancreatic cancer, early recognition and diagnosis of AIP are critical. Over the past few years, AIP has been shown to be comprised of two distinct subtypes - type 1 and type 2 AIP. Type 1 AIP is the pancreatic manifestation of a systemic disorder known as IgG4-related disease [2], and is commonly associated with extrapancreatic manifestations such as sclerosing cholangitis. On the other hand, type 2 AIP is a pancreatic disorder without extrapancreatic manifestations that is not related to IgG4, and typically occurs in younger patients [3]. This chapter provides a review of current knowledge of autoimmune pancreatitis with a focus on biliary manifestations of the disease.

Classification

AIP was first described in 1961 in a case of pancreatitis associated with hypergammaglobulinemia [4]. In 2001, AIP was shown to be associated with elevated serum IgG4 concentrations [5]. Subsequently, Kamisawa reported the presence of

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abundant IgG4 positive plasma cells in multiple organs in patients with AIP [6]. However, Notohara and colleagues reported two distinct histologic patterns in patients with autoimmune pancreatitis. Specifically, some patients with disease confined to the pancreas without IgG4 association had evidence of a neutrophilic infiltrate in the ductal epithelium with duct destruction [7]. Patients with these clinical and pathologic findings were subsequently classified as having type 2 AIP, whereas the former group were thought to have type 1 AIP [8, 9]. Accurate classification of AIP is important given that the subtypes have distinct clinical presentations with different outcomes and relapse rates [10].

Epidemiology

AIP is a rare condition with a reported prevalence in Japan of 0.82 per 100,000 [11]. The incidence and prevalence of AIP in the USA are unknown, and reports of this condition are limited to series from tertiary referral centers. Type 1 AIP is the more common subtype, and is the exclusive subtype in Japan where this subtype was first described [12]. Type 2 AIP has been shown to account for 37 % of cases from resected AIP in the USA [13], and 45 % of cases in a European series [14]. In a recent multicenter study, the mean age of patients with type 1 AIP was 61.4 years, compared to a mean of 39.9 years for patients with type 2 AIP. In addition, type 1 AIP patients were more likely to be male (77 % of type 1 AIP versus 55 % of type 2 AIP patients) [15].

Clinical Presentation

As type 1 AIP is a pancreatic manifestation of a systemic, multi-organ disorder known as IgG4-related diseases, patients with type 1 AIP may have a variety of different clinical presentations. Since the clinical and radiologic profile of disease may change over time, pancreatic manifestations of Type 1 AIP can be divided into active and late phase presentations. Patients in the active phase most commonly present with painless obstructive jaundice. These patients may also present with a focal mass or pancreatic enlargement which can be difficult to distinguish from pancreatic cancer [16]. In contrast, patients presenting late in the course of disease may have pancreatic atrophy with calcification and stones similar to that seen in chronic pancreatitis [17]. Patients with type 2 AIP may also present with obstructive jaundice, but also frequently present with acute pancreatitis. These patients also are more likely to have associated inflammatory bowel disease [18].

Compared to patients with type 2 AIP, a typical feature of type 1 AIP is presentation with extrapancreatic organ involvement, especially IgG4-sclerosing cholangitis, or IgG4 related cholangiopathy. As this is a biliary manifestation of IgG4-related disease, it is important to distinguish IgG4-sclerosing cholangitis from malignancy

such as pancreatic cancer or cholangiocarcinoma, as well as primary sclerosing cholangitis (PSC) [19]. Of note, 80 % of patients with AIP may develop complications related to distal CBD stenosis [20, 21]. The stricture may be related to both inflammation related to pancreatitis or thickening of the bile duct related to infiltration of IgG4-positive plasma cells. In a retrospective study of patients with AIP, Hirano and colleagues found that 93 % of patients with AIP and pancreatic head lesions had intrapancreatic bile duct strictures compared to 17 % of patients without pancreatic head lesions [22]. The authors argued that both pancreatic edema and biliary wall thickening influenced the development of intrapancreatic biliary strictures in AIP, and favored differentiating these types of strictures from extrapancreatic biliary strictures caused by biliary wall thickening only.

Patients with IgG4-sclerosing cholangitis typically also present with obstructive jaundice in the setting of biliary strictures. In addition, these patients typically have dilation after a confluent biliary stricture. Unlike patients with PSC, patients with IgG4-sclerosing cholangitis do not present with a beaded, or pruned-tree appearance of the bile ducts [23]. Although magnetic resonance cholangiopancreatography (MRCP) may provide useful clinical information, the bile duct typically should be assessed directly via endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC).

Four types of cholangiographic features of IgG4-sclerosing cholangitis based on location of the stricture have been reported (Table 6.1): type 1, where stenosis is only located in the distal CBD; type 2, where there is diffuse stenosis throughout the intrahepatic and proximal bile duct; type 3, where stenosis is located in the hilar hepatic and lower common bile duct; and type 4 where the stricture is located in the hilar hepatic lesion. Type 1 IgG4-sclerosing cholangitis should be distinguished from chronic pancreatitis, pancreatic malignancy, or cholangiocarcinoma. Cholangiographic features of types 3 and 4 should be distinguished from cholangiocarcinoma, whereas type 2 must be distinguished from PSC [24]. Of note, type 2 IgG4-sclerosing cholangitis can be further broken down into two subtypes—type 2a

Table 6.1 Patterns of clinical findings in IgG4-related sclerosing cholangitis (adapted from Okazaki et al. [24])

Type	Location of stenoses	Differential diagnosis	Useful diagnostic modalities
1	Distal CBD	Pancreatic cancer Bile duct cancer Chronic pancreatitis	IDUS (bile duct) EUS-FNA Bile duct biopsy
2	Diffusely through intrahepatic and extrahepatic bile ducts	Primary sclerosing cholangitis	Liver biopsy Colonoscopy (R/o coexistence of IBD)
3	Hilar hepatic lesions and lower part of CBD	Bile duct cancer Gallbladder cancer	EUS (bile duct, pancreas) IDUS (bile duct) Bile duct biopsy
4	Hilar hepatic lesions	Bile duct cancer Gallbladder cancer	EUS (bile duct, pancreas) IDUS (bile duct) Bile duct biopsy

with narrowing of the intrahepatic bile ducts with prestenotic dilation and type 2b with narrowing of the intrahepatic bile ducts and reduced bile duct branches without prestenotic dilation.

Modalities that can help discriminate between these diagnoses include intraductal ultrasound, endoscopic ultrasound-guided fine-needle aspiration, and bile duct cytology [19]. Nakazawa et al. reported that 56 % of cases of IgG4-sclerosing cholangitis presenting to their institution were classified as type 1 IgG4-sclerosing cholangitis [25]. In a series of 28 patients with AIP and biliary involvement suspicious for IgG4-sclerosing cholangitis, 82 % of patients had both intrahepatic and extrahepatic bile duct strictures [26]. In addition to the findings above, circular and symmetric thickening of the bile duct wall can also be observed in areas of the bile duct that do not have stenosis and appear normal on cholangiography [27].

Patients with IgG4-sclerosing cholangitis are responsive to steroids; if lesions do not respond, then reevaluation for malignancy should be performed. However, the response should be interpreted cautiously as some malignant lesions occasionally improve after steroid administration [28]. Unlike biliary strictures in PSC, strictures in IgG4-sclerosing cholangitis typically respond to steroid therapy [29, 30]. However, untreated IgG4-sclerosing cholangitis could lead to end-stage liver disease [30].

In addition to biliary involvement, patients with Type 1 AIP may also present with manifestations due to other organ involvement, such as Sjogren's disease due to salivary gland involvement, retroperitoneal fibrosis, tubulointerstitial nephritis, or bilateral submandibular masses [3].

Imaging Findings

Given that patients presenting with obstructive jaundice usually have cross sectional imaging with a CT scan or MRI, the diagnosis of AIP is often first made by radiologists. Classic findings on cross-sectional imaging include focal or diffuse pancreatic enlargement with distortion and/or loss of the lobular architecture known as "sausage-shaped pancreas" [31]. The enhancement pattern on CT/MRI is also helpful to suggest a diagnosis. AIP shows persistent or delayed enhancement in over 90 % of cases [32]. Other findings include a hypoattenuating capsule-like peripheral rim, occurring in up to 40 % of cases [33]. Unlike other forms of pancreatitis, peripancreatic stranding is usually minimal in AIP. One of the most important radiologic presentations in AIP is the focal pancreatic mass, which can be present in 30–40 % of cases. This occurs commonly in the pancreatic head as a result of localized involvement [34]. Other findings such as prominent lymphadenopathy, vascular occlusion, abrupt narrowing of the pancreatic duct, and marked atrophy of the pancreas upstream to the mass can point towards a diagnosis of pancreatic cancer rather than AIP [31].

Another hallmark finding in AIP is a diffusely narrowed main pancreatic duct. Other typical abnormalities of the pancreatic duct system include the absence of the normal duct branching structure and minimal duct dilation proximal to any stricture [31, 35]. Magnetic resonance cholangiopancreatography (MRCP) was shown in a study to be less accurate compared to ERCP in evaluating pancreatic ductal changes

[36]. Biliary abnormalities on imaging are also common in AIP. Smooth narrowing of the intrapancreatic portion of the common bile duct can be seen in patients with AIP [37]. As described previously, patients with IgG4-sclerosing cholangitis may have irregularity or stricturing of the intra- and extra-hepatic bile ducts with findings similar to those seen in PSC [25].

Endoscopic ultrasound (EUS) findings of AIP can include diffuse hypoechoic pancreatic enlargement, bile duct wall thickening, and peripancreatic hypoechoic margins [38, 39]. These findings, however, are relatively nonspecific, and a diagnosis of AIP cannot be made solely based on EUS findings. Intraductal ultrasound may be used to differentiate AIP- or IgG4-sclerosing cholangitis from cholangiocarcinoma. Affected bile ducts with AIP have concentric wall thickening with a smooth configuration and luminal surface, compared to the eccentric wall thickening and irregular luminal surface characteristic of cholangiocarcinoma [38].

Histology

As described previously, patients with type 1 AIP have a pattern of lymphoplasmacytic sclerosing pancreatitis (LPSP) characterized by periductal lymphoplasmacytic infiltration rich in IgG4-positive cells, storiform fibrosis, and obliterative venulitis. In type 2 AIP, there is typically neutrophilic infiltration in the pancreatic ductal epithelium with duct destruction and occasionally microabscess formation [7, 40].

In IgG4-sclerosing cholangitis, characteristic histopathologic findings include massive infiltration of IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis in the wall of the bile duct. These findings are typically referred to as lymphoplasmacytic sclerosing cholangitis (LPSC) [19]. This fibroinflammatory involvement is typically seen in the submucosa of the bile duct wall, while the bile duct epithelium remains uninvolved [41]. Because of the lack of mucosal involvement, endoscopic transpapillary biopsy and cytologic examination often does not reveal the characteristic histopathologic findings in IgG4-sclerosing cholangitis, although they are valuable in excluding cholangiocarcinoma [19]. Patients with IgG4-sclerosing cholangitis and intrahepatic biliary strictures on imaging commonly may have small bile duct damage and infiltration of IgG4 plasma cells detected on liver biopsy [42]. Steroid therapy in patients with AIP and IgG4-sclerosing cholangitis has been shown to reduce the number of infiltrating IgG4 plasma cells on liver biopsy [43].

Serology

Type 1 AIP is typically considered an autoimmune disease given that it is associated with immune cell infiltration into the pancreatic tissue and is responsive to corticosteroids. In addition, type 1 AIP is associated with hypergammaglobulinemia and nonspecific elevation of autoantibodies. As described earlier, IgG4-positive plasma

cells are increased in type 1 AIP. Ghazale and colleagues showed that a serum IgG4 > 140 mg/dL has a sensitivity of 76 % and specificity of 93 % in diagnosing autoimmune pancreatitis [44]. A subsequent meta-analysis showed that serum IgG4 was useful for the diagnosis of AIP, with a sensitivity ranging from 67 to 94 %, and specificity ranging from 89 to 100 % [45]. However, elevated levels should be interpreted in the appropriate clinical context, as 10 % of patients with pancreatic malignancy, and 5 % of healthy persons can have elevated IgG4 [46]. Similarly, a subset of patients with type 1 AIP do not have elevated serum levels of IgG4. Sah and colleagues reported that approximately 20 % of patients with type 1 AIP were seronegative at initial diagnosis [18].

Pathophysiology

Our understanding of the pathophysiology of type 1 and type 2 AIP is rapidly changing. In both subtypes, the pancreas is infiltrated with a variety of immune cells. These include CD4-positive T cells, IgG4-producing plasma cells in type 1 AIP, and granulocytes in type 2 AIP [3]. In addition, a number of circulating autoantibodies have been detected in AIP, although it is unclear whether these antibodies are directly involved in pathogenesis, or represent an epiphenomenon of AIP [2, 20]. In addition, the exact role of serum IgG4 in the pathogenesis of AIP is not fully elucidated. Prolonged antigen exposure may induce a physiological IgG4 response mediated by type 2 helper T cells [2] and thus the mechanism leading to induction of IgG4 production may play a larger role in the pathogenesis as opposed to IgG4 itself. A few genetic studies have also suggested involvement of T cells in pathogenesis. Genetic polymorphisms in the gene for cytotoxic T-lymphocyte antigen-4 has been associated with AIP in the Japanese population [47]. Experimental models have also suggested that treatments which influence regulatory T-cell or effector T-cell activity have a positive effect on the course of experimental AIP [48]. In addition to T-cell involvement, the relative role of B-cells in the pathogenesis of AIP also remains unclear. Treatment directed directly against B cells in the form of Rituximab has been shown to be effective in patients with AIP who recur after steroid treatment. Future research is necessary to elucidate the relative role of B-cells, T-cells, and other immune cells in the pathogenesis of types 1 and 2 AIP.

Diagnosis

The diagnosis of AIP is challenging, especially given that misdiagnosis of AIP in the setting of pancreatic cancer must be avoided. Several scoring systems for AIP have been developed around the world, reflecting the variety of practice patterns and clinical presentations. The HISORt criteria were developed at the Mayo Clinic based on a prospective cohort of 29 patients meeting histologic criteria for AIP [49].

These criteria were based on Diagnostic **H**istology, Characteristic **I**maging, Elevated serum IgG4 levels on **S**erologic testing, **O**ther organ **i**nvolvement, and **R**esponse to glucocorticoid **t**herapy. In order to distinguish between type 1 and type 2 AIP and account for regional differences in clinical practice, the International Consensus Diagnostic Criteria (ICDC) were developed in 2011 [8]. The ICDC use a combination of five features of AIP: pancreatic imaging (including parenchymal imaging via CT/MRI or ductal imaging via endoscopic retrograde pancreatogram), serology, other organ involvement, histology and immunostaining, and steroid responsiveness. For each criteria, there is level 1 (highly suggestive) or level 2 (supportive) evidence. Type 1 AIP can be confirmed with a combination of level 1 and level 2 evidence. In contrast, a diagnosis of type 2 AIP requires histology. ICDC details and definitions are provided in Table 6.2.

Table 6.2 Level 1 and level 2 criteria for type 1 AIP (adapted from Shimosegawa et al. [8])

	Criterion	Level 1	Level 2
P	Parenchymal imaging	Typical: Diffuse enlargement with delayed enhancement	Indeterminate (including atypical): Segmental/focal enlargement with delayed enhancement
D	Ductal imaging (ERP)	Long (>1/3 length of main pancreatic duct) or multiple structures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size, <5 mm)
S	Serology	IgG4, >2× upper limit of normal value	IgG4, 1–2× upper limit of normal value
O	Other organ involvement	1 or 2 1. Histology of extrapancreatic organs (any 3 of the following): (a) Marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration (b) Storiform fibrosis (c) Obliterative phlebitis (d) Abundant (>10 cells/HPF) IgG4-positive cells 2. Typical radiological evidence (at least one of the following): (a) Segmental/multiple proximal (hilar/intrahepatic) or proximal and distal bile duct stricture (b) Retroperitoneal fibrosis	1 or 2 1. Histology of extrapancreatic organs including endoscopic biopsies of bile duct: (Both of the following) (a) Marked lymphoplasmacytic infiltration without granulocytic infiltration (b) Abundant (>10 cells/HPF) IgG4-positive cells 2. Physical or radiologic evidence (at least one of the following): (a) Symmetrically enlarged salivary/lacrimal glands (b) Radiologic evidence of renal involvement in association with AIP

(continued)

Table 6.2 (continued)

	Criterion	Level 1	Level 2
H	Histology of the pancreas	Lymphoplasmacytic sclerosing pancreatitis (LPSP) (core biopsy/resection) At least three of the following: 1. Periductal lymphoplasmacytic infiltrate without granulocytic infiltration 2. Obliterative phlebitis 3. Storiform fibrosis 4. Abundant (>10 cells/HPF) IgG4-positive cells	LPSP—Any two of the following: 1. Periductal lymphoplasmacytic infiltrate without granulocytic infiltration 2. Obliterative phlebitis 3. Storiform fibrosis 4. Abundant (>10 cells/HPF) IgG4-positive cells
Rt	Response to steroid	Diagnostic steroid trial: Rapid (<2 weeks) radiologically demonstrable resolution or marked improvement in pancreatic or extrapancreatic manifestations	
Diagnosis of Definitive and Probable Type 1 AIP using ICDC			
Diagnosis	Primary basis for diagnosis	Imaging evidence	Collateral evidence
Definitive type 1 AIP	Histology	Typical/indeterminate	Histologically confirmed LPSP (level 1 H)
	Imaging	Typical indeterminate	Any non-D level 1/level 2 Two or more from level 1 (+ level 2 D)
	Response to steroid	Indeterminate	Level 1 S/OOI + Rt or level 1 D + level 2 S/OOI/H + Rt
Probable type 1 AIP		Indeterminate	Level 2 S/OOI/H + Rt

Using the ICDC, a noninvasive diagnosis of type 1 AIP can be made in the following settings: (1) highly suggestive parenchymal imaging (level 1 P) if there is any collateral evidence of AIP—one of elevated **S**erology or presence of **O**ther organ involvement (one of S, OOI (level 1 or 2)); (2) only supportive parenchymal imaging (level 2 P) with a negative cancer work-up if there are at least two pieces of collateral evidence (two or more level 1 S/OOI) + ductal imaging (level 1 or 2 D)). An invasive diagnosis of type 1 AIP can be made if there are features of LPSP on resection specimens or core biopsy (Level 1 H) regardless of presence or absence of collateral evidence.

The ICDC also provides the option for a steroid trial in a select group. This involves use of prednisolone with re-imaging after 2 weeks of the steroid trial [50]. However, the option should be exercised only after a negative workup (including endoscopic ultrasound –guided fine needle aspiration) for malignancy. Additionally, multiple caveats clarifying what a steroid response entails are included in the guidelines. A general feeling of well-being, resolution of mild symptoms such as arthralgias, and reduction in antibody levels are not included in "response" as they can occur in any patient on high-dose steroid therapy. In addition, patients who have

clinical pancreatitis at presentation can have spontaneous improvement in pancreatic swelling with resolution of pancreatitis; thus steroid response must be interpreted with caution. In order to diagnose type 1 AIP in patients who have a characteristic response to steroids, patients must satisfy all of the following criteria: (1) supportive parenchymal imaging (level 2 P), (2) negative cancer work-up, (3) one of the following—(i) one level 1 S/OOI, (ii) two level 2 S/OOI, or 9iii) one level 2 S/OOI with ductal imaging (level 1 or 2D). Chari et al. conducted a validation study showing that approximately 70 % of suspected patients could be diagnosed with type 1 AIP noninvasively with highly suggestive imaging plus either other organ involvement or serum IgG4 elevation [51]. However, the 30 % of remaining patients require either histology or a steroid trial for diagnosis.

In patients who do not have collateral evidence, pancreatic histology is required for the diagnosis. However, histology is often not available in patients undergoing workup for suspected AIP. EUS-FNA is widely available; however, it is usually not adequate for histologic diagnosis. If malignancy cannot be definitively excluded, transcutaneous core biopsies should be avoided [3].

Diagnostic criteria for IgG4-sclerosing cholangitis have also been recently proposed [19]. The diagnosis is based on a combination of the following criteria: (1) biliary imaging consistent with diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with bile duct wall thickening, (2) elevation of serum IgG4 > 135 mg/dL, (3) coexistence of AIP, IgG4-related retroperitoneal fibrosis, or IgG4-related dacryoadenitis/sialadenitis, and (4) classic histopathologic features. It is important to note that it is challenging to obtain adequate biliary tissue in order to show characteristic histopathologic findings via biopsy [27]. The effectiveness of corticosteroid therapy has also been proposed as an additional diagnostic criterion to confirm an accurate diagnosis. However, this is with the caveat that this occurs at a specialized treatment facility after pancreaticobiliary malignancy has been excluded with endoscopic biliary biopsy and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA).

Practical Approach to Distinguish AIP from Malignancy

In patients initially presenting with obstructive jaundice, usual clinical practice involves obtaining a CT or MRI. Based on the imaging characteristics, patients can usually be stratified into three groups: suggestive of malignancy, suggestive of AIP, and supportive of AIP [10]. After searching for other organ involvement on imaging and evaluation of serum IgG4, about 70 % of patients can be diagnosed with stage 1 AIP [51]. Patients not diagnosed at this stage may subsequently undergo ERCP with ampullary biopsies or EUS-guided core biopsy, although the utility of this approach remains controversial [52, 53]. EUS-guided core biopsy is not widely available; however it will likely become a useful diagnostic tool once its performance and interpretation improves [54]. As described previously, a steroid trial should only be considered in a select patient group with suggestive imaging and collateral evidence, after a negative malignancy work-up.

For younger patients who do not have other organ involvement and are seronegative, a diagnosis of type 2 AIP is often suspected. After a complete work-up to exclude malignancy, pancreatic core biopsy is recommended given that a definitive diagnosis of type 2 AIP requires histology [8]. As histologic diagnosis is often difficult, under-recognition of type 2 AIP is far more common.

Despite this diagnostic evaluation, some patients may not fit into either category. A patient may present with obstructive jaundice with a negative work-up for malignancy, and may have typical parenchymal imaging findings without other organ involvement or elevated serology. If their histology shows a lymphoplasmacytic infiltrate with storiform fibrosis without IgG4 staining, this patient could be classified as AIP-NOS, and managed with steroid treatment [10].

For patients with suspected IgG4-sclerosing cholangitis, the diagnostic evaluation to exclude malignancy likely depends on the regions of stricture. For example, patients with a distal CBD stenosis likely benefit from intraductal ultrasound (IDUS) of the bile duct, EUS-FNA, or bile duct biopsy in order to exclude pancreatic or biliary malignancy. Other useful modalities depending on the region of stricture are listed in Table 6.1.

Initial Management

AIP is extremely responsive to steroid therapy. Given the rapid clinical improvement regardless of subtype, steroids are the standard therapy for inducing remission in AIP [15, 55]. The characteristic imaging response after steroid induction for a patient with AIP presenting with a localized pancreatic head mass is demonstrated in Fig. 6.1a, b. There is no consensus on the duration of induction therapy and tapering schedule. Additionally, there is no clear definition on what radiologic findings are necessary in order to initiate a steroid taper [56]. Some groups in the USA recommend a protocol of 40 mg/day for 4 weeks followed by a taper of 5 mg/week to complete a course of 11 weeks. The taper is initiated once an objective treatment response is confirmed, as defined by monitoring symptoms, follow-up imaging, and liver function tests [57]. In patients who have contraindications to steroid therapy (e.g., poorly controlled diabetics, or those with adverse effects during steroid therapy), rituximab has been shown to induce remission [58].

Most patients with AIP have evidence of obstructive jaundice on presentation. For patients with a definitive diagnosis of AIP, routine ERCP with biliary decompression is usually unnecessary given that steroid therapy improves jaundice in the majority of patients [30]. However, when the diagnosis not certain, ERCP with biliary decompression can be considered prior to treatment as the procedure may aid in diagnosis [30, 57].

Patients with IgG4-sclerosing cholangitis also typically have dramatic responses to corticosteroid therapy. The protocol for induction treatment is similar to AIP; in addition, a lack of initial response should trigger a re-evaluation to exclude pancreatic or biliary malignancy. In a multicenter trial, Hart and colleagues reported the

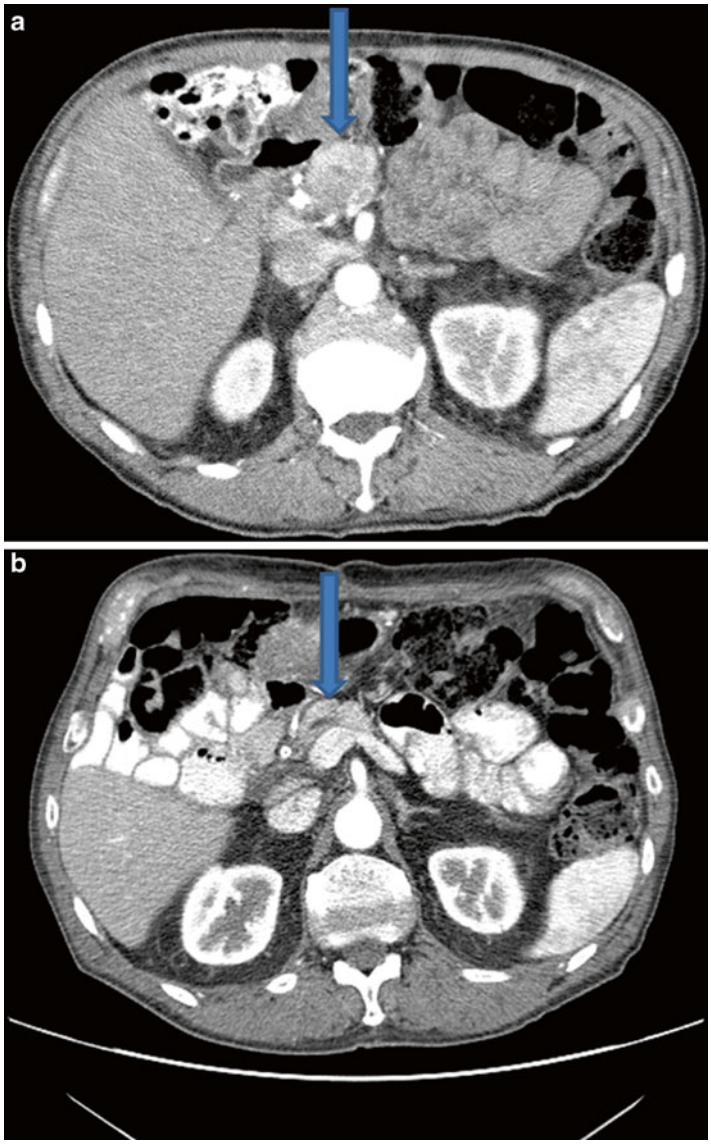

Fig. 6.1 (**a**) Characteristic findings at initial presentation of a patient with type 1 AIP. *Arrow* points to localized hypoenhancing mass in the pancreatic head. (**b**) Images of same patient after 2 months of steroid treatment. Arrow points to interval resolution of previously seen hypoenhancing lesion in the pancreatic head (*images received courtesy of Martin Smith*, *MD*)

relapse rates after treatment for patients with types 1 and 2 AIP. Patients with type 1 AIP were treated with steroids most commonly for jaundice, and over 50 % of those treated who subsequently relapsed had relapse in the biliary system [15]. This may suggest that patients with type 1 AIP with IgG4-sclerosing cholangitis should be monitored closely for biliary relapse.

Furthermore, rituximab has also been shown to be effective in a patient with persistent biliary strictures that were refractory to oral corticosteroids and 6-mercaptopurine [59].

Remission of Maintenance

Relapse of disease in patients with type 1 AIP can range from 30 to 50 %, while patients with type 2 AIP do not typically relapse [12, 18]. Patients with recurrent relapses can develop irreversible fibrotic damage, which may not be steroid responsive [2, 17]. Relapses commonly occur in the proximal bile duct, and patients can present with a biliary stricture and jaundice. Less commonly, patients can experience relapse in the pancreas, and present with pancreatitis, diffuse swelling of the parenchyma, or steatorrhea. [18] The Mayo group showed that initial proximal bile duct involvement and diffuse pancreatic swelling were factors predictive of disease relapse in type 1 AIP [18].

In order to prevent relapse in patients with type 1 AIP, Japanese groups have recommended low dose prednisone as extended maintenance therapy after induction of remission [55, 60]. In a multicenter Japanese study, maintenance therapy reduced the relapse rate from 34 to 23 % in those patients who were tapered off of steroids after induction [55]. In contrast, the Mayo Clinic group showed that half of their AIP patients did not relapse after initial induction with steroids, suggesting no benefit to maintenance treatment [30]. US groups have recommended maintenance therapy with azathioprine (2–2.5 mg/kg) after the first or second relapse [57]. In a recent study of patients with relapsing AIP, Hart and colleagues demonstrated that relapse-free survival was similar in patients treated with steroids alone compared to patients treated with steroids and immunomodulator maintenance [58]. The same group also showed that rituximab is effective for patients with AIP with or without IgG4-related sclerosing cholangitis, including those patients with relapsing disease. At the current time, there does not appear to be a definite role for obtaining serum IgG4 levels in order to monitor for treatment response. The Mayo group noted that the proportion of patients with type 1 AIP who normalized serum IgG4 did not differ between patients with and without relapse [30].

Patients with IgG4-sclerosing cholangitis may have higher relapse rate, as compared to patients with solely pancreatic involvement. In a group of 53 patients with IgG4-sclerosing cholangitis, Ghazale and colleagues reported a relapse rate of 53 % after steroid withdrawal. Specifically, those patients with proximal intrahepatic or extrahepatic strictures were more likely to have a relapse [30].

Prognosis

Long-term survival has not been shown to be different in patients with type 1 or 2 AIP compared to age and gender matched controls [18]. In the last several years, several case reports of pancreatic cancer were described in patients with AIP [55, 61, 62]. In a Japanese study, 108 patients with AIP were followed for a median of 3.3 years. Fifteen percent of these patients developed cancer in follow up, with the highest risk occurring within the first year of AIP diagnosis [63]. However in a recent case–control study, cancer risk before and after a diagnosis of AIP was found to be similar to age- and gender-matched controls [64].

Conclusions

AIP is a rare inflammatory condition of the pancreas that is exquisitely steroid responsive. Given that patients with AIP can present with obstructive jaundice and a pancreatic mass, it is vital to accurately diagnose this condition after conducting a thorough workup to exclude malignancy. The more common subtype, type 1 AIP, is the local pancreatic manifestation of a systemic condition called IgG4-related diseases and is associated with a relapsing course. Patients with IgG4-sclerosing cholangitis are also responsive to steroids, but are at risk of relapse. Type 2 AIP is limited to pancreatic involvement, and has a distinct histologic profile with a low rate of relapse. Although the diagnosis of type 1 AIP can be made noninvasively in the majority of cases, type 2 AIP is diagnosed on histology. Lack of a prompt response to steroids should trigger consideration of an alternative diagnosis, such as pancreatic cancer.

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Chapter 7
Counterpoint: Biliary Manifestations in Autoimmune Pancreatitis

Suresh T. Chari

IgG4-related sclerosing cholangitis (IgG4-SC) and type 1 autoimmune pancreatitis (AIP) (also called IgG4-related pancreatitis) are the biliary and pancreatic manifestations, respectively, of IgG4-related disease (IgG4-RD) [1]. IgG4-RD is characterized by (1) multiorgan involvement, (2) elevated serum IgG4, (3) typical histology in many of the involved organs, (4) tissue infiltration with IgG4-positive plasma cells, and (5) responsiveness to steroids. Individual patients with IgG4-SC or AIP do not always have all the above mentioned features; however, as a cohort these features are present in both IgG4-SC and AIP.

IgG4-SC may present with a distal bile duct stricture resembling pancreatic cancer [2, 3]. Usually this presentation is associated with AIP in the neighboring pancreas. Less commonly, there is isolated involvement of the distal CBD without AIP [2]. IgG4-SC may also present with proximal extrahepatic bile duct stricture with or without an accompanying mass. This presentation may be indistinguishable from that of cholangiocarcinoma. Finally diffuse intrahepatic strictures may be present resembling primary sclerosing cholangitis. There are patients who have strictures in multiple regions mimicking PSC with superadded complication of cholangiocarcinoma [2]

Despite the recognition of IgG4-SC as a distinct entity, there are a number of areas where there is uncertainty:

Diagnostic criteria:

Traditionally AIP diagnostic criteria include *h*istology, *i*maging, *s*erology, *o*ther organ involvement, and *r*esponsiveness to steroid *t*herapy (*HISORt* criteria) [4].

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1. Histology: Histologic diagnosis is possible only in resected bile ducts which show a pattern called lymphoplasmacytic sclerosing cholangitis characterized by (1) periductal lymphoplasmacytic infiltrate, (2) storiform fibrosis, (3) obliterative phlebitis, and (4) abundant IgG4+ plasma cells which account for >40 % of IgG+ plasma cells. IgG4 staining of tissues (bile duct biopsies or resection specimens) for IgG4+ plasma cells has been studied in patients with biliary strictures. These studies have observed that 20–30 % of PSC and cholangiocarcinoma patients have abundant IgG4+ plasma cells on tissue staining [5]. Thus, IgG4 staining alone can lead to misdiagnosis.
2. Imaging: The strictures in IgG4-SC are not consistently distinguishable from the diseases they mimic (PSC and cholangiocarcinoma and pancreatic adenocarcinoma) [6].
3. Serology: Attempts have been made to diagnose IgG-SC by measuring serum IgG4. These studies have observed that 10–15 % of patients with PSC-like changes have elevated serum IgG4; majority of these subjects do not have IgG4-SC [7].
4. Other organ involvement: Currently, other organ involvement in the form of AIP is the best predictor of the diagnosis of IgG4-SC in the non-operated patient with a biliary stricture. Isolated IgG4-SC without other organ involvement remains a diagnostic challenge.
5. Steroid responsiveness as a diagnostic tool: IgG4-SC is, by definition, a steroid-responsive disorder [2]. However, it is also a fibro-inflammatory disease and the fibrotic component can permanently distort the bile ducts. Assessing steroid response becomes a challenge when ducts remain strictured despite therapy. In such patients, normalization of liver enzymes can be used for determining response. However, other treatments for biliary strictures, such as ursodeoxycholic acid (UDCA) used in primary sclerosing cholangitis and primary biliary cirrhosis can also significantly improve liver enzymes, but are not known to be effective in IgG4-SC. Also, steroids can cause a nonspecific improvement in liver enzymes in other forms of hepatitis. There is as yet no consensus on definition of steroid response in IgG4-SC.
6. Diagnosis of IgG4-SC: Patients with bile duct strictures can be diagnosed with IgG4-SC if they have any one of the following (1) diagnostic histology on resected bile ducts, (2) proven AIP, and (3) elevated IgG4 and resolution of strictures or normalization of liver tests with steroid therapy [2].

Spectrum of manifestations of IgG4-SC:

In the absence an easy way to diagnose IgG4-SC, its full spectrum of manifestations is unknown. It is unclear, for example, how often IgG4-SC presents with isolated biliary involvement. It is also unclear how often untreated IgG4-SC progresses to secondary biliary cirrhosis requiring organ transplant. A study of explants of PSC subjects did not identify patients with IgG4-SC [5].

Treatment:

Like AIP, treatment for IgG4-SC includes initial therapy to induce remission and subsequent therapy to maintain remission. However, in AIP up to 50 % of patients do not relapse after induction of remission. Therefore, some groups, including ours, have chosen to use maintenance therapy only in those who relapse; the Japanese protocols include maintenance low-dose steroid therapy for all subjects [8].

In IgG4-SC, relapse rates are high in those who have proximal duct stricture(s). Hence, it is advocated that such patients be placed on maintenance therapy after induction of remission. The options for maintenance therapy include low-dose steroids, steroid sparing immunomodulators such as azathioprine or B-cell depletion therapy with rituximab. Rituximab has shown promise as a single agent that can induce and maintain remission [9].

Prognosis:

In our experience, patients with IgG4-SC who are diagnosed and treated till remission is maintained have no adverse outcomes. However, we have seen progression to biliary cirrhosis and death in undiagnosed and untreated IgG4-SC. Elevated serum IgG4 has been reported to predict worse outcomes in patients with PSC [10]. It is unclear if that also reflects the worst outcomes of undiagnosed IgG4-SC in this cohort or if serum IgG4 is an independent predictor of advanced disease in PSC.

Future Considerations

A better diagnostic test will likely identify more patients with this highly treatable disease that can otherwise lead to major hepato-biliary surgery or progress to secondary biliary cirrhosis needing transplant. The best therapy regimen for IgG4-SC also needs to be worked out. Since this is a rare disease, experience from multicenter studies will be needed to answer some of the unmet needs.

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Chapter 8
Recurrent Pyogenic Cholangitis

Jerome M. Laurence and Paul D. Greig

Introduction

Recurrent pyogenic cholangitis (RPC) is an inflammatory condition of the liver and biliary tree characterized by recurrent attacks of cholangitis combined with pathological changes in the liver including dilation and stricturing of the intra- and extrahepatic bile ducts, pigmented stones, and atrophy of the liver. This disease entity is also known as Oriental Cholangitis, cholangiohepatitis, primary cholangitis, intrahepatic stone disease, hepatolithiasis and Hong Kong disease. Many aspects of this disease remain incompletely understood. Indeed the fundamental pathogenesis of the condition, the reasons behind its predilection for people from certain Asian countries and its dominant effect on the left lobe of the liver remain obscure. Significant improvements in the treatment of the disorder have been achieved in the post 30 years, primarily as a result of improved imaging and interdisciplinary management approaches involving radiological, endoscopic and surgical techniques. However, there are no universally recommended protocols for the treatment of RPC and management is predominantly directed towards treatment of the complications of the disease and occasionally their prevention, and the surveillance for cholangiocarcinoma.

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Epidemiology

The disease is restricted primarily, but not exclusively to the communities which border the South China Sea. The disease also afflicts individuals from these areas when they migrate to other regions of the world. There are also sporadic reports of the disease in people with no geographic or ethnic links to the endemic areas [1–3]. It is more common in lower socioeconomic groups and appears to be declining in incidence with increasing wealth in the region [4].

Pathogenesis

No single aetiological factor has been identified as the cause of RPC. It is therefore likely that the disorder is multi-factorial in origin resulting from a complex interplay of environmental (such as infection and diet) and host factors (including congenital and acquired disorders). The most consistent association with RPC is that with stones composed of pigmented calcium bilirubinate and dilatation or ectasia of segments of the biliary tree. The preeminent theory involves a fundamental inciting role for bacterial beta-glucuronidase [5]. This hypothesis is based on the observation that bacterial β-glucuronidase generates free bilirubin from bilirubin di-glucuronide and that the ionized unconjugated bilirubin will readily precipitate under various experimental conditions with calcium ions to form calcium bilirubinate. The latter may then lead to stone formation. The biliary tract and liver are sterile under normal conditions but when stones are present, various microbes can be isolated from bile, and it is unknown whether this infection is primary or secondary to disorders of biliary structure or motility. Moreover, whether infection originates from hematogenous portal venous spread, via direct intraluminal ascending infection or the lymphatic system is also a matter of conjecture. The common finding of biliary dilatation or ectasia in the absence of distal stricturing raises the question whether the ectasia itself is primary or secondary to the stones and/or repeated infection.

Pathology

Gross pathological features may include scarring of the liver capsule with adhesions of the liver surface to surrounding viscera and the diaphragm. The biliary tree commonly contains soft pigmented stones and debris. Dilatation of the bililary tree may become visible externally, particularly as the liver parenchyma becomes more atrophic. The atrophy of the liver typically affects the left lobe with compensatory right lobe hypertrophy often in association with thrombosis of the left portal vein. Early histopathological features are those of suppurative cholangitis. Polymorphonuclear cells fill the duct with extension into the surrounding tissues. This may be associated with abscess formation. There may be necrosis of the cells in the peri-duct lobules.

Repeated acute inflammation gives way to a chronic fibrotic process that affects both the liver parenchyma and the large and small bile ducts. The extra- and intrahepatic bile ducts progressively dilate with the formation of strictures. The stricturing pattern differs between the intra- and extrahepatic biliary tree. The smaller intrahepatic bile ducts typically exhibit tubular narrowing giving rise to a pruned appearance, whilst the larger bile ducts are dilated with strictures concentrated at points of ductal confluence. The gallbladder is typically free of stones. There is an association reported between cholangiocarcinoma (CCA) and RPC, specifically intrahepatic lithiasis. It has been suggested that the rate of cancer development is about to 5 % [6, 7]. The putative mechanism for this association is the sequential development of regenerative hyperplasia associated with repeated and chronic inflammation around the bile ducts, progressing to atypical hyperplasia of the biliary epithelium, dysplasia, and eventually carcinoma [8].

Clinical Presentation

The presenting features of RPC can be protean, with a wide spectrum of severity. The course can relapse and remit spontaneously or with treatment. The more severe cases present with Charcot's triad: right upper quadrant abdominal pain, jaundice, and fever. Typically the hyperbilirubinemia is not severe and jaundice can be difficult to appreciate clinically particularly if cholangitis is confined to a segment or sector of the liver. Examination findings include tenderness primarily in the right upper quadrant. In severe cases this is associated with evidence of systemic sepsis including hypotension, tachycardia, oliguria, and delirium. Early in the disease evolution, symptoms may resolve rapidly with antibiotic treatment alone. Later, the development of complications may lead to other clinical features. Intrahepatic abscess formation which is typically signified by spiking pyrexia. Cirrhosis accompanied by features of portal hypotension may develop later. The development of unexplained weight loss and deep jaundice (particularly without cholangitis) should raise suspicion of CCA. Portal vein thrombosis is uncommon but may occur and characteristically parallels the distribution of the most severe peri-ductal inflammation (typically the left main or right posterior segmental branches of the portal vein), and is not typically apparent clinically.

Investigation

Laboratory investigations including a complete blood count and liver biochemistry are usually, but not universally abnormal. There is typically mild leukocytosis. Significant elevation of the WBC may indicate an abscess. The liver panel is typically abnormal with mild elevation in bilirubin. The pattern of liver enzymes is usually that of obstruction.

Quality imaging is essential in the management of RPC and the goal of radiological investigation is to confirm the diagnosis, define the anatomic extent of the disease, detect complications, and exclude concomitant malignancy [9]. Early in the disease evolution, differentiation from simple calculus disease of the gallbladder with secondary choledocholithiasis and cholangitis can be difficult. Later, as disease complications become more severe, excluding CCA becomes a significant issue. The radiological hallmarks of RPC are intrahepatic stones, biliary dilatation and strictures. These features are not exclusive to RPC. The differential diagnosis includes: choledocholithiasis from gallstones (requires the presence or history of gallstones) primary sclerosing cholangitis (usually associated with more diffuse strictures and less ectasia and few stones), Choledochal cystic disease (which is more associated with cystic malformations, and few stones) and CCA (with a mass or malignant-appearing stricture). Patients may have undergone previous interventions (surgical, radiological, and endoscopic) and the investigations should be interpreted with this in mind.

Ultrasound (US) is often the first investigation used but is neither a sensitive nor specific study in this context. Even in early RPC, US will likely reveal some abnormality if only intrahepatic stones or biliary dilatation [10, 11]. Characteristic US findings include: extra- or intrahepatic ductal stones, extra-hepatic biliary dilatation with mild or no dilatation of the intra-hepatic ducts, isolated dilatation of intrahepatic ducts, peri-portal echogenicity, atrophy of parts of liver, and stones in the common bile duct or gallbladder [11, 12]. Although US is normally a sensitive modality for stone detection. the RPC pigment stones may be isoechoic and their detection may be impaired by acoustic artefact from pneumobilia or peri-portal echogenicity from cholangitis. US alone therefore will generally not provide all the ultrastructural information required to make a diagnosis, especially outside of endemic areas where the positive predictive value of these findings declines.

Contrast-enhanced computed tomography (CT) will generally confirm features detected on US, such as bile duct dilation, hepatic atrophy, and portal vein thrombosis, as well as detect liver abscess and intrahepatic biloma (Fig. 8.1a) [9, 13, 14]. CT has some advantage over US in detection of isoechoic stones (as a result of the dynamic nature of liver enhancement after contrast administration) and due to the absence of confounding from artifact associated with pneumobilia. From the perspective of the surgeon, CT is particularly valuable for operative planning and in the operating room when interpreting operative findings. CT is also the imaging modality most useful in the evaluation of potential CCA [7].

Magnetic resonance cholangiography (MRC) is the optimal modality for the diagnosis of RPC and mapping of the extent of disease and its biliary and intrahepatic complications. It has now superseded invasive endoscopic or percutaneous diagnostic cholangiography [15]. Notwithstanding the expense and risks to the patient of direct cholangiography, its sensitivity in detection of stones, strictures and focal ductal dilatation is significantly inferior to MRC (Fig. 8.1a). Direct cholangiography should therefore only be used where intervention is needed. MR imaging is also useful for evaluating the possibility of malignancy in hepatic masses associated with RPC [16].

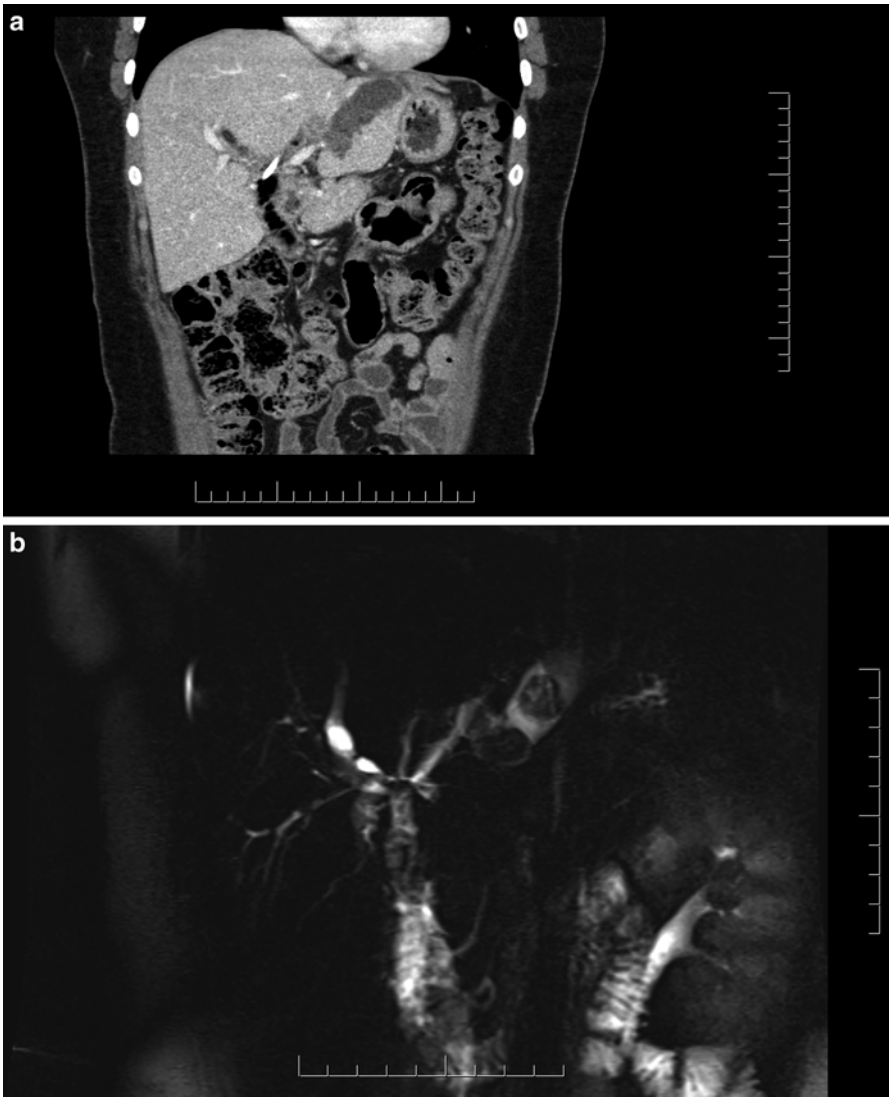

Fig. 8.1 Imaging of recurrent pyogenic cholangitis. (**a**) Coronal CT image. Left lobar atrophy is a prominent feature with massive dilatation of intrahepatic left duct. (**b**) T2-weighted haste radial MR image. Diffuse cisternal dilatation of the left biliary tree, left-predominant stone distribution with left lobar atrophy

Disease Management

Management of RPC can be classified into strategies aimed at (a) treatment of acute cholangitis, (b) prevention of disease recurrence, (c) facilitation of future access to the biliary tree, and (d) investigation of malignancy. There is also a role for

long-term surveillance of patients with RPC, particularly for the development of asymptomatic recurrence of stones and malignancy.

Management of Acute Presentation

Acute presentations with cholangitis are initially treated with supportive measures. In general, the patient with pyrexia and pain should be admitted to hospital. Antibiotic treatment should be instituted rapidly. Blood (and if possible) bile cultures should be examined to tailor the antibiotic to specific sensitivities and because bacteraemia is an important factor determining the duration of antibiotic treatment [17]. *E. coli, Klebsiella*, and *Enterococcus* are the most common bacteria associated with cholangitis [18]. Monotherapy with broad-spectrum antibiotics directed towards enteric organisms, such as piperacillin-tazobactam, is usually adequate. Because of the infrequency of anaerobic isolates from bile, the addition of metronidazole may be reserved for patients with previous biliary-enteric anastomosis [19]. However, patients with previous antibiotic treatment and biliary instrumentation (stents, drains, and postoperative states) are more likely to have infection with organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *enterococcus* (VRE), and *Pseudomonas* and this should influence empiric antibiotic choice. Initial empiric treatment is combined with intravenous hydration. In the majority of cases (70 % approximately), the acute symptoms will resolve rapidly [20]. If the symptoms do not improve within 24–48 h biliary decompression is indicated. The mode and route of decompression is dependant primarily on the location of the dominant obstructing lesion as determined by imaging. In most instances, the patients with cholangitis resistant to conservative measures have extra-hepatic obstruction due to stones or strictures in the distal common bile duct [20] in which case ERPC drainage would generally be considered first. In the setting of a patient who is septic with cholangitis, the initial intervention should only be that required to drain the biliary tree with a nasobiliary drain or endoprosthetic stent with no attempt at comprehensive cholangiography or stone removal. Subsequent procedures, once the cholangitis has resolved, can deal with residual stones and strictures. Patients with isolated intrahepatic segmental stones or stricture making ERPC drainage impossible require percutaneous transhepatic drainage (PTC-D) to decompress the infected biliary tree. Emergency surgery is seldom required and historically carried a high rate of morbidity and mortality [21, 22]. Emergency drainage surgery procedures most commonly included a combination f choledochotomy, irrigation of the biliary tree, gentle proximal stricture dilatation and T-tube placement in the common bile duct. In contemporary practice, these procedures have been supplanted by endoscopic or percutaneous techniques to drain the biliary tree, with surgery reserved for conditions where there is intraperitoneal contamination such as perforation of the gallbladder or a liver abscess or gangrenous cholecystitis [23]. Once sepsis is controlled, definitive management options should be evaluated as the risk of recurrent symptoms is high.

Definitive Treatment

The primary goal of definitive treatment is to minimize the incidence of symptom recurrence and complications relating to RPC. Specifically, treatment is directed to address the apparent structural abnormalities in the biliary tree and liver including stones, strictures, and atrophic areas of the liver. Many different procedures have been developed and described, but standardized treatment approaches have been hampered by the heterogeneous nature of the disease and its complications. There are no randomized studies comparing the outcomes of different treatment modalities for RPC. However significant advances have been made in rationalizing treatment selection based on more precise diagnostic evaluation [24–26].

The first systematic attempt to classify the disease for the purpose of planning definitive treatment was that proposed by Tsukasa Tsunoda and colleagues [27]. Subsequently other groups have classified the disease in a number of ways (Table 8.1). Although different, the unifying themes of these classifications distinguish the involvement of extra- and intrahepatic biliary tree as a significant watershed in management strategy. Moreover, when the intrahepatic biliary tree is involved, bilateral involvement is recognized as distinct in its treatment from unilateral involvement [25, 26, 28, 29].

Surgery

RPC has widely variable effects on the liver and biliary tree and a wide variety of surgical procedures have been developed as treatment of the disorder. The surgical management strategy relies upon understanding the specific manifestations of the disease at that particular point in time. The patient may suffer complications of RPC that increase the risk associated with the ideal operation (such as cirrhosis, portal venous thrombosis with portal hypertension or liver abscess). Such complications must be identified and factored into the decision making process. The surgical operation should aim to remove all the stones in the bililary tree and liver and achieve adequate drainage. Particular attention must be paid to strictures of the bile ducts. Most procedures will aim to dilate, remove or by-pass these strictures. Stone and stricture recurrence is recognized as a frequent occurrence. Many procedures have been developed which facilitate post-operative access to the biliary tree in recognition of the high rate of recurrent stones. The surgical procedures for RPC have never been subject to a rigorous comparative clinical study and choice of procedure depends largely on rationalization based on clinical experience.

Liver Resection

Resection of a part of the liver which is involved exclusively or predominantly by the disease has been associated, in contemporary series, with low rates of disease and symptom recurrence [30–39]. This modality is selected preferentially when a

Table 8.1 Surgical disease classifications

Author	Summary of classification	Reference
Chan et al.	*Simple*—absence of intrahepatic stricture *Complicated*—presence of intrahepatic stricture	[28]
Koh et al.	*Simple*—confined to first-order duct *Complex*—involving second or third-order ducts	[25]
Parray et al.	*Grade 1* Disease limited to the extrahepatic ducts. CBD < 1.5 cm. *Grade 2* Disease limited to the extrahepatic ducts. CBD > 1.5 cm. *Grade 3* Disease involving unilateral intrahepatic ducts with dilatable strictures and no liver parenchymal disease. *Grade 4* Disease involving bilateral intrahepatic ducts right or left, with severe non-dilatable strictures or parenchymal disease on same side. *Grade 5* Disease involving both intrahepatic ducts, with stones/worms with severe non-dilatable strictures or parenchymal disease on both side.	[26]
Tsunoda et al.	*Type 1*: had no marked dilatation of intrahepatic bile ducts. Small stones and sludge were demonstrated in the intrahepatic biliary tree. *Type 2*: had diffuse dilatation of the intrahepatic biliary tree and often an obstructive lesion of the distal common bile duct. *Type 3*: unilateral solitary or multiple cystic localized dilatation which was frequently accompanied by stenosis of the left or right intrahepatic bile ducts. *Type 4*: bilateral solitary or multiple cystic localized dilatation which was frequently accompanied by stenosis of both left and right intrahepatic bile ducts.	[27]
Feng et al.	*Type I*: Localized stone disease: unilobar or bilobar. *Type II*: Diffuse stone disease. *Type IIa*: No atrophy of the hepatic parenchyma or stricture of the intrahepatic bile ducts. *Type IIb*: Segmental atrophy or/and stricture of the intrahepatic bile ducts. *Type IIc*: Biliary cirrhosis and portal hypertension. Additional type E *Ea*: Extrahepatic stones. *Eb*: Relaxation of the sphincter of Oddi. *Ec*: Stricture of the sphincter of Oddi.	[29]

resectable part of the liver is atrophic, or occupied mostly by stones and cisternal biliary structures. Resection may also be pursued when concomitant CCA is diagnosed or suspected or when a resectable part of the liver is replaced by abscesses. The morbidity and mortality rates in contemporaneous practice are typically 30–40 % and 1–2 %, respectively. Laparoscopic resection, particularly left lateral segmental resection is feasible and safe and may facilitate earlier recovery from the procedure [40–45]. Overall the initial stone clearance rate reported with hepatectomy is approximately 85–95 % [30–33, 38, 39, 46]. Of the studies which report such data, the rate of recurrence of cholangitis or stones in 5 years is approximately 5–15 % [30, 32, 34, 46, 47]. This data compares favourably with every other treatment modality for

intra-hepatic stones or strictures and has led many to conclude that hepatic resection is the modality of choice for this type of disease.

Most studies describing liver resection for RPC include predominantly left lateral sectionectomy and left hepatectomy. This is a consequence of the natural predilection of RPC for the left side of the liver [28]. Right-sided liver resection is invariably a small proportion of resections reported and right hepatectomy is associated with a higher rate of postoperative complications [30]. Nevertheless, the results reported for right hepatectomy for isolated right-sided RPC are excellent [48]. For bilateral disease, the approach most often reported is left-sided resection combined with intra- and postoperative choledochoscopic lithotomy [49]. An alternative approach for bilateral disease is bilateral resection [50]. Bilateral resection carries a reduced risk of residual stones, but at the cost of increased surgical mortality when compared to unilateral resection and post-operative choledoscopic lithotomy.

The importance of strenuous attempts to remove stones from the extrahepatic biliary tree and future liver remnant during hepatectomy cannot be overemphasized. The traditional approach during a left-sided resection is via an incision in the extrahepatic biliary tree, usually a choledochotomy [23, 28] or alternatively in the left duct in the fissure of the ligamentum teres during parenchymal transaction (Fig. 8.2) [51]. The site of left hepaticodochotomy can then be resected or closed at the resection margin. Although there are no data to confirm a lower rate of postoperative biliary fistula with the left-duct technique, it simplifies the approach to the bile duct and may help reduce the need for subsequent T-tube placement. The technique will generally allow choledochoscopic access even to the right-sided hepatic ducts and can even be

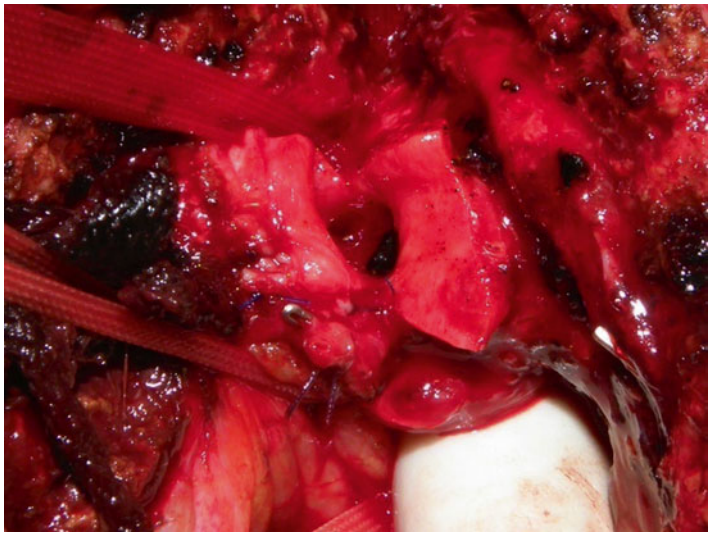

Fig. 8.2 Intraoperative image of left lateral sectionectomy. The left hepatic duct is opened in the fissure of the ligamentum teres exposing the dilated duct containing pigmented stones and debris. Courtesy of Professor Krishna Kumar Madhavan (Department of Surgery, National University of Singapore)

accomplished during laparoscopic hepatectomy [52]. One problem with this approach is the group of patients who also have right-sided disease associated with either a stricture at the right duct origin, sharp angulation of the right bile duct [53], or aberrant right sectoral duct insertion, [54] in whom choledochoscopic access cannot be accomplished either antegrade (via the left duct) or retrograde (via a choledochotomy). Ventral hilum exposure (VHE) is an alternative adjunctive technique to remove stones and strictures during hepatectomy [39]. It can be used in patients with left or right side predominant disease undergoing left or right hepatectomy (+segmentectomy 4b). The technique involves exposing the confluence of the right and left ducts at the base of segment 4B after parenchymal transaction. It provides a means of accessing the intrahepatic bilary tree for intra-operative choledochoscopy and stricturoplasty.

Recurrent Stones Following Resection: T-Tube vs. Roux-Loop

In patients with intrahepatic strictures or extensive stone deposition, the risk of incomplete clearance or recurrence of stones is clearly increased and two approaches have been proposed as an adjunct to liver resection to either reduce this risk or facilitate management of residual or new stones: (1) combined liver resection with biliary-enteric anastomosis (along with some means of accessing the biliary tree postoperatively via the Roux limb), [55] or (2) choledochotomy and T-tube placement [56]. The nonrandomized comparative studies in this area have suggested the counterintuitive conclusions of a benefit of T-tube over Roux limb, probably as a consequence of selection bias. For example, one large series found a significantly lower symptom recurrence rate (8 %) associated with resection and T-tube drainage compared to resection and hepatico-jejunostomy (22 %) [56]. However, this likely reflects the fact that patients undergoing drainage via T-tube have disease distribution and severity (predominantly extra-hepatic) intrinsically associated with a lower risk of treatment failure than those patients undergoing HJ (more likely bilateral and intra-hepatic disease distribution). Hepatectomy for bilateral disease is associated with inferior outcomes compared to unilateral hepatectomy in terms of initial stone clearance rate and recurrence rates [50]. This again likely reflects the function of selection basis rather than intrinsic treatment efficacy.

Biliary Access Limbs ("Hutson Loop")

In recognition of the high rate of stone, stricture and cholangitis recurrence and the need for future biliary manipulation, surgical procedures have been devised to facilitate future access to the biliary tree. Initially performed most often without resection of the liver, such techniques were devised as a means of avoiding

repeated percutaneous transhepatic radiological, endoscopic biliary interventions, or open surgical procedures [57]. Although many procedures have been described, in general the route of access is through a Roux limb of jejunum used for biliary enteric anastomosis that has been fixed to the anterior abdominal wall, often referred to as a "Hutson Loop." If left in a subfascial position, this is most often intended for percutaneous radiological access [34, 58]. Alternatively, a stoma may be matured at the time of construction, or the jejunum placed in a subcutaneous position without opening the lumen [59]. As a means of avoiding any percutaneous intervention, internal access limbs (most commonly to the duodenum) have been described [26, 60, 61]. Whilst such procedures may be advocated in some centres as routine, [23] postoperatively there is an incidence of failure to enter the biliary tree through the access limb or inability to achieve the therapeutic goal within the bile duct, especially if jejunal access limb is too long [28]. Moreover there is a proportion of patients in who the access limbs never needs to be utilized [34, 57].

Surgical Drainage Procedures

The use of drainage procedures as a primary treatment modality evolved from techniques used to manage western-type choledocholithiasis including choledochotomy and T-tube placement, choledochojejunostomy or hepaticojejunostomy [22]. Such surgery was carried out primarily for extra-hepatic disease and was associated with a high recurrence rate. By the 1980s, drainage procedures on the extra-hepatic biliary tree had largely been supplanted in efficacy and safety by ERPC [62, 63]. The traditional drainage operation is proceeded by choledochotomy or hepaticodochotomy (the location and orientation of which is dictated by the location of strictures or stones in the extra-hepatic bile ducts) followed by attempts to remove stones and dilate strictures manually (both inside and outside the liver) using a combination of irrigation, massage, stone forceps, flexible choledochoscopy and electrohydraulic lithotripsy through the working channel of the choledochoscope. The biliary enteric anastomosis is then performed to make a widely patent drainage through which small debris and fragments can enter the bowel. Generally a means of maintaining therapeutic choledochoscopic access to the biliary tree is then created [24, 57, 59]. Initially a hepatico-cutaneous jejunostomy (HCJ) was performed most frequently. Later, a modified technique using a t-tube to maintain a fistula between the subcutaneous access limb and the bile duct was advocated [55]. The HCJ is predominantly advocated by centres in Hong Kong which report initial stone clearance rate using this technique (combined with liver resection in about 50 % of instances) of approximately 95 % [64]. Recurrences are reported as rare and universally treated successfully by flexible choledochoscopy through the stoma. By contrast, in the experience reported in western practice (without concomitant liver resection) the initial stone clearance rate is as low as 30 %. Recurrence was universal and repeated choledochoscopy through the stoma was performed on almost all patients [65]. This stark

difference in outcome likely reflects centre experience and the understanding of the importance of initial attempts at achieving stone clearance, combined with an understanding of the utility of hepatectomy.

Liver Transplantation

Although not a common indication for transplantation, RPC may lead to secondary biliary cirrhosis with portal hypertension, particularly if treatment is delayed or neglected at an early stage. Liver transplantation is generally considered in circumstances where the patient has developed end-stage liver disease and its attendant symptoms [66, 67]. In centers where the Model for End Stage liver Disease (MELD) system is used for deceased donor organ allocation, [68] the priority for the recipient will generally be based on levels of Bilirubin, INR and creatinine without regard to the septic complications related to RPC or development of cholangiocarcinoma unless exception is granted. This situation is analogous to candidates with primary sclerosing cholangitis (PSC) and although it has been suggested that MELD-based allocation disadvantaged this group, the most recent long-term analysis of the outcomes for listed PSC candidates suggests that the current practice of MELD exception and preemptive live donor transplantation confers upon them a lower risk of wait-list removal or death than the remainder of the wait-list population [69, 70]. Whilst undoubtedly advantageous for the candidate, some have called into question the equity of practices (exception points and advocacy for preemptive live donation) aimed to equalizing disadvantage for patients with cholangitic disorders. These issues are likely pertinent to the few patients who may require transplantation for RPC.

Endoscopy

Since the advent of MRC, ERPC should be considered to be primarily a therapeutic/interventional procedure and less importantly a diagnostic one. Outside of its emergency use for acute cholangitis associated with CBD or CHD obstruction with stones or stricture, there is limited data suggesting that ERPC, endoscopic sphincterotomy and stone extraction can be used as a sole therapeutic modality in RPC, with a probability of success that depends on the distribution of the disease and institutional expertise. Stone clearance rates for ERPC in isolated extrahepatic disease have been reported to be in excess of 90 % [34], and are comparable to choledochotomy stone extraction and T-tube placement [62, 63], except when very large stones are encountered [71]. However, treatment of intra-hepatic stones and strictures using endoscopic techniques is less effective [72–75]. Notwithstanding the selection bias in these studies, all series report inferior results for endoscopy compared to surgery for the latter indication. Therefore endoscopic treatment for non-urgent intrahepatic disease should generally be reserved for the patient who is unfit or unwilling to undergo surgery [28].

Interventional Radiology

Percutaneous transhepatic biliary imaging techniques are not used purely as diagnostic modalities since the widespread availability of MRC. These techniques are the principle means of decompressing the obstructed bilary tree in treating acute cholangitis when ERPC is not possible (usually as a result of previous surgery) or not available. Percutaneous or endoscopic techniques used after the creation of a surgical access limb ("Hutson Loop") will be discussed with surgical treatments and this section refers primarily to transhepatic biliary access as a definitive treatment in the non-acute setting.

Percutaneous transhepatic cholangioscopic lithotomy (PTCSL) is a technique used particularly for intra-hepatic stones. PTCSL is reported in contemporary literature to produce initial stone clearance rates of 70–95 % [33, 38, 76]. The overall rate of recurrent hepatolithiasis or cholangitis is approximately 30–50 % in these studies. This is likely attributable, at least in part to difficulties encountered in treating intra-hepatic strictures by the percutaneous route. The use of expandable metal endobiliary stenting for strictures refractory to other interventions may reduce the risk of stone recurrence, number of interventions and time in hospital [77]; however the long-term effects of the metallic endoprostheis as a nidus for stone formation remains unresolved. It appears that refinement of technique significantly improves the success rate, and reduces the complication and recurrence rate associated with these procedures [78].

When compared directly with PTCSL, hepatic resection has a similar initial stone clearance rate, a lower rate of recurrent stones and a lower rate of residual bile duct strictures [33, 38, 46]. However, there is a significant intrinsic bias in these studies in that surgery is used mainly for isolated left-sided disease (precisely because the clinical success rate in this context is high), whilst PTCSL is used for bilateral or right-sided disease where hepatectomomy less likely to be feasible or safe. Not surprisingly, bilateral strictures and stones are a risk factor for failure of PTCSL [75]. Nevertheless percutaneous transhepatic interventions will likely retain a role in the patient who requires post-operative intervention in the absence of an access limb, or is not fit for surgery.

CCA and RPC

Whilst the association of CCA and RPC cannot be in doubt, the true incidence of this complication is difficult to define and is likely related to the severity of the disease, length of disease history, and treatment strategy. The lifetime risk of having CCA for a person diagnosed with RPC is in the range of 5–10 % [6, 7, 79, 80]. The malignancy is predominantly (about 80 %) peripheral, 10 % hilar and 10 % centred on the extra-hepatic biliary tree [7]. It can be difficult to differentiate the symptoms of concomitant RPC and CCA from those of RPC alone. Clinical

features associated with the presence of CCA include advanced age (>40 years), a longer history of RPC, loss of weight, a high level of serum alkaline phosphatase (in the range of 400 IU), a low serum albumin, a serum carcinoembryonic antigen level above 4.2 ng/mL, and right-sided or bilateral distribution of stones. CT features suggestive of peripheral CCA include a mass with the imaging features of an adenocarcinoma: marked hypoattenuation and thin and lobulated contrast enhancement at the tumor periphery. The mass is more likely to be in the atrophic segment of the liver and associated with stones. Thrombosis or narrowing of the portal vein is highly associated with CCA. Extra-hepatic and hilar CCA invariably presents as a biliary stricture with mass effect although on occasion a mass may not be appreciated. The survival of patients with RPC and CCA, even after resection with negative margins, is significantly inferior to CCA in the absence of RPC [81]. Although it is often claimed that resection for RPC with stone and stricture eradication reduces the risk of the development of CCA, [28] there is no evidence to substantiate this contention [82]. In their retrospective analysis, Lee at al. showed that the group previously treated with liver resection for RPC had a similar incidence of the development of CCA to the non-resection cohort. Since treating strictures and stones *per se* does not appear to reduce the incidence of CCA in RPC and given the very poor treatment outcomes, the utility of aggressive surveillance for RPC must be questioned.

Conclusion

RPC is a chronic inflammatory disorder characterized by repeated episodes of pyogenic cholangitis associated with intra- and extrahepatic biliary stones, biliary ectasia and strictures, and often chronic progression to hepatic segmental or lobar atrophy often with portal vein thrombosis, and long-term risk of cholangiocarcinoma. It is likely multifactorial in origin and related to environmental and genetic factors. Although relatively common in endemic areas, it is nonetheless a rare disease in absolute terms and so difficult to subject to clinical studies of high methodological quality. Although expeditious medical treatment is essential for acute episodes of cholangitis, there is no evidence that medical therapy alone can provide a definitive treatment. Surgery is focused on the ultrastructural consequences of the disease: stones, strictures and hepatic atrophy and facilitating percutaneous access to the biliary tree for future manipulation of stones and strictures. For intrahepatic disease, all the data suggest that resection is associated with the best outcome, and resection should be attempted whenever feasible and safe, and supplemented with a biliary access jejunal loop if feasible. In cases where resection is not possible, judicious multidisciplinary management is essential. With aggressive treatment it is likely that the risk of septic complications and secondary liver damage can be minimized.

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Chapter 9
Commentary: Recurrent Pyogenic Cholangitis

Henry A. Pitt

Hepatolithiasis occurs commonly in Southeast Asia but is uncommon in Western societies. This disparity is most likely due to the relatively high incidence of congenital biliary cysts and hepatobiliary parasites as well as to low protein, high carbohydrate diets in parts of Asia. Patients with intrahepatic stones frequently experience right upper abdominal and/or back pain, and they also are prone to develop cholangitis. When the disease is advanced, recurrent episodes of fever and chills may occur, and pus may be found in the biliary tree. In this setting the term "Recurrent Pyogenic Cholangitis" (RPC) may be appropriate.

Terminology

In the Asian literature, the terminology "Recurrent Pyogenic Cholangitis" is frequently employed as historically many patients presented with this advanced form of the disease. However, the terms "Oriental Cholangitis," cholangiohepatitis, primary cholangitis, and "Hong Kong Disease" also have been applied to the same patient population. In general, these terms have been utilized when the associated disease is hepatolithiasis or intrahepatic stones. However, hepatolithiasis usually is secondary to other biliary pathology. In Asia parasites and congenital biliary cysts are common underlying diseases. In comparison in Western societies, benign biliary strictures, choledocholithiasis, and sclerosing cholangitis are the more common reasons for biliary stasis and intrahepatic stone formation. In addition, in both the East

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and the West a biliary malignancy may be the cause, as opposed to the result, of hepatolithiasis.

In Western series of patients with hepatolithiasis more than half will present with fever and chills, usually with associated pain, and frequently with jaundice. Some of these patients who present with cholangitis will have recurrent episodes before the diagnosis of intrahepatic stones is established. However, only a small percentage of these patients are found to have pus within the biliary tree. Thus, the term "Recurrent Pyogenic Cholangitis" only applies to a small subset of Western patients. As a result, this discussion will focus on hepatolithiasis with or without associated cholangitis, and the term "Recurrent Pyogenic Cholangitis" will not be routinely employed.

Pathogenesis

Cholangitis occurs when bacteria in the biliary tree reflux via the hepatic veins and/or lymphatics into the systemic circulation. This situation occurs when intrabiliary pressures exceed 20–25 cm H_2O. The most common cause for cholangitis is common duct stones which are associated with bactibilia, obstruct the flow of bile, and cause increased biliary pressure. The organisms isolated most frequently in these patients are *E. coli*, klebsiella species, and enterococci. In general, anaerobes are uncommonly isolated from the biliary tree but are found in 15–30 % of patients who present with cholangitis.

Intrahepatic stones occur in patients with diminished bile flow. In Southeast Asia these patients usually are of lower socioeconomic class who often has parasitic infections including *Clonorchis* and *Opisthorchis*. In addition, diets which are low in proteins and high in rice starch have been demonstrated to cause pigment stones in rodent models and, therefore, may contribute to stone formation in Asian populations who consume these diets. The relatively higher incidence of biliary cystic disease in Asians also contributes to biliary stasis and stone formation. In comparison, intrahepatic stones occur in well less than 1 % of Western patients who tend to be older (50–60 years) and to have some underlying biliary pathology. Benign postoperative strictures, extensive choledocholiathiasis, sclerosing cholangitis, choledochal cysts, and biliary malignancies cause the majority of intrahepatic stones in the West.

Intrahepatic stones usually are brown pigment stones which are associated with biliary stasis and infection. Most primary common duct stones also are brown pigment stones which contain large proportions of calcium bilirubinate as well as modest (10–15 %) amounts of cholesterol. In comparison, secondary common duct stones are most often cholesterol or black pigment stones which originated in the gallbladder. Occasional Western patients with intrahepatic stones have cholesterol stones, but this situation is unusual.

The majority (55 %) of patients with intrahepatic stones have involvement of both the right and left hepatic lobes. Approximately 30 % of patients with

hepatolithiasis have stones only in the left lobe. Thus, overall 85 % of patients with hepatolithiasis have left lobe involvement. Intrahepatic stones confined to the right lobe occur in only 15 % of patients. Many of these patients have a right posterior ductal system which enters the left hepatic duct, an anatomic anomaly which may predispose to bile stasis. The presence of stones within the intrahepatic biliary system results in further bile stasis and cholangitis which leads to strictures of the secondary and tertiary bile ducts. Eventually, hepatic fibrosis and atrophy occurs, most frequently, in the left lateral sector (segments II and III). Approximately 5 % of these patients also are at risk for developing cholangiocarcinoma, and they should undergo periodic imaging as well as measurement of serum CA 19-9 and CEA which may assist in the diagnosis of a biliary malignancy [1].

Presentation and Diagnosis

Up to two-thirds of patients with intrahepatic stones will present with cholangitis. While almost all of these patients will have fever and chills, only 60 % will have pain, and less than half will present with jaundice. Thus, the minority of patients will have a complete Charcot's triad at the time of presentation. In the West up to 40 % of patients with hepatolithiasis will have undergone a prior biliary operation. As outlined by Laurence and Greig, magnetic resonance cholangiography is the most useful noninvasive method to diagnose intrahepatic stones. In comparison, computerized tomography (CT) will detect ductal dilation and abscesses, but CT is less sensitive at detecting stones. Similarly, ultrasound will visualize hepatolithiasis, but interpretation is difficult if a prior biliary-enteric anastomosis has been performed because air within the intrahepatic ducts also causes acoustic shadowing. In addition, visualization of segments VII and VIII with ultrasound is difficult because of the overlying rib cage.

Nonoperative Management

The initial management of patients with cholangitis includes prompt obtainment of blood cultures, timely initiation of antibiotics and fluids, as well as close hemodynamic monitoring. Patients who present with altered mental status and/or septic shock (Reynold's pentad) should be carefully monitored in an Intensive Care Unit and receive all elements of the Surviving Sepsis Campaign. In patients who are not allergic, broad spectrum penicillins provide excellent coverage for common biliary organisms as well as adequate coverage for anaerobes. However, when patients with hepatolithiasis who have had recurrent episodes of cholangitis and have received multiple courses of antibiotics; resistant organisms, such as multiple drug resistant gram negative rods, vancomycin resistant enterococcus (VRE), and yeast, are commonly isolated form the bile and/or blood. This subset of patients will require

additional antimicrobial and antifungal agents especially if they have severe "toxic" cholangitis. However, when culture results are known, the antibiotic/antifungal regimen should be altered appropriately. The vast majority of patients with cholangitis will respond over 72 h to these maneuvers and will not require urgent or emergent biliary decompression.

Endoscopic biliary drainage with sphincterotomy and stent placement is the treatment of choice for patients with common duct stones as well as those with a distal biliary stricture. However, adequate endoscopic management of patients with intrahepatic stones and those with proximal strictures rarely can be achieved [2]. In addition, the efficacy of endoscopic management is significantly diminished if a prior Roux-en-Y choledocho- or hepaticojejunostomy has been performed as well as in those patients with strictures of the secondary and tertiary biliary branches.

Percutaneous management of patients with hepatolithiasis can be performed successfully in more than half of the patients. This approach should be limited to the subset of patients with a modest stone burden, preferably in one lobe without severe fibrosis and/or atrophy [3]. Even in this subset of favorable patients, multiple procedures frequently will be required to upsize transhepatic stents to a 20 F size and to perform percutaneous choledochoscopy. However, in carefully selected patients where complete stone removal is possible with only a few procedures the percutaneous approach is recommended. In addition to choledochoscopy, stone retrieval with baskets and balloons may facilitate the process and result in stone clearance with relatively fewer procedures. In patients with larger stones, electrohydraulic lithotripsy and laser (Holmium Yag) lithotripsy may be required to dislodge and disintegrate the stones. Another criterion to pursue this nonoperative approach is the presence of relatively proximal strictures which dilate easily. If strictures are present, stenting for several months can result in a low recurrence rate.

Surgical Management

As outlined by Laurence and Greig, multiple surgical options are available. The safety of hepatectomy has improved significantly in recent decades. Therefore, in those patients where hepatolithiasis is limited to one lobe or sector, hepatectomy is the procedure of choice [4]. This approach is particularly appropriate for patients with isolated involvement of segments II and III on the left, especially if atrophy already has occurred. In these patients a laparoscopic approach has become popular in recent years. One caution in managing these patients with a limited resection is to be sure that an underlying biliary malignancy either is not present or, if so, that the tumor is adequately resected with negative margins. Another caution in performing a hepatectomy in patients with hepatolithiasis is the possibility of initiating severe, life-threatening sepsis. Manipulation of the liver with an abscess or pus in the bile ducts may result in massive bacteremia via cholangiovenous reflux. Thus, care should be undertaken to avoid undue parenchymal compression prior to hepatic vein ligation.

Results of a hepatectomy for hepatolithiasis are significantly better in patients with unilateral as opposed to bilateral disease [5]. However, these patients with bilateral disease rarely have significant hepatic fibrosis with associated liver failure which warrants liver transplantation. Thus, as more than half of patients with intrahepatic stones have bilateral disease, hepaticojejunostomy with intraoperative choledochscopy is a strategy that also can achieve excellent results (Fig. 9.1a). Preoperative placement of percutaneous transhepatic stents will facilitate upsizing to 20 F stents during surgery (Fig. 9.1b). In approximately 60 % of patients all intrahepatic stones can be removed intraoperatively. In the 40 % of patients with an extensive bilateral stone burden, the vast majority of the intrahepatic stones can be removed intraoperatively. Any residual stones can then be extracted percutaneously via the transhepatic stent tracks (Fig. 9.1 c, d). Once all residual stones have been retrieved, the stents can be removed, usually within 6 months.

Transhepatic Team Approach

The transhepatic team approach has been demonstrated to have long-term success in 90 % of patients [3]. This combined hepaticojejunostomy/transhepatic stent/intra- and postoperative choledochoscopy technique has a number of advantages over other nonresective operative methods. For example, the use of transhepatic stents has fewer problems with bilioentric fistulas than when the jejunum is employed for endoscopic postoperative stone removal. Also, creation of a "Hudson loop" may compromise the integrity of the hepaticojejunal anastomosis by causing increased tension or torsion. The hepaticojejunostomy should be performed without tension or torque as well as in a retrocolic, not anticolic, fashion so that bile will flow freely across the anastomosis.

The transhepatic stent/hepaticojejunostomy approach also facilitates complete stone retrieval from distal ducts that may not be possible if a T-tube in the hepatic duct is the only postoperative access point. Moreover, for patients with strictures in secondary and tertiary ducts, the transhepatic stents can be employed on a more long-term basis to maximize dilation and prevent recurrent strictures and stones. Further biopsies of residual strictures via the stent tracts also can be performed to completely rule out a cholangiocarcinoma. In summary, the transhepatic team approach employs (a) percutaneous placement of transhepatic access catheters, (b) surgery for underlying biliary pathology, extensive stone removal and placement of large-bore stents, as well as (c) postoperative percutaneous manipulation via the transhepatic stent tracts to assure complete stone removal.

This "team approach" of interventional radiologists and hepatobiliary surgeons permits preoperative diagnosis of biliary malignancies, intraoperative removal of an extensive, bilateral stone burden, postoperative complete stone removal, and stenting of secondary and tertiary strictures. In a recent analysis of 86 patients managed at Indiana University Hospital, approximately 75 % of patients were treated with percutaneous methods while 25 % required surgery. Postoperative, percutaneous

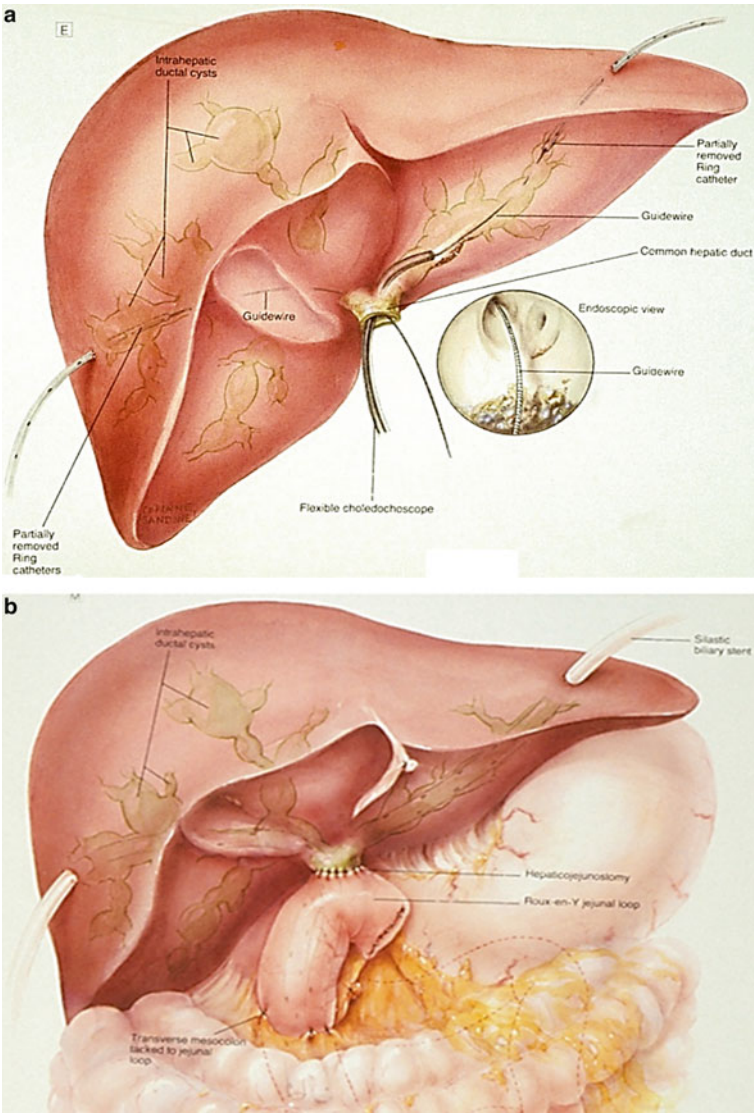

Fig. 9.1 (**a**) Illustration of a patient with bilateral intrahepatic cysts and stones. Preoperatively, bilateral transhepatic stents have been placed. Intraoperatively, stiff guidewires are passed through the stents which are pulled back to facilitate choledochoscopy. Strictures are biopsied to rule out cholangiocarcinoma. (**b**) After extensive intraoperative stone extraction, bilateral 20 F silastic transhepatic stents are placed. A retrocolic Roux-en-Y cholangiojejunostomy is performed with the transhepatic stents crossing the anastomosis and extending into the jejunum for 15–20 cm. The stent ends which exit the liver are brought out of the right and left upper quadrant, respectively, to facilitate postoperative choledochoscopy. (**c**) Postoperative flexible choledochoscopy via the left hepatic ducts. The anastomosis is demonstrated in the inset. The peripheral right hepatic ducts can be visualized from the left, and the peripheral left hepatic ducts can be accessed from the right for further stone removal. (**d**) Interventional radiologist performing choledochoscopy via a transhepatic stent track in the patient's left upper quadrant. Baskets and balloons as well as electrohydraulic and laser lithotripsy may be employed to remove any residual stones

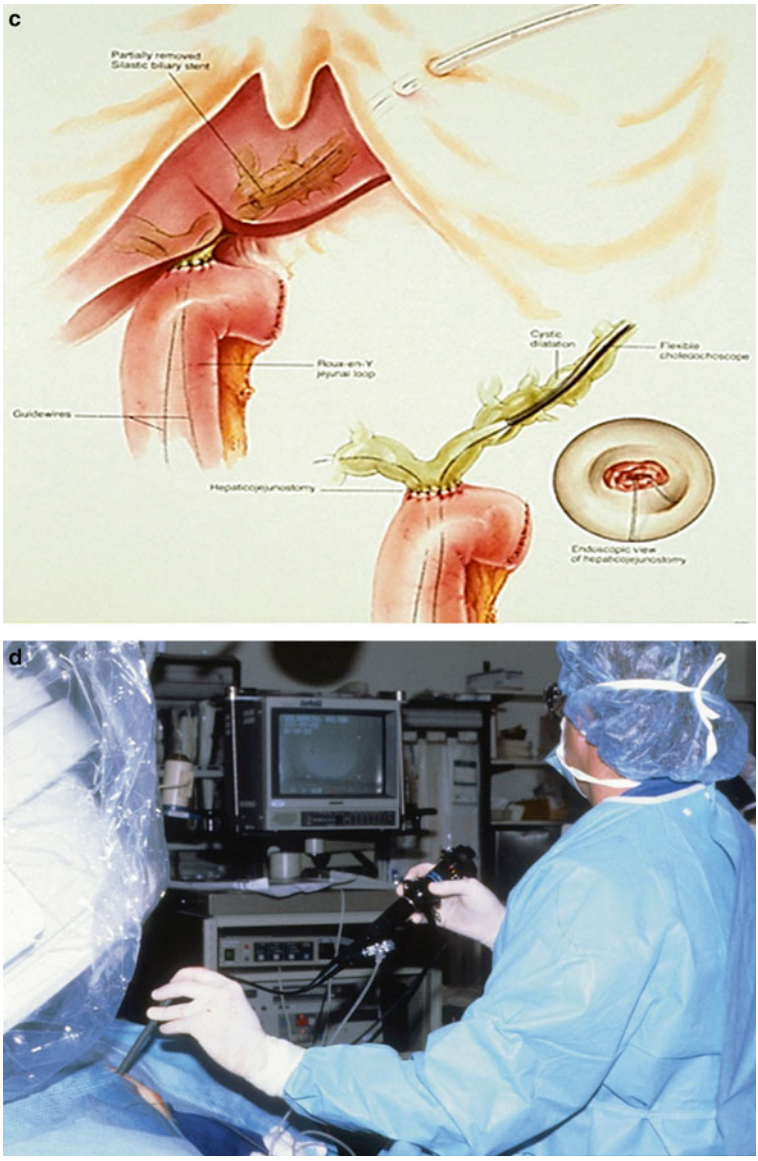

Fig. 9.1 continued

procedures will be required in the 40 % of patients undergoing surgery who have an extensive stone burden. With this approach more than 95 % of patients will have all stones removed most often with one preoperative stent placement, one operation, and two to three postoperative procedures. In most patients the stents can be removed within six months of surgery. With this "team approach" 90 % of patients become symptom free, 90 % will have no evidence of stone recurrence, and 85 % will be stricture free with long-term follow-up. Thus, a combined interventional radiology and surgical approach with large-bore transhepatic stents is a safe and effective method for managing intrahepatic stones.

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Chapter 10
Proximal Biliary Strictures Mimicking Hilar Cholangiocarcinoma

Kelly Nahum, J. Joshua Smith, and William R. Jarnagin

Synopsis

This chapter addresses basic biliary tract anatomy and the clinical manifestation and diagnostic workup of patients with benign tumors and pseudotumors of the biliary tract that can masquerade as hilar cholangiocarcinoma. These benign neoplasms or conditions may present as localized masses or strictures resulting in biliary obstruction. They can be classified in the following broad categories: (1) Papilloma and adenoma, (2) Granular cell tumor, (3) Neuroendocrine tumors, (4) Neural tumors, and (5) Pseudotumors.

Basic Anatomy

The gallbladder is located in a fossa on the inferior surface of the liver. It is divided into four anatomical areas: fundus, body, infundibulum, and neck. Histologically, it is distinct from the remainder of the gastrointestinal tract, as it lacks a muscularis mucosa and a submucosa [1]. The extrahepatic biliary system consists of the right and left hepatic ducts, the common hepatic duct (CHD), the cystic duct, and the common bile duct (CBD), as illustrated in Fig. 10.1. Most commonly, the right and

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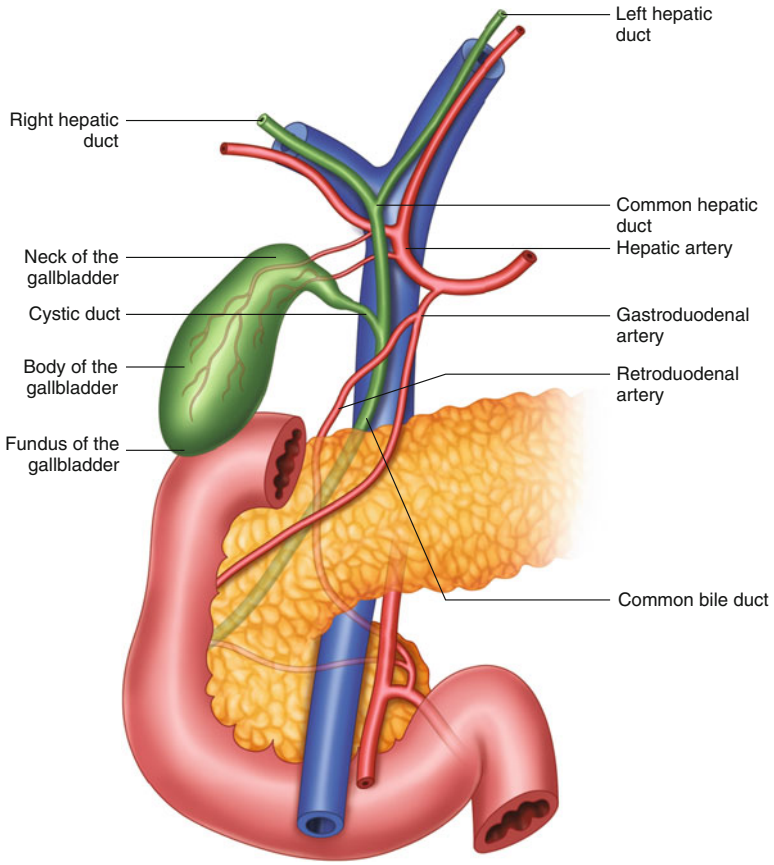

Fig. 10.1 Anatomy of the biliary tree. Shown is the standard anatomy of the biliary tree and the anterior aspect of biliary anatomy related to the pancreas, right hepatic duct (a), left hepatic duct (b), common hepatic duct (c), hepatic artery (d), gastroduodenal artery (e), cystic duct (f), retroduodenal artery (g), common bile duct (h), neck of the gallbladder (i), body of the gallbladder (j), fundus of the gallbladder (k). Note particularly the position of the hepatic bile duct confluence anterior to the right branch of the portal vein, the posterior course of the cystic artery behind the common hepatic duct, and the relationship of the neck of the gallbladder to the right branch of the hepatic artery. Note also the relationship of the major vessels (portal vein, superior mesenteric vein, and artery) to the head of the pancreas

left hepatic ducts join to form the common hepatic duct, although there are several important anatomical variations that must be recognized. Within the porta hepatis, the common hepatic duct usually lies anatomically anterior to the portal vein and to the right of the hepatic artery [1]. The cystic duct typically joins the common hepatic duct acutely forming the common bile duct. Extrahepatic bile duct walls are lined by a single layer of columnar epithelium with minimal smooth muscle [2]. The supraduodenal portion of the common bile duct runs inferiorly in the hepatoduodenal ligament anterior to the portal vein and to the right of the hepatic artery. By the

middle third of the CBD (retroduodenal portion), it deviates laterally from the other vasculature and curves behind the first portion of the duodenum. In roughly 70 % of patients, the main pancreatic duct joins the pancreatic portion of the CBD outside the second portion of the duodenum and they traverse the duodenal wall as a single unit [1]. On the other hand, in 20 % of people, the pancreatic duct and CBD unite inside the duodenal wall itself and in 10 %, the two ducts enter the duodenum separately through two distinct openings [1, 2]. The intraduodenal segment of the duct is termed the ampulla of Vater. It is roughly 10 cm distal to the pylorus and is encircled by the Sphincter of Oddi, which helps control bile outflow.

In clinical practice, this classic picture of biliary anatomy only exists in less than half of patients. A number of anatomic variations are relatively common, making awareness of them essential in order to prevent significant intraoperative complications. Variants of the hepatic and cystic arteries are of the more frequently encountered, as seen in roughly 50 % of patients [1]. The main arterial supply to the bile ducts is the gastroduodenal artery (GDA) and the right hepatic artery (RHA), whose trunks run along the medial and lateral duct walls. Most commonly, the RHA branches from hepatic artery proper, a branch of the common hepatic artery. However, significant anatomic RHA variants exist, such as a replaced RHA (20 %), which instead comes off the superior mesenteric artery (SMA), or an accessory RHA (5 %), where two RHAs are present, one from the SMA and from the common hepatic [1]. Specifically in patients with a replaced RHA, the RHA may course anterior to the CHD in the porta hepatis, making it easily susceptible to injury if not properly identified. In regard to the cystic artery, 80–90 % branch from the RHA. However, variants can occur and can branch from a replaced RHA, an accessory RHA, left hepatic artery, SMA, GDA, or common hepatic artery [1].

Benign Tumors

Accounting for roughly 6 % of neoplasms that occur in the biliary tract, biliary obstruction secondary to benign biliary tumors is significantly less common when compared to other inflammatory, iatrogenic, or malignant etiologies. However, despite the rarity of these benign neoplasms, it is important to include them in the differential diagnosis when a patient presents with obstructive jaundice or evident biliary stricture. A complete list of benign tumors and pseudotumors of the biliary tract can be seen in Table 10.1.

The clinical presentation of patients with benign biliary tumors often parallels those with an underlying biliary malignancy, as both commonly present with signs of obstruction, such as jaundice, scleral icterus, and pruritus [3]. Regarding symptoms, either group may present with associated colicky epigastric pain, nausea, and vomiting, while others may remain relatively asymptomatic. Rarely is significant weight loss or anorexia present in patients with benign disease, in comparison to those with a malignant stricture etiology [4]. Ultimately, however, no clinical symptoms or physical exam findings have been found to be specific enough to differentiate

Table 10.1 Benign biliary tumors

Benign tumors and pseudotumors that can cause biliary obstruction
Epithelial tumors
Adenoma
Papilloma
Cystadenoma
Nonepithelial tumors
Leiomyoma
Lipoma
Hemangioma
Lymphangioma
Granular cell tumor
Neural tumors
Neurofibroma
Schwannoma
Neuroendocrine tumors
Pseudotumors
Idiopathic benign focal stricture
Lymphoplasmacytic focal stricture
Sclerosing cholangitis
Heterotopic tissue

Adapted (with permission) from Linehan DC, Jarnagin WR, Blumgart LH. Benign Tumors and Pseudotumors of the Biliary Tract. 2012; 50:751–763

a benign biliary tumor from malignancy or inflammatory pseudotumors. Because of the lack of characteristic symptoms and physical findings, benign biliary tumors are not generally diagnosed preoperatively.

Papilloma and Adenoma

The most common type of benign tumor of the extrahepatic biliary tree is that developing from the glandular epithelium lining the ducts themselves [2, 5]. The majority of these neoplasms fall into the category of polyps, papillomas, adenomas, or cystadenomas. This is evident in the historic review of benign extrahepatic biliary tumors by Chu (1950), which referenced a total of 55 documented cases with the following type and frequency: 24 biliary papilloma/polyp (44 %); 18 bile duct adenoma (33 %); 3 neuroma, lipoma, and fibroma; 2 granuloma; 1 melanoma and 1 carcinoid [2, 5, 6].

In regard to biliary cystadenomas, extrahepatic cases are exceptionally rare, as they predominantly tend to occur within the intrahepatic bile ducts [7]. Soochan et al. (2012) reported a unique case of a 62-year-old woman ultimately found to

have an intra- and extrahepatic biliary cystadenoma. The clinical manifestation was obstructive jaundice and the initial radiologic workup included contrast-enhanced CT and MRCP, which revealed significant atrophy of the left lobe of the liver, as well as dilatation of the common bile duct (CBD), common hepatic duct, and left intrahepatic duct [7]. ERCP with brush cytology sampling was negative. Unable to definitively rule out malignancy, the patient underwent an extended left hepatectomy with CBD excision and Roux-en-Y anastomosis. Macroscopically, the specimen appeared to be a mucin-containing mass, which arose from the left hepatic duct and prolapsed into the CBD [7]. Microscopic examination confirmed the diagnosis of biliary cystadenoma, as it displayed the classic findings of a cyst lined with mucinous columnar or cuboidal epithelium [7].

Chen and associates reported a patient referred for surgical resection of a suspicious liver nodule found as an incidental finding on CT scan. The patient did not manifest any symptoms of obstructive jaundice nor were his liver function tests abnormal. Suspicious for carcinoma, the decision was made to pursue surgery. Intraoperatively, a hard 1.4 cm mass was identified near the diaphragmatic dome of the left hepatic lobe [8] without evidence of infiltration into the liver capsule. Interestingly, after postoperative microscopic examination, the mass was shown to be a bile duct adenoma. As illustrated in these reports, the clinical presentation and radiographic features of extrahepatic bile duct adenomas remain difficult to distinguish from cholangiocarcinoma, making preoperative diagnosis challenging and surgical resection the mainstay of treatment [2, 7, 8].

Granular Cell Tumors

Granular cell tumors are extremely rare, benign tumors, which occasionally occur in the extrahepatic biliary tree. More commonly occurring in the oral cavity, subcutaneous tissue, or skin, it is believed that less than 1 % of all granular cell tumors arise from the biliary tree [2, 9–11]. First reported in 1952, the majority of cases are found in young, African-American females [11–13]. This is evident in a case report from 2010 describing a 16-year-old, African-American female who underwent orthotopic liver transplant for liver failure secondary to severe biliary tract obstruction from a granular cell tumor [13]. Initially thought to arise from myoblasts, it is now believed that granular cell tumors may indeed originate from Schwann cells. This theory is supported by the positive immunohistochemical staining for the S-100 protein, which is normally found in Schwann cells of the peripheral nervous system [11, 13, 14].

Uniquely, Saito et al. reported the occurrence of a granular cell tumor of the common bile duct in a 36-year-old Japanese woman. The patient initially presented with a sudden elevation of liver and biliary tract enzymes 3 days following delivery of twins by Cesarean section. Scleral icterus was evident within 1 week. Abdominal ultrasound revealed an enlarged gallbladder with associated debris and a common bile duct with a diameter of 7 mm [11]. CT and MRCP were then performed, and

displayed stenosis and wall thickening of the mid-bile duct. ERCP further confirmed the presence of the respective stenosis. Subsequent endoscopic brush cytology and forceps biopsy failed to diagnose the etiology of the identified stricture. Unable to definitively rule out cholangiocarcinoma, the patient underwent a pancreaticoduodenectomy roughly 1 month after her Cesarean section. Gross inspection of the specimen revealed the tumor to be small, ill-defined and located in the distal CBD, with involvement of all three layers of bile duct wall. On microscopic examination, the tumor cells were polygonal with eosinophilic granular cytoplasm that exhibited partial infiltration of the peripheral nerve fibrous tissue of the bile duct wall [11]. Immunohistochemistry revealed cells positive with the periodic acid-Schiff reaction as well as positive for S100. Given these findings, the authors concluded that this was a benign granular cell tumor. The patient was reported as stable, with no complications or recurrences 5 years later [11].

Neural Tumors

Schwannomas are benign tumors that arise from Schwann cells. Schwann cells are the myelin-producing cells that form the inner portion of peripheral nerve sheaths [15]. Madhusudhan and coworkers reported a case of a 46-year-old man who presented with 2-month history of progressive jaundice, dark urine, and pruritis. Physical examination revealed an enlarged yet non-tender liver. Laboratory findings included elevated bilirubin and alkaline phosphatase. Imaging studies performed in the diagnostic workup included ultrasound, CT, and MRI. Contrast-enhanced CT showed a mass extending along the CBD and right and left hepatic ducts beyond the secondary confluence, as well as dilatation of the intrahepatic bile ducts [16]. No abnormalities were visualized in the associated vasculature. MRI exhibited a branching solid mass along the extrahepatic and intrahepatic bile ducts. The working diagnosis was cholangiocarcinoma on the basis of these findings. Further exploration followed with an ultrasound-guided biopsy of the suspicious mass. Immunohistochemistry of the biopsied mass revealed the tumor cells to be positive for S100 and neurofibrin, which are markers consistent with Schwannoma. Schwannomas of the biliary tree are rare, and when they do arise, it is typically from the neural elements present in the wall of the ducts [16, 17]. Patients can present with indistinguishable signs of obstructive jaundice and indistinct imaging, as seen in this patient, which again makes definitive diagnosis difficult without surgical resection. A Schwannoma in a 54-year-old woman with prior diagnoses of melanoma who was found to have liver panel abnormalities undergoing routine surveillance studies is shown in Fig. 10.2. After confirmation that this lesion was not consistent with metastatic melanoma (e.g., negative PET scan), the tumor was resected, noted as a Schwannoma on pathology review and the patient recovered well without issue or further sequelae.

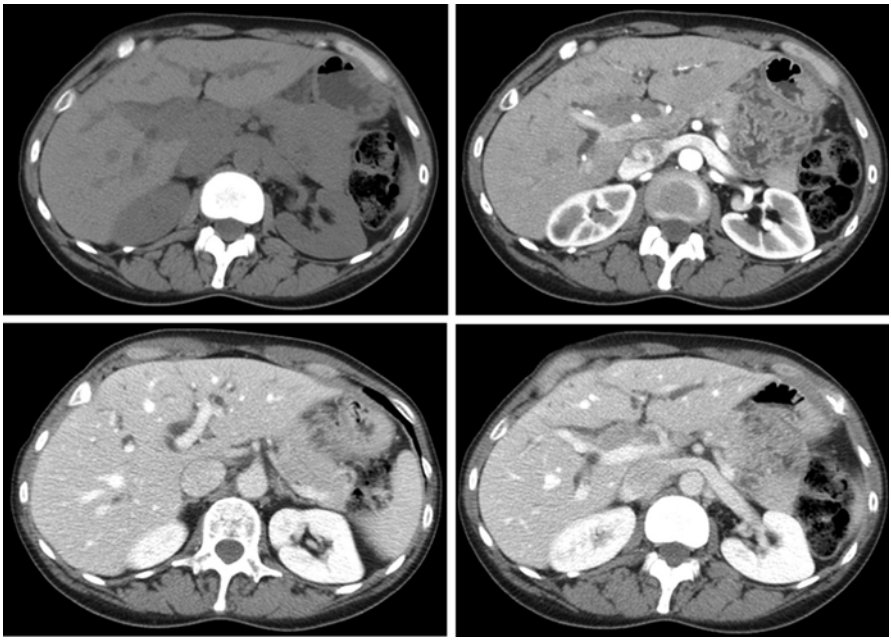

Fig. 10.2 Shown is a CT angiogram of the liver from a 54-year-old woman with abnormal liver enzymes with history of melanoma of the back, upper arm and labia status post definitive resection for all. Physical examination was unremarkable and laboratory examination during surveillance for melanoma yielded a normal total bilirubin, AST = 145 U/l, ALT = 516 U/l, and ALKP = 158 U/l. A PET scan to rule out melanoma was negative for FDG avidity. Fine needle aspiration by referring physician showed a spindle cell neoplasm that was S-100 positive and c-Kit, desmin and synaptophysin negative. At operation, a soft mass was noted arising from the proximal bile duct extending into the base of segment IV. On frozen section, a low grade spindle cell neoplasm consistent with a Schwannoma was noted. Resection of the extrahepatic bile duct ensued and the patient recovered well with normalization of liver enzymes and no further sequelae

De Rosa et al. reported a 70-year-old woman who presented with obstructive jaundice for 1 month. The patient was status post open cholecystectomy 2 years prior to presentation. Laboratory studies were consistent with biliary obstruction and a contrast-enhanced CT identified a stricture at the mid-CBD. There was no evidence of a mass, vascular invasion, or enlarged lymph nodes. The patient underwent exploratory laparotomy with intraoperative frozen section biopsies to confirm clean margins. Excision of the extrahepatic bile duct and subsequent Roux-en-Y hepaticojejunostomy was performed. Postoperative histological findings were consistent with neurofibroma positive for S-100. The authors concluded that while solitary neurofibromas may occur, the majority of neurofibromas are seen more frequently in the setting of Neurofibromatosis [2, 17, 18].

Neuroendocrine Tumors

Neuroendocrine tumors of the extrahepatic bile ducts are particularly uncommon, accounting for 0.2–2 % of all gastrointestinal neuroendocrine tumors [19–21]. When they do occur, the most commonly reported presenting symptom is jaundice and the most common anatomic sites of occurrence are the common bile duct (58 %), perihilar region (28 %), cystic duct (11 %), and the common hepatic duct (3 %) [19, 21, 22]. Most reported biliary neuroendocrine tumors fall into the category of carcinoid, gastrinoma, and somatostatinoma, the majority of which are hormonally nonfunctional [2, 22]. However, in a recent Italian study, 17 patients diagnosed with Multiple Endocrine Neoplasia (MEN) Type 1 affected with Zollinger-Ellison syndrome (ZES) were analyzed and 3 of 17 were found to have functioning ectopic biliary tree gastrinomas [23]. Two of these were incidental findings during pancreaticoduodenectomy for ZES and were removed intraoperatively. The third case was discovered 1 year after pancreaticoduodenectomy for ZES recurrence and was subsequently removed [23].

Most carcinoid tumors occur in the gastrointestinal tract, particularly in the ileum (45 %), the rectum (20 %), or the appendix (16 %) [24]. As previously mentioned, carcinoid tumors arising from the extrahepatic biliary tract are rare [21]. Since first depicted by Pilz in 1961, only 70 documented carcinoid cases of biliary origin have been reported [22, 25, 26]. Carcinoids are derived from enterochromaffin cells (or Kulchitsky's cells), which are located at the base of the crypts of Lieberkühn [21, 27]. Since the biliary tree naturally contains a paucity of enterochromaffin cells, it has been hypothesized that biliary inflammation may serve as a template for biliary carcinoid development [2, 27]. The reasoning behind this theory is that persistent inflammation can lead to intestinal metaplasia of the biliary tree, resulting in an increased number of enterochromaffin cells [27]. Recently, Khuroo and associates reported a 56-year-old woman with a history of right upper quadrant pain and progressive jaundice. The patient's past surgical history was significant for cholecystectomy 7 years prior for symptomatic cholelithiasis. Based on preoperative imaging, the patient was presumed to have hilar cholangiocarcinoma (Klatskin tumor) and subsequently underwent surgery. Histological analysis of the surgical specimen revealed small round argyrophilic cells that stained positive for chromogranin A and serotonin [21, 22]. Based upon these findings they concluded that the hilar mass was in fact a carcinoid tumor. Carcinoid tumors of the biliary tree are considered to be of low malignant potential with a favorable 5-year prognosis of 60–100 % following complete resection [21, 22]. Although slow growing, if left untreated, these tumors still have the ability to metastasize. Figure 10.3 depicts gross photos of a resected biliary carcinoid originally noted due to hepatic transaminase elevation noted in the course of routine blood work [21]. This lesion was subsequently resected after preoperative imaging was concerning for hilar cholangiocarcinoma [21]. Therefore, these data illustrate that albeit rare, neuroendocrine tumors can be the etiology of a suspected malignancy in roughly 2 % of cases and should therefore not be ignored as part of the differential diagnosis.

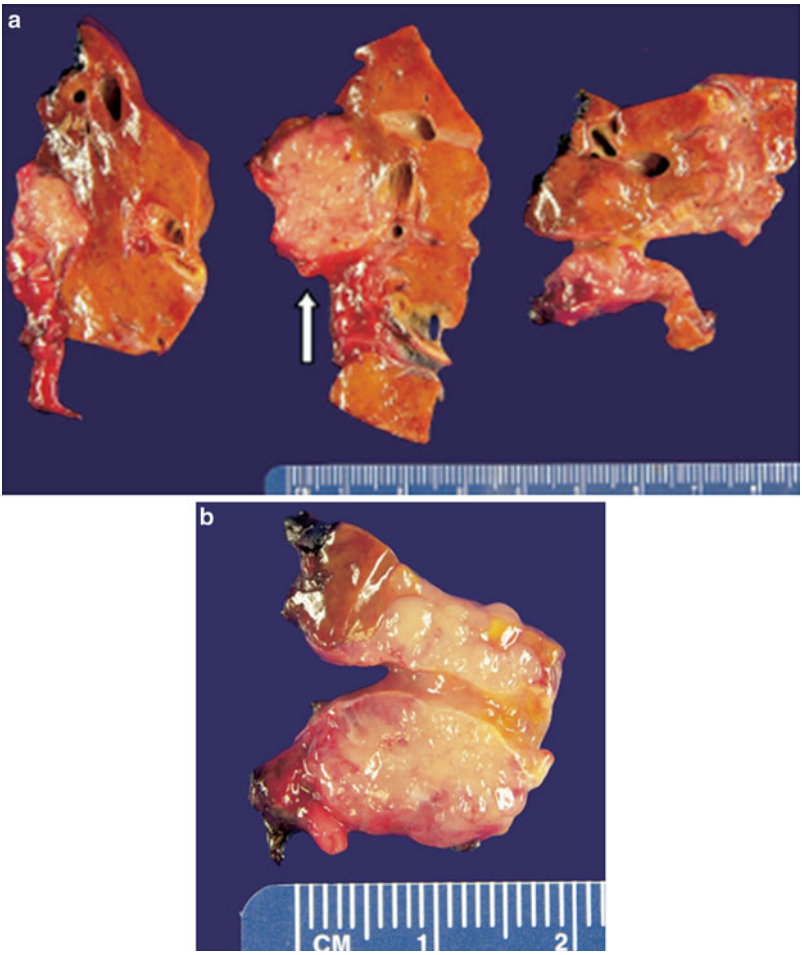

Fig. 10.3 Shown are photos of a right trisegmentectomy with biliary carcinoid (**a**) involving the bile duct with extension to periductal soft tissue (**b**); adapted with permission from [21]. The patient is a 52-year-old male with coronary artery disease s/p coronary artery bypass in 1999 noted to have elevated liver function tests on routine blood work, including an alkaline phosphatase of 289 U/L (33–88 U/L), an aspartate aminotransferase of 67 U/L (10–37 U/L), and an alanine aminotransferase of 85 U/L (5–37 U/L). Physical examination was unremarkable. Liver ultrasonography demonstrated right-sided biliary dilation terminating in a mass arising from the right hepatic duct, consistent with a papillary cholangiocarcinoma. A magnetic resonance cholangiopancreatogram confirmed this finding and showed no evidence of metastatic disease. Additionally, there was no evidence of portal vein involvement or hepatic lobar atrophy. Endoscopic retrograde cholangiogram, performed before referral, demonstrated a mass completely obstructing the right hepatic duct, with a normal left biliary system and common bile duct. Clinically, the patient was well, had no jaundice or pruritus, and denied any symptoms related to the biliary tumor. The patient was taken to the operating room in June 2006 with a presumptive diagnosis of hilar cholangiocarcinoma. The operative findings were consistent with a proximal biliary cancer, confirming the preoperative imaging data. A right trisegmentectomy, common bile duct resection, and portal lymph node dissection were performed. Macroscopically, the tumor appeared as a 2.2-cm homogeneous tan lesion arising from the right hepatic duct and extending into the hilar soft tissue and hepatic parenchyma as shown in panels **a** and **b**

Pseudotumors

Nonmalignant lesions that cause obstruction of the extrahepatic biliary ductal system may closely resemble hepatobiliary malignancies. It has been reported that 5.2–24.5% of biliary strictures prove to be benign after histological examination of the resected specimen [3, 28–30]. Some of the causes of obstruction in these benign cases are listed in Table 10.2. These benign conditions occur frequently enough to be carefully considered in the differential diagnosis of any lesion suspicious for a bile duct tumor. This is evident in a large series in which 5 of the 153 patients (3.3 %) who underwent surgical resection for a suspected biliary malignancy had postoperative histopathologically proven benign disease [30]. Those proven benign were further diagnosed as immunoglobulin G4-related sclerosing cholangitis ($n=3$) and nonspecific fibrosis ($n=2$) [30]. Erdogan and colleagues investigated 185 patients, who underwent resection of proximal bile

Table 10.2 Malignant masquerade. The table highlights recent reports of biliary strictures that were proven to be of benign etiologies following surgical resection or antituberculosis therapy

Reference	Number of patients	Location	Etiology	Treatment
Wakai et al. [30]	3	–	Sclerosing cholangitis	Hemihepatectomy
	2		Fibrosis	Hemihepatectomy
Oh et al. [40]	16	Hilus	Sclerosing cholangitis	–
Khan et al. [43]	1	CBD	Mirizzi syndrome	Cholecystectomy
Deng et al. [38]	1	Hilus	Inflammatory tumor	–
Kanhere et al. [44]	1	Cystic duct, CBD	Atypical mycobacterium	Roux-en-Y hepaticojejunostomy
Corvera et al. [32]	22	Hilus	Lymphocytic sclerosing cholangitis (2) Primary sclerosing cholangitis (3) Granulomatous (3) Stone disease (6) Idiopathic benign biliary strictures (8)	Resection
Vasiliadis et al. [37]	1	CBD	Inflammatory tumor	Resection
Dutta et al. [45]	1	Hilus	Biliary tuberculosis	EUS-FNAC, antituberculosis therapy
Fukuda et al. [51]	1	Hilus	Heterotopic gastric mucosa	Hepatectomy, caudate lobe and extrahepatic bile duct resection
Erdogan et al. [31]	32		Benign proximal biliary strictures	Resection
Ferrone et al. [21]	1	RHD	Neuroendocrine tumor	R trisegmentectomy, CBD resection, portal lymph dissection

Adapted from (with permission) Linehan DC, Jarnagin WR, Blumgart LH. Benign Tumors and Pseudotumors of the Biliary Tract. 2012; 50:751–763

ducts for preoperative diagnosis of cholangiocarcinoma between January 1984 and June 2005. Following postoperative histological examination, 32 (17.3 %) were found to be benign biliary strictures [32]. These data indicate that while suspicion of malignancy is initially high, a minority of patients will eventually be found to have benign disease on final pathologic examination.

Similarly, in a surgical series of 275 patients with preoperative radiological diagnosis of cholangiocarcinoma, postoperative diagnosis changed after histology in 22 (8 %) of the cases [33]. Again, all 22 patients had undergone surgical resection of the extrahepatic biliary tree for presumptive malignancy, 10 with combined partial hepatectomy. Some of the various etiologies of the benign pseudotumors missed were primary sclerosing cholangitis, granulomatous disease, nonspecific fibrosis/inflammation, and lymphoplasmacytic sclerosing pancreatitis and cholangitis [33]. Corvera et al. (2005) concluded that this "malignant masquerade" of the proximal bile ducts can result from numerous benign processes, often making differentiation from malignancy challenging. Highlighted above is the recurrent fact that preoperative diagnosis of biliary strictures is challenging and usually equivocal. For a presumed malignancy, surgical intervention remains the gold standard, as tissue diagnosis is essential to definitively rule out malignancy [34–37].

Inflammatory Tumors

Inflammatory pseudotumors are rare, idiopathic, benign, mass lesions composed of fibrous tissue with distinct, nonspecific inflammatory infiltrate [34, 38]. This infiltrate typically consists of a combination of inflammatory cells such as lymphocytes, plasma cells, eosinophils, and macrophages [38]. Vasiliadis and associates reported a benign endoluminal inflammatory pseudotumor in a 71-year-old female, who initially presented with jaundice, scleral icterus, and anorexia. Transabdominal ultrasonography revealed dilatation of intra- and extrahepatic bile ducts, proximal to the level of the mid-distal common bile duct (CBD) with no evidence of stones. MRCP and ERCP were performed, which revealed an obstructing mass in the mid-CBD suggestive of neoplasm. Attempts made to biopsy the mass during ERCP were unsuccessful and the patient subsequently underwent surgery. Intraoperatively, the CBD was dilated proximal to a palpable, firm mass in the mid-distal portion. A fibrosing lesion was found surrounding the mass, the adjacent lymph nodes, and the portal vein. Frozen sections of the proximal and distal CBD margins, in conjunction with the regional lymph nodes, were found negative for malignancy. An extrahepatic bile duct resection en-bloc with gallbladder and regional lymph nodes was subsequently performed [38]. Macroscopic examination revealed a 3 cm gray-white pedunculated mass protruding into the CBD. Microscopically, the inner epithelial layer of the CBD exhibited considerable reactive inflammatory changes with no evidence of atypia, dysplasia, or stenosis. The authors concluded that the endoluminal growing mass was consistent with a benign inflammatory

pseudotumor [38]. The patient recovered well with no evidence of recurrence 8 months following treatment. Deng and colleagues published a similar clinical occurrence of a patient in China, with a mass identified by abdominal ultrasound and MRCP to be in the right hepatic duct. The patient underwent surgical resection and the final diagnosis of inflammatory pseudotumor was confirmed following post-operative histopathological examination [39].

Immunoglobulin (IgG4)-associated sclerosing cholangitis (ISC) is another reported benign etiology that can mimic hilar cholangiocarcinoma when localized [32, 40]. Sixteen patients with ISC that manifested as localized hilar strictures were analyzed in attempt to illustrate certain clinical characteristics specific to ISC, as to assist in differentiating this disease from hilar cholangiocarcinoma [41]. Findings noted to be specific to ISC on biliary imaging included prominent bile duct thickening with relatively mild proximal dilatation ($n=11$), multifocal biliary tree involvement ($n=14$), and concentric bile duct thickening with luminal patency ($n=13$) [41]. Liver or endobiliary biopsy revealed significant infiltration of IgG4-positive cells in 11 of 16 patients (69 %), which was not evident in cholangiocarcinoma [41]. Furthermore, all ISC patients expressed significant improvement of respective strictures upon completion of appropriate steroid therapy. Based on these findings, Oh et al. concluded that certain clinical characteristics, such as specific biliary imaging or biopsy findings and improvement following steroids, could help in differentiating hilar strictures secondary to IgG4-associated sclerosing cholangitis from a malignant etiology like cholangiocarcinoma [41]. Even though a limited number of patients were analyzed in this study, the results offer potential new imaging guidelines to consider when diagnosing suspicious hilar strictures. Furthermore, this study highlights that ISC can be a significant cause of biliary stricture and therefore should not be forgotten in the differential diagnosis.

Mirizzi syndrome is a rare cause of biliary obstruction. It is characterized as an impaction of a stone in the cystic duct or neck of the gallbladder, which leads to mechanical or inflammatory compression and obstruction of the common hepatic or common bile duct. As a result, ongoing inflammation transpires, potentially leading to the formation of a cholecystocholedochal or cholecystoenteric fistula [42, 43]. This association between Mirizzi syndrome and fistula development is highlighted in a retrospective review of the 5673 elective or emergent cholecystectomies performed at Hospital De Ovalle in Chile from 1995 to 2006. Out of these 5673 patients, 327 (5.7 %) had Mirizzi syndrome and 105 (1.8 %) had a cholecystoenteric fistula [42]. Furthermore, 94 (89.5 %) of the 105 cholecystoenteric fistulas were found to be in association with Mirizzi syndrome [42]. Numerous variables such as age, sex, duration of gallbladder disease, presence of fistulas, or operations performed were analyzed to identify significant associations with this syndrome. Beltran and associates (2008) concluded that older age, female gender, and the presence of a cholecystoenteric fistula were all significantly associated with the development or presence of Mirizzi syndrome [42].

This established association of Mirizzi and cholecystoenteric fistulas validated the modified Mirizzi classification system developed by Csendes et al. (2007), which included the presence of cholecystoenteric fistula as a distinct type of Mirizzi syndrome, Type V [43]. According to this new classification, there are seven types

of Mirizzi syndrome (I-Vb), which addresses the presence of an associated cholecystobiliary fistula, cholecystoenteric fistula, or gallstone ileus [43]. The type of Mirizzi syndrome a patient has will ultimately dictate their respective treatment.

In addition to the development of fistulas, the chronic inflammation established by Mirizzi syndrome may cause significant biliary strictures that mimic cholangiocarcinoma. Patients with Mirizzi syndrome can manifest with obstructive jaundice, similar to those with malignant biliary etiologies, making definitive preoperative diagnosis challenging, as seen in a case of a 44 year old Asian man with a 2-month history of progressive jaundice. Abdominal ultrasound and ERCP were performed. ERCP demonstrated a stricture of the proximal bile duct, which extended to the confluence of the right and left hepatic ducts [44]. Initially endoscopic stenting was performed but failed. Further workup revealed an elevated CA19-9 level and on abdominal CT: dilated intrahepatic ducts, swelling of the proximal bile duct and gallbladder, and enlarged abdominal lymph nodes [44]. The patient underwent surgical exploration with dissection and delineation of the biliary tract anatomy. Intraoperatively, a thickened gallbladder wall with a large stone impacted in the cystic duct was discovered, resulting in external compression of the common hepatic duct, unveiling a classic picture of Mirizzi syndrome [44]. Subsequently, cholecystectomy with T-tube placement was performed. The patient had an uneventful postoperative course and was identified as stable 18 months later [44].

More recently, there have been reports of biliary tract infections raising a concern for potential malignancy upon initial presentation. Kanhere et al. reported a 45-year-old Caucasian woman who initially presented with obstructive jaundice. The patient had a significant past surgical history of a laparoscopic cholecystectomy 5 years prior with subsequent ERCP exploration and CBD stone extraction. Upon initial workup, the patient had elevated enzymes consistent with obstruction. Subsequent ERCP revealed a stricture at the junction of the cystic duct and CBD with dilatation of the proximal bile duct. No retained stones were visualized. Further workup with CT exhibited multiple hypodense right liver lesions, which ultimately led to the preoperative diagnosis of metastatic cholangiocarcinoma [45]. The shared multidisciplinary plan was to attempt percutaneous biopsy of a liver lesion and initiate systemic chemotherapy [45]. Unsuccessful with percutaneous approach, CT-guided core biopsy of the liver was then performed and a specimen was obtained for analysis. Histological examination of the liver core biopsies revealed a granulomatous process with Langhans giant cells, leading to suspicion of mycobacterial involvement [45]. As a result of the unique findings, Roux-en-Y hepaticojejunostomy was performed to resect the stricture. The final histopathology of the liver lesions was consistent with a multiple granulomas, which grew *Mycobacterium abscessus*, sensitive only to Amikacin [45]. The patient had no previous history of TB exposure, recent travel, or immunodeficiencies. The authors hypothesized that the cause of this unique occurrence may have been the result of minor trauma, which led to inoculation and later hematogenous spread of *Mycobacterium abscessus* to the hepatobiliary system [45].

From India, Dutta et al. reported a similar finding of biliary tuberculosis mimicking hilar cholangiocarcinoma in a 25-year-old male, who presented with 2-month history of intermittent, high-grade fevers, jaundice, and significant weight loss. Comparable to the previous cases mentioned, diagnostic-imaging modalities led to the suspicion of cholangiocarcinoma, which ultimately requires surgery. However, in this particular case, they deemed the mass unresectable as CT revealed encasement of the portal vein, superior mesenteric vein, superior mesenteric artery, and inferior vena cava [46]. As a result, ultrasound-guided fine needle aspiration cytology of the porta hepatis lymph nodes was performed instead for definitive tissue diagnosis. Histological examination revealed granulomatous pathology and the patient was started on antitubercular therapy. Six months following therapy completion, the patient remained asymptomatic with alleviation of obstruction. The authors indicated that biliary tuberculosis is a rare entity that involves the bile duct leading to obstructive jaundice either by enlargement of adjacent lymph nodes or direct tuberculoses involvement of biliary epithelium [46], and that it was extrinsic compression from enlarged infected lymph nodes that led to obstructive jaundice evident in this young male patient. Thus, although negative preoperative tissue diagnosis will not avert surgery, it is of value as it might identify infectious causes of strictures, like tuberculosis, which can dramatically alter treatment.

Recent studies have attempted to improve preoperative diagnosis of biliary strictures, by exploring novel imaging or histologic techniques that may enhance sensitivity and specificity of less invasive measures. A study assessing the sensitivity of endoscopic ultrasound-guided fine needle aspiration cytology (EUS-FNA) in diagnosing malignant biliary strictures found that, out of 22 patients, EUS-FNA identified 16 cases to be malignant and 6 to be benign [47]. Following final histological examination, EUS-FNA was accurate on all accounts, correctly identifying the 16 histologically proven malignant cases and the 6 benign cases. Ohshima and colleagues concluded that EUS-FNA is a sensitive and safe diagnostic modality in patients with suspected malignant biliary strictures and may prove to be useful in the preoperative workup of these patients when imaging studies are unclear or biopsy results are negative. In a recent retrospective study, Yu and coworkers set to assess criteria for differentiating infiltrative cholangiocarcinoma from benign CBD strictures using three-dimensional dynamic contrast-enhanced (3D-DCE) magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) imaging [48]. The ultimate goal was to establish certain imaging predictors that are specific to cholangiocarcinoma versus benign strictures. 3D-DCE MRI and MRCP images were retrospectively reviewed from 28 patients with infiltrating cholangiocarcinoma and 23 patients with benign CBD stricture etiologies [48]. The results established two statistically significant predictors on 3D-DCE MRI and MRCP that suggest infiltrating cholangiocarcinoma when present. These two malignancy predictors were increased ductal thickness and hyperenhancement of the involved CBD during the equilibrium phase of the study [48]. Utilization of both predictors concomitantly led to the correct identification of 92.9 % ($n = 26$) of malignant strictures and 91.3 % ($n = 21$) of benign strictures [48]. They concluded that the use of 3D-DCE MRI and MRCP should be implemented in the diagnostic

workup of strictures suspicious for malignancy, although the number of patients is small in this series and the findings should be validated in other series prior to broad application.

Garcea et al. evaluated whether initial bilirubin values could assist in early discrimination between malignant versus benign causes of obstructive jaundice. Over 1000 patients with documented obstructive jaundice were analyzed during the time period of 2008–2010. The authors concluded that the greatest sensitivity and specificity for malignancy was a bilirubin >100 μmol/L [49]. While bilirubin level alone is not sufficient to rule out malignancy, it may aid clinicians as an adjunct test in the initial work up of biliary strictures and subsequently influence later treatment options. Similarly, Hashim and associates reported that the phosphatidylcholine concentration in the bile of cholangiocarcinoma patients was significantly less than those with benign biliary disease. Furthermore, it was discovered that taurine-conjugated (H-26) and glycine-conjugated (H-25) bile acids were significantly elevated in cholangiocarcinoma bile versus that from benign etiologies [50]. Adapting the routine use of these biomarkers, in conjunction with new imaging modalities, may enable physicians to significantly improve the sensitivity and specificity of a preoperative diagnosis. Improvements in less-invasive, diagnostic measures may ultimately help avoid radical surgical procedures in patients with benign etiologies.

Heterotopic Tissue

Symptomatic heterotopic tissue arising in the biliary tree is exceedingly rare. In 1967, Whittaker and colleagues initially observed heterotopic gastric mucosa in a cystic duct that had obstructed the gallbladder [2]. Later, Kalman and associates (1981) reported a 1-cm papillary tumor in the common hepatic duct. On histological examination, the tumor expressed gastric fundal mucosa that replaced the full thickness of the bile duct wall [51]. More recently, Fukuda and associates reported the occurrence of heterotopic gastric mucosa in the hilar bile duct in an asymptomatic 58-year-old male. Workup included an abdominal CT, which exhibited wall thickening from the upper common hepatic duct to the left hepatic bile duct, and subsequent ERCP, which revealed stenosis at the junction of left hepatic bile duct [52]. Again, unable to rule out malignancy, the patient underwent a left hepatectomy, caudate lobe and extrahepatic bile duct resection. Microscopic analysis of the surgical specimen revealed a polypoid lesion composed of mucous glands resembling gastric fundic glands, with parietal and chief cells [52]. The authors concluded that the lesion was heterotopic gastric mucosa in the hilar bile duct. Kim et al. reported a biliary duplication cyst with heterotopic gastric mucosa obstructing the biliary system in an 8-year-old girl who initially presented with several months of abdominal pain. Preoperative workup revealed a mass in the portal triad. Intraoperative exploration revealed a cystic mass, with significant inflammation, which ultimately created a “Mirizzi-like” picture [52]. Consequently, this led to complete obstruction of the right and left hepatic duct confluence. Postoperative histological examination

revealed the specimen to be a duplication cyst that was lined with heterotopic gastric mucosa [52]. The diagnosis could only be ascertained with surgical resection in this case, further underlining the difficulties of making a firm diagnosis in the preoperative setting for these complex biliary processes.

Summary

Although biliary lesions resulting in obstruction are commonly due to malignancy, benign tumors or pseudotumors are differential diagnoses that warrant significant consideration when the clinician is faced with a patient suffering from obstructive jaundice. As highlighted throughout this chapter, definitive preoperative diagnosis of these benign etiologies remains a considerable challenge. While recent advances have been noted in regard to new imaging or tissue sampling techniques, surgery continues to remain the gold standard for diagnosis and treatment of these benign processes "masquerading" as malignant entities.

Conflicts or Disclosures None

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Chapter 11
Counterpoint: Proximal Biliary Strictures Mimicking Hilar Cholangiocarcinoma

David Nagorney

The management of hilar cholangiocarcinoma remains challenging. Its incidence is increasing, diagnostic methods have limited accuracy, and surgical approaches are evolving continually. Diseases that masquerade as hilar cholangiocarcinoma confound the surgical management of this already complex clinical problem. Nahum, Smith, and Jarnagin importantly outline the benign diseases that masquerade as hilar cholangiocarcinoma and attempt to highlight their clinical and imaging features to provide clinical clues for others to avoid overtreatment of benign diseases. There are valuable lessons worth learning from their work.

Jaundice is the clinical hallmark of cholangiocarcinoma and occurs in nearly all patients but is hardly pathognomonic. The authors appropriately emphasize that any process or disease affecting the hilar bile ducts can cause jaundice. Importantly, however, patients with hilar cancer are older and frequently present with constitutional symptoms of malignancy—fatigue, anorexia, weight loss, and vague abdominal discomfort. However, some patients with hilar cholangiocarcinoma are puzzled by their jaundice because their performance status is normal and they otherwise feel well. Although the latter patients are those in whom the malignant masquerade most closely mimic, and those patients should raise concerns for the non-malignant disease. Most gastroenterologists and hepatobiliary surgeons are adept in making the clinical diagnosis hilar cholangiocarcinoma based on symptoms and imaging. The importance of a careful history irrespective of imaging cannot be underestimated. An astute clinical often recognizes subtleties that collectively support either the diagnosis of cancer or not.

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Importantly most of the references cited herein are from small, limited case series and even single case reports. Some reports were from major centers of expertise and some were not. I reviewed several of the references from each of the Author's broad categories. Details of clinical presentation were terse and the overall frequency and severity of symptoms for the malignant masquerade disease process were seldom mentioned. Although many of malignant masqueraders simply are associated with few symptoms, some such as sarcoidosis, immune cholangiopathy, and rarely granulosa cell tumors may be associated with a symptom complex that enhances the clinician's suspicion for benign disease. Such wasn't stated often in cited reports. Moreover, publication bias of these uncommon diseases may have resulted in understating signs and symptoms in lieu of pathology, treatment, and outcomes. Finally neither the reader nor the authors can discern how astute the physicians were who examined the patients in these reports or whether reviewer of the articles valued clinical presentation enough to warrant emphasis for text. Cleary careful clinical evaluation is key to diagnosis. Proximal biliary strictures have multiple causes but patient response to obstruction is limited clinically. Cholangiocarcinoma is the most common cause of malignant hilar biliary obstruction, but awareness of benign malignant masqueraders and their clinical recognition may permit limited and less risky treatment.

The clinicopathologic diagnosis of hilar cholangiocarcinoma has become increasingly more accurate with modern imaging and endoscopic ductal cytologic evaluation and biopsy. Although uncommon, the diagnosis of benign tumors should be no less accurate. The accuracy of preoperative diagnoses of benign tumor of the hilus was not reviewed. These tumors, if evident on imaging, should be a target for image directed biopsy, whether by US or CT imaging or by endoscopic ultrasonography or retrograde endoscopic cholangioscopy. In general, biopsy is performed preoperatively after imaging and if a pathologic diagnosis will affect treatment. Although one could argue that the existence of malignant masqueraders thus dictates routine biopsy, their low prevalence, imaging features, and often times the same operative approach support selective biopsy. Imaging of the hilar bile ducts is key to accurate diagnoses of either benign or malignant tumors. Given the number of benign tumors, an overview of the select imaging features of benign tumors would have been useful and noteworthy. There are features of hilar cholangiocarcinoma that benign tumors lack. Portal vein and hepatic artery encasement with or without vessel obstruction and hepatic lobar atrophy may be present with locally advanced cholangiocarcinoma. Hepatoduodenal lymphadenopathy associated with a hilar stricture and adjacent liver invasion are seen with cholangiocarcinoma or other malignancies but rarely with benign tumors. Finally benign tumors typically are discrete and have a nodular morphology. Strictures are more frequently eccentric and smooth rather than concentric and irregular like those of malignancy. An abbreviated analysis of imaging features of benign hilar tumors was presented but the data set is small. Subsequent imaging analysis will be a welcome addition to the literature and likely lead to increased recognition of the masqueraders. The vascularity of benign tumors is also

bland. Although recognition of select morphologic tumor features and adjacent regional findings are useful clinically in identifying both benign and malignant hilar tumors, definitive diagnosis may require tissue.

Invasive diagnostics for cytological, chromosomal, or histological confirmation of cholangiocarcinoma have improved over the timeframe of reports cited herein. Transluminal biopsy, biliary brush cytology, fluorescence in situ hybridization (FISH) analysis of cytology showing polysomy coupled with imaging suggestive of a malignant stricture with a CA 19-9 serum level >100 U/ml is strongly predictive and sufficient for the diagnosis of cholangiocarcinoma [2, 3]. Admittedly the accuracy for these tests is not perfect but accuracy continues to improve. False positive findings are uncommon. Whether the use of these diagnostics would exclude categorically many masqueraders is unknown. While clinical masqueraders will persist, it seems likely with such tools that pathologically suspicious masqueraders will decrease in frequency. Lastly, there was no mention of change or progression of benign lesions over time. Even if today's diagnostics fail to confirm cholangiocarcinoma, malignant strictures progress. Again, progression would be expectedly very slow indeed for benign strictures. Hopefully future reports will cite such observations for other clinicians to use.

In practice, malignant masquerades of hilar cholangiocarcinoma will persist. Despite the best diagnostics and imaging, pretreatment diagnosis for malignancy will not be confirmed. What should the physician team managing these patients recommend? The authors note the problem and detail the culprits to emphasize its scope. They affirm that resection remains the gold standard for treatment. Clearly that approach—resection—must be the recommendation. That rationale needs only a little emphasis. First, most of the patients with malignant masquerades will require bile duct resection and reconstruction to alleviate the problem. Some patients, those with immune cholangiopathy, tuberculosis, and pseudotumors, may have alternative treatment options but recurrence or persistence of the process will not be negligible. Second, the data herein showed that outcome for resection provided acceptable outcomes though long-term follow-up was limited. Thus, the risk-benefit ratio favored operation. Third, the risk of biliary resection and reconstruction is small. The patient encounters major risk when major hepatic resection is added. Often surgeons can recognize a "red herring" or masquerader intraoperatively and biopsy the lesion before proceeding to hepatic resection. If benignancy is confirmed, hepatic resection can be aborted. Finally, in today's medical climate, a false positive diagnosis, i.e., malignant masquerade, is far more acceptable, understandable, and relieving to most patients than a false negative diagnosis of cholangiocarcinoma, i.e., observing or not resecting an early cancer that might be curable by resection. That consideration is the trump card dictating resection for these lesions. The authors have provided an in-depth resource of the malignant masquerades of hilar cholangiocarcinoma. This chapter will increase our clinical awareness of the problem but in the end it confirms that the best clinical course remains resection and reconstruction when technically feasible and clinically permitting.

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Part III
Traumatic and Iatrogenic

Chapter 12
Traumatic Biliary Strictures

Chad G. Ball

Despite their rarity, injuries to the extrahepatic biliary tree are always challenging and often deadly. More specifically, they occur in only 0.5 % of the subset of injured patients who actually require a laparotomy. In the context of trauma, the extrahepatic biliary tract is also a component of the anatomical region commonly referred to as the "surgical soul." Whether you are a Trauma or Hepatobiliary surgeon, these injuries will engage all of your senses, test your technical skills, require the utmost focus, and demand great teamwork from you and your colleagues.

Extrahepatic Biliary Tract Injuries

Gallbladder Injuries

The dominant mechanism causing extrahepatic biliary tract injuries remains penetrating trauma (gunshots and stabbings). Despite its relatively protected location (surrounded by the liver, omentum, intestines, and thoracic cage), the vast majority of these injuries involve the gallbladder itself [1, 2]. This also explains the observation that gallbladder injuries are typically accompanied by trauma to additional organs within the torso [1, 3]. Fortunately, management is simple and follows the general axiom that all injuries to the gallbladder represent an absolute indication for subsequent cholecystectomy. This includes unusual cases of blunt injury where the gallbladder is filled with hemorrhage/clot, leading to cholecystitis secondary to a blocked cystic duct. Although primary repair and/or tube drainage is occasionally

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described in case series and dated textbooks, it is almost never indicated outside of a true damage control scenario for patients in the throes of physiologic extremis [1]. While the diagnosis of gallbladder trauma is most often confirmed during a laparotomy for associated injuries, which demand immediate operative intervention, ultrasonography and/or cross sectional imaging may be helpful diagnostic tools as well.

Acute Management of Trauma-Related Biliary Injuries

Although non-gallbladder, extrahepatic biliary tract injuries are also incredibly uncommon, the dominant and most urgent issue in the acute scenario remains trauma to other structures that reside in close proximity within the porta hepatis [4]. More specifically, concurrent injuries to the hepatic artery, portal vein, and/or vena cava must be addressed first [5]. While these injuries are not the focus of this chapter, they do require significant knowledge of regional anatomy as well as damage control and vascular reconstruction techniques [6–8]. The dominant challenge inherent in managing patients with biliary trauma is therefore addressing hemodynamic instability secondary to ongoing hemorrhage, as well as gastrointestinal leakage (duodenum, stomach, pancreas, liver) from regional structures. These patients often present in physiologic extremis and require damage control resuscitation techniques [6]. Early recognition of their critical condition, as well as immediate hemorrhage control, is essential to survival. Immediate, definitive repair of the biliary injury is not the emphasis in this scenario.

Once ongoing hemorrhage has been temporized, the surgeon can then begin to address the biliary tract injury itself. In patients who remain in shock and physiologic extremis due to concurrent trauma (i.e., major liver and/or vascular injuries), deploying damage control resuscitation principles is paramount [6]. This life-saving concept mandates early truncation of all operative interventions once persistent hemorrhage has been arrested and gastrointestinal contents are controlled. This typically includes intraperitoneal packing and the educated placement of closed suction drainage in the region of the injured bile duct to control any persistent bile leakage. These patients also often require negative suction wound therapy (i.e., temporary abdominal closure) to preserve fascial integrity and avoid abdominal compartment syndrome [6]. Once the patient's abnormal physiology (coagulopathy, acidosis, hypothermia) has been reversed in the critical care suite, re-exploration can be initiated in the context of skilled surgeons with discrete experience operating on the biliary tract. In summary, the true damage control response to an injured and leaking biliary tract is adequate drainage and an eventual return to the operating theater with experienced assistance once patient physiology and hemodynamics are stabilized.

In cases of moderate patient stability and/or surgeon inexperience with biliary tract injuries, other temporizing measures include insertion of a soft T-tube into the site of injury [9]. This technique is simple and will control the biliary injury/fistula until the patient is ready for repair, or the team has included a member with advanced biliary knowledge. It should also be noted that intentional occlusion of the common bile duct in the event of a complete traumatic transection is not helpful. More specifically, upstream dilation of the proximal bile duct in preparation for an "easier" reconstruction

does not occur in a predictable fashion. When occluded, this more often leads to necrosis of the distal duct and therefore an elevation of the injury to a more proximal location [10]. Impaired hepatic physiology may also ensue. Intentional occlusion of more proximal bile ducts (e.g., right or left hepatic ducts, secondary bile ducts) via suture ligature or clipping has also been described. Similarly, this misguided approach typically results in chronically obstructed hepatic segment(s), parenchymal atrophy, and most concerning, an infected (i.e., cholangitic) liver that eventually requires formal resection with a partial hepatectomy after prolonged patient suffering. Complete external drainage via soft catheters/tubes with a planned/delayed definitive reconstruction and/or resection is a much preferred option.

If the patient is completely stable and definitive repair of the biliary injury is contemplated, multiple options are available. It must be remembered however that these injuries typically occur in the context of normal sized (small, nondilated) bile ducts that often require advanced reconstruction techniques to avoid long-term biliary stenoses and/or occlusions. It should also be noted that textbooks and journals are littered with accounts of a complex hierarchy of operative interventions aimed at repairing partial bile duct injuries. These include, but are not limited to, the generous insertion of large T-tubes for small primary ductal repairs, cystic duct tissue rotations, gallbladder wall tissue transpositions, and saphenous vein or prosthetic material patches to close various bile duct defects. These maneuvers have largely been abandoned due to the high incidence of long-term stenosis. As a result, most experienced biliary surgeons recommend two dominant techniques. The *first* is a simple interrupted primary repair for small lacerations (5 or 6-0 PDS). This approach should only be considered in the context of non-gunshot and non-cautery injuries (i.e., no concern for the vascular integrity of the ductal wall). The *second* option is a Roux-en-y choledocho- or hepaticojejunostomy [4, 11, 12]. This technique is preferred in the context of ductal transections, significant ductal tissue loss, and/or complex lacerations of the extrahepatic bile duct.

Although tension-free end-to-end primary anastomoses have been advocated by some authors in the context of both laparoscopic cholecystectomy-related bile duct injuries and trauma-induced transections of the common bile duct, this approach is clearly associated with a higher risk of long-term ductal strictures [13–15]. Unlike the case with hepatic transplantation, these patients do not suffer the benefits of low stricture rates facilitated by chronic pharmacologic immunosuppression. It should also be noted that the concurrent insertion of a T-tube for "control" of the anastomosis is generally not necessary, and potentially problematic, in patients who are reconstructed with a hepaticojejunostomy by an experienced surgeon. Placing small T-tubes in normal sized bile ducts is fraught with difficulties (tearing the duct, occluding the ductal lumen, damaging the vascular supply, ejection of the T-tube) and therefore should be avoided if possible. Although most high-volume HPB surgeons do not utilize closed suction drainage for their hepaticojejunostomies or other biliary reconstructions, injury in the context of patients with additional trauma and physiologic stressors may provide an indication for drainage in some scenarios.

It should also be noted that the classic cholecystojejunostomy is a rarely required, but potentially helpful salvage maneuver in the scenario of a complete inability to restore

biliary continuity from within the porta hepatis (e.g., extensive portal varices) [16]. Prior to performing this anastomosis however, patency of the cystic duct must be ensured by the presence of significant bile within the gallbladder itself and/or formal cholangiography.

Another consideration of vital importance in selecting the correct biliary reconstruction option is the status of the right hepatic artery. It remains clear that concurrent injuries to the right hepatic artery lead to delayed strictures of the biliary-enteric anastomosis [17]. As a result, a high/proximal hepaticojejunostomy that incorporates the hilar plate (crossing arterial plexus) is essential to ensure durable long-term patency. Techniques such as a modified biliary hilum Carrel patch and/or Blumgart-Kelly anastomosis can be helpful [18] (Fig. 12.1). As a final note, the ability to dilate chronic strictures within the biliary tree using either endoscopic or percutaneous approaches (balloon and/or stent techniques) has improved substantially over the past decade. This has led to a re-contemplation of the potential role of end-to-end primary anastomoses in some scenarios, with the potential for salvage with a minimally invasive approach, should a stricture eventually manifest.

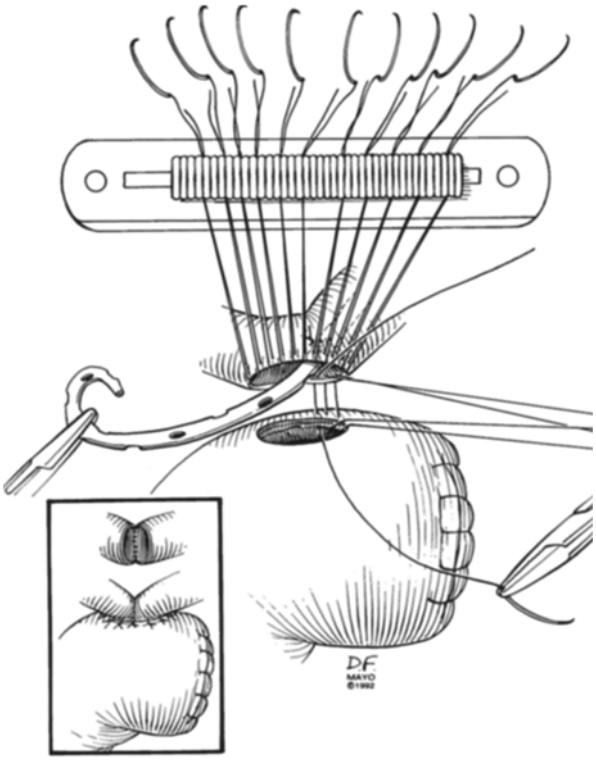

Fig. 12.1 Blumgart-Kelly anastomosis. The anterior ductal wall sutures are placed through the bile duct first and then suspended superiorly to "open" the duct and allow excellent visualization of the posterior wall. Once the posterior wall sutures are placed and tied, the front wall is completed with the corresponding intestinal suture bites

Complex distal biliary injuries are treated with a pancreatoduodenectomy. Similarly, combined complex duodenal, pancreatic head and biliary injuries also benefit from a single stage pancreatoduodenectomy by an experienced surgeon. Young patients clearly have improved long-term quality of life measures if the injury is managed in a single definitive approach. Textbooks are ripe with descriptions of local repairs utilizing transduodenal sphincteroplasties, distal biliary diversions, and other exotic case report techniques. These procedures should be avoided unless the surgeon of record has significant expertise using them within the biliary tree. It must also be restated that the damage control and/or temporizing approach to distal biliary tract injuries remains controlled drainage and delayed resection and/or reconstruction by an experienced surgeon. Attempts at pancreatoduodenectomy in the immediate traumatic setting are not advocated unless absolutely necessary.

A final acute scenario of interest remains the patient who inadvertently requires or sustains complete occlusion of a major bile duct (common and/or right/left hepatic duct). This most commonly occurs when massive porta hepatis or hilar hemorrhage requires life-saving, nontargeted suture ligation. The salvage methodology for achieving biliary decompression in these patients remains insertion of a percutaneous transhepatic catheter [19]. These tubes provide both biliary drainage and cholangiographic planning for a delayed reconstruction. It must also be noted that in some centers where this technique is less commonly performed, the procedure may have to be delayed for up to 1 week to allow progressive dilation of the intrahepatic biliary tree and therefore easier targeting for our interventional radiology colleagues.

Delayed Diagnosis of Trauma-Related Biliary Tract Injuries

Unlike the acute diagnosis of extrahepatic biliary tract injuries that occur at the time of an urgent laparotomy for concurrent injuries (i.e., identification of bile within the peritoneal cavity), delayed diagnoses typically present as a consequence of bilomas in the setting of an otherwise sterile field. Patient symptoms will consist of nausea, mild right upper quadrant discomfort, and often an ileus. Their white blood cell count and bilirubin levels may also be elevated. These patients require identification of the biloma with either ultrasound or computed tomography, in addition to subsequent percutaneous drainage and cholangiography. In scenarios of very small partial wall common bile duct injuries, placement of an intrabiliary stent via ERCP may be sufficient. With any significant injury however, immediate control of sepsis and subsequent, appropriately timed exploration by an HPB surgeon are warranted [20]. These principles are analogous to those presented elsewhere in this book regarding the management of biliary injury incurred during cholecystectomy.

In the setting of physiologic stability, the delayed diagnosis of an extrahepatic biliary tract injury/stenosis mandates complete cholangiography (MRCP, tube cholangiogram) prior to any operative exploration [21]. Similar to bile duct injuries generated during a laparoscopic cholecystectomy, an experienced colleague and/or team approach is crucial to ensure a single successful repair and therefore a

Table 12.1 American association for the surgery of trauma grading system for extrahepatic biliary tree injuries

I.	Gallbladder contusion/hematoma
	Portal triad contusion
II.	Partial gallbladder avulsion from the liver bed; cystic duct intact
	Laceration or perforation of the gallbladder
III.	Complete gallbladder avulsion from the liver bed
	Cystic duct laceration
IV.	Partial of complete right hepatic duct laceration
	Partial or complete left hepatic duct laceration
	Partial common hepatic duct laceration (<50 %)
	Partial common bile duct laceration (<50 %)
V.	>50 % transection of common hepatic duct
	>50 % transection of common bile duct
	Combined right and left hepatic duct injuries
	Intraduodenal or intrapancreatic bile duct injuries

normal quality of life for the patient [20, 22]. It should also be noted that although the classification of extrahepatic biliary tree injuries (American Association for the Surgery of Trauma injury scale) is helpful with regard to a lexicon for communication and research, it does not correlate well with the potential level of difficulty predicted during biliary reconstruction for higher grade injuries (grades IV and V) [23] (Table 12.1).

Postoperative Management, Complications, and Follow-Up

The dominant long-term potential complications associated with biliary injuries and/or reconstructions remain stenosis of the biliary anastomosis and occasional biliary fistulas. Strictures are particularly plausible in the context of hepaticojejunostomies required for very youthful patients with a long life expectancy (i.e., the typical trauma patient). As a result, these operations mandate a detailed discussion with the patient prior to discharge (i.e., risks and symptoms of potential stenosis (cholangitis, jaundice)). Fortunately, chronic strictures in this scenario are often amenable to dilation with either an endoscopic or percutaneous approach given a significantly improved rate of success over the past decade [24, 25]. However, definitive surgical revision may be required for some.

Biliary fistulas may result from incomplete repairs (poor technique, progressive necrosis of tissue due to poor vascular supply), missed injuries, prolonged external drainage through a T-tube or drain site, and/or the omission or inability to ligate the distal bile duct in the context of more proximal biliary diversions. These leaks must be rapidly converted into controlled biliary fistulae, in combination with resolution of sepsis, optimized nutrition, and complete cholangiography (MRCP, drain cholangiography, ultrasound, ERCP). For chronic fistulae that do not close, operative intervention by an experienced biliary surgeon may be required. For those that do close, the patient must be counseled regarding potential signs and symptoms of long-term biliary strictures. Planned surveillance using cross-sectional imaging (e.g., CT) is not required for repaired biliary tract injuries (as opposed to splenic injuries). Repeat imaging should, instead, be based on any deterioration in laboratory tests or patient symptoms.

Conclusion

Injury to the extrahepatic biliary tree is unusual. Cholecystectomy is indicated for all trauma to the gallbladder. Full thickness common bile duct injuries require a Roux-en-Y hepaticojejunostomy in the stable patient, whereas very minor injuries can occasionally be treated with primary repair. All patients displaying physiologic extremis should undergo initial damage control resuscitation/surgery by arresting ongoing hemorrhage and controlling the biliary fistula with an appropriate modality of drainage. Chronic biliary stenoses can be managed in a manner similar to patients with a delayed diagnosis of bile duct injury (complete cholangiography, potential balloon or stent dilation, and/or operative biliary reconstruction by an experienced surgeon).

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Chapter 13
Commentary: Traumatic Biliary Strictures—Comprehensive Management of Benign Biliary Stenosis and Injury

Bill Schwab

Professor Schwab presents a concise and excellent overview of biliary injuries and provides the reader with several important *guiding principles* for the early management. He emphasizes (a) Damage Control surgery and resuscitation, (b) use of *simple* maneuvers to provide control of bile drainage/leakage/repair, and (c) involvement of a hepatobiliary surgeon once physiologic recovery has been achieved.

Injuries by external force to the extrahepatic biliary tree are uncommon in occurrence and in isolation. Penetrating injury, especially gunshot wounding, in our experience, is the more common mechanism. Any trajectory that crosses the RUQ (especially medially) regardless of entrance or exit sites, should raise suspicion for biliary tract injury. Most of these, along with the much less common high energy blunt force mechanisms, present with concomitant vascular and hepatic parenchymal disruption as a part of the injury complex; therefore they present in shock. Thus, the surgeon is initially focused on rapid reversal of shock and moving to the operating room, while assessing and prioritizing other extra-abdominal threatening injury.

The initial hour of any damage control laparotomy focuses on hemorrhage control and gross examination for vascular and visceral injury. Most surgeons are knowledgeable about the maneuvers for vessel, solid viscera bleeding, and bowel contamination control. These can be accomplished expeditiously and with the necessary accelerated efficiencies. In reality, these are cases of competing priorities and the recognition of the extrahepatic biliary injury will most likely occur *late* in the initial damage control laparotomy when the surgeon notes bile staining, tissue destruction, or the "sense" that it is present from the array of RUQ injuries. At this point, the surgeon should be comfortable, *if conditions allow*, with a period of *slower and methodical* inspection of the gallbladder, bile ducts, duodenum, and

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pancreas. Proper exposure and lighting is mandatory to evaluate the extent of all injuries and a period of reflection on how to control the source(s) of bile and other visceral leakage is necessary. As suggested, this may involve a few simple sutures for small and partial bile duct lacerations or *more commonly,* the placement of a small, soft catheter within the injured bile duct as an external drainage conduit. In addition, Dr. Schwab emphasized some form of "educated placement of closed suction drainage," intraperitoneal packing and temporary open abdominal wall management with negative pressure dressing systems. I would add that this is *preferred* to a hurried and less than optimal attempt at a biliary repair. The damage control pathway provides the advantage of a second look when physiology and coagulation have returned to normal. In stable patients with complete transection, he recommends the time tested Roux-en-Y biliary-jejunostomy procedures for definitive repair and avoidance of more esoteric procedures. Again, I agree. I would further advise any surgeon who is *not* comfortable with small ductal-enteric anastomosis or in a patient with other critical injuries to provide external biliary drainage and safer solution, deferring biliary reconstruction to later.

A few additional comments:

1. Hepatic disruption with deep parenchymal bleeding not amendable to direct control may benefit from perihepatic packing and immediate angio-embolization. In the RUQ packing cases, one may *not* be able to examine the extrahepatic ductal system as the packing obscures the infra-hepatic area. The objective here is to expedite the angiographic interrogation. As well, the angiography should delineate arterial anatomy with variants and address the status of the right hepatic artery to further inform the team as to repair options if a proximal ductal injury is subsequently found. In these cases, an early return to the OR with inspection of the extrahepatic biliary system, ductal drainage, and insertion of regional drains with repacking should be considered.
   (a) In some centers with capable hands, ERCP and investigation of the biliary anatomy can be accomplished in the interim period and temporary biliary stenting considered.
2. In those cases with a transected hepatic or common bile duct, the placement of a soft, small drain into the proximal duct and brought out externally with *minimum dissection* to the bile duct is my preferred method of control along with regional dependent suction drains.
3. In all cases of hepatic and biliary injury regardless of type, at the time of the take back surgery (damage control part III), I am a strong proponent and user of dependent closed suction *drains* away from the site of visceral injury. I have found that in most of the cases, there are several sites needing drainage (liver, pancreas, retroperitoneal, kidney, and biliary) and provision of multiple channels of egress affords better drainage than a single large stiff drain.
4. Despite my own experience, I strongly support the principle of involving a surgical specialist as a consultant for uncommon and rare injuries whether biliary or otherwise. Almost all low grade injuries to the biliary system, liver, and pancreas

can be managed with the established surgical principles and techniques. However, the more complex and extensive injuries to the RUQ, especially disruption of the biliary tree, are facilitated with the input of a hepatobiliary surgeon *with an understanding of trauma management*.

(a) If necessary, transfer to a regional trauma center with such capability is in the best interest of the patient.

5. Biliary reconstruction can and should be delayed if necessary because of other life- and limb-threatening injury and the physiologic consequences. Once adequate external biliary drainage is assured, there is no rush to enter into reconstruction until the patient is fully recovered. Thus, when appropriate, I counsel the patient that definitive surgery may take place months from discharge.

   (a) In these cases, as soon as visual inspection at the initial or subsequent damage control laparotomy is completed, a well-crafted anatomic picture and a few descriptive notes about the injuries are helpful for long-term records and conveying the pathology to subsequent consultants.

6. Last, my approach to any surgeon referring one of these cases to our center has been to compliment them on saving a life, managing a very complex situation and setting the stage so we could help further in the recovery of the patient.

Chapter 14
Perceptual Errors Leading to Bile Duct Injury During Laparoscopic Cholecystectomy

Lygia Stewart

Cholecystectomy is a common procedure, and 750,000 cholecystectomies are performed annually in the United States. Because of this, most surgeons have a well-developed schema for the performance of cholecystectomy. Bile duct injuries (BDI) are a serious complication of laparoscopic cholecystectomy. While laparoscopic cholecystectomy has a lower morbidity, it is associated with a higher rate of major bile duct injury compared to open cholecystectomy (0.5 % vs. 0.1–0.2 %, respectively) [1–7]. Practicing surgeons are now beyond their learning curve [6], but despite many reports on the significance of the problem and means of prevention [8–25], bile duct injuries continue to occur at a relatively steady rate. BDI are also more common in cases with associated inflammation [22–25].

In addition, extensive surgical experience does not seem to reliably protect against laparoscopic bile duct injuries. Studies correlating surgeon experience with BDI report conflicting results. In one study, surgeons with 20 years of experience with laparoscopic cholecystectomy were reported to have fewer BDI [26] while in another study, this same level of experience correlated with a more BDI [27]. Also, during a recent expert panel on bile duct injury prevention at the American College of Surgeons (2014), all the expert surgeons on the panel reported that they had experienced a BDI. Some have even suggested that BDI is an accepted inherent risk of laparoscopic cholecystectomy, much like possible mortality following CABG [28].

We previously reported the mechanism of injury, guidelines for prevention, clinical findings, associated arterial injuries, and success of treatment [8–15]. We previously applied the principles of human factors and cognitive psychology to the problem to gain insight into the cognitive processes facilitating these injuries [8, 10, 11]. We also compared operation reports from uncomplicated and complicated laparoscopic cholecystectomy cases to understand surgeon's documentation of the operation as well as irregular operative findings [12].

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This chapter analyzes the human factors involved with BDI and enlarges on the perceptual issues that are unique to the laparoscopic environment to understand the factors underlying this problem.

Mechanism and Injury Classification of Laparoscopic Bile Duct Injuries

To understand the issue we developed a Laparoscopic Bile Duct Injury Classification based on the mechanism and anatomy of injury. Laparoscopic bile duct injuries fall into four general categories as defined by the Stewart-Way Classification (Fig. 14.1, Table 14.1).

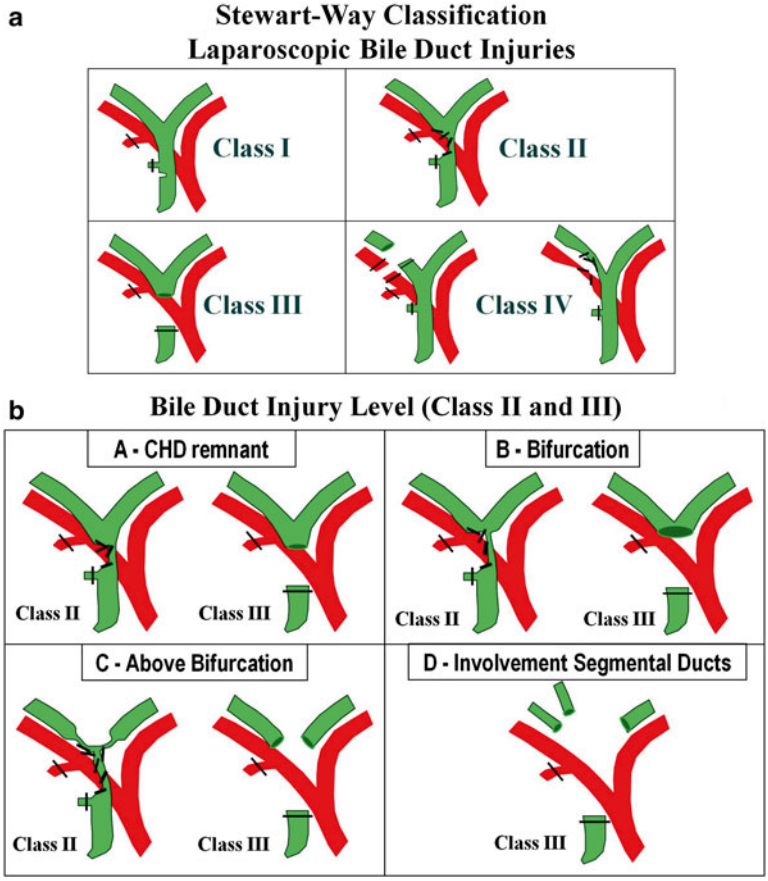

Fig. 14.1 (**a**) Stewart-Way classification of bile duct injuries. This classification incorporates the mechanism of injury as well as anatomic considerations. (**b**) Stewart-Way subclassification of levels of bile duct injury. This subclassification defines the levels of the Class II and Class III bile duct injuries, depending on the level of the injury. Note that the highest level, D, only occurs with Class III injuries (resectional injury with complete excision of the extrahepatic biliary tree). The Class III D injury pattern is not accounted for in the Bismuth and Strasberg classifications

Table 14.1 Mechanism of laparoscopic bile duct injury

Injury class	Mechanism
Class I	CBD mistaken for cystic duct, but recognized
	Cholangiogram incision in cystic duct extended into CBD
Class II	Lateral damage to the CHD from cautery or clips placed on duct
	Associated bleeding, poor visibility
Class III	CBD mistaken for cystic duct, not recognized
	CBD, CHD, RHD, LHD transected and/or resected
Class IV	RHD (or right segmental duct) mistaken for cystic duct, RHA mistaken for cystic artery, RHD and RHA transected
	Lateral damage to the RHD from cautery or clips placed on duct

CBD common bile duct, *CHD* common hepatic duct, *LHD* left hepatic duct, *RHA* right hepatic artery, *RHD* right hepatic duct

Class I injuries (6 %) involve an incision in the common bile duct (CBD) with no loss of duct. These injuries occur when the CBD is mistaken for the cystic duct but the mistake is recognized during the initial operation (with cholangiogram), or when an incision in the cystic duct for a cholangiogram catheter is unintentionally extended into the CBD.

Class II injuries (21 %) consist of damage to the hepatic duct with a resultant stricture and/or fistula. These injuries occur when the surgeon works unknowingly too close to the hepatic duct during the dissection, and result from unintended application of clips or cautery to the bile duct, often during attempts to control bleeding. The right hepatic artery was injured in 20 % of these cases. This mechanism of injury is more common in cases with acute inflammation.

Class III injuries, the most common (62 %), involve transection and excision of a variable portion of the duct, including the cystic duct-common duct junction (Fig. 14.2). These injuries result from a misperception whereby the CBD is misidentified as the cystic duct. The surgeon transects the CBD (deliberately, thinking it is the cystic duct) and then transects the common hepatic duct (unknowingly) later in the process of separating the gallbladder from the liver bed. Thus, a portion of the bile duct is removed along with the gallbladder. The upper extent of the bile duct removed varies in these cases. In some cases the injury is in the CHD, but the injury can be extended to the bifurcation of the right and left ducts, above the bifurcation, or even to include a near complete excision of the extrahepatic biliary tree (Fig. 14.1b). In 22 % of cases the upper hepatic duct was clipped. The right hepatic artery was injured in 31 % of these cases.

Class IV injuries (11 %) involved damage (transection or injury) of the right hepatic duct usually (63 %) combined with injury to the right hepatic artery [15]. These injuries resulted from misidentification of the right hepatic duct (or a right sectoral hepatic duct) as the cystic duct, or from a lateral injury to an unseen low-lying right hepatic duct (or a sectoral duct) during dissection.

In addition, these injuries can be subdivided into cases where the surgeon actively cuts (or transects) a bile duct (Class 1, III, and some IV) perceiving it to be the cystic duct; or cases where the bile duct is passively injured during dissection

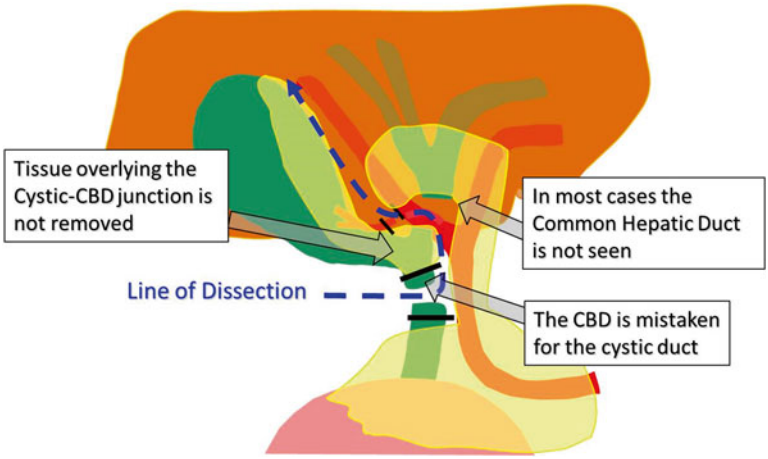

Fig. 14.2 Mechanism of class III bile duct injury. The *dashed line* shows the line of resection. The common bile duct (CBD) was identified as the cystic duct and tissue overlying the CBD-cystic duct junction was not removed. Once the misperception error occurred, the surgeon assumes that tissue about the area of CBD transection is the cystic plate, and the proximal hepatic duct is transected—usually without appreciating the duct

(Class II, some IV). Both circumstances involve misperception; one misperception of one structure for another, the other misperception of distances in the triangle of Calot.

Importantly, active injuries account for 76 % of laparoscopic bile duct injuries, while this was not the case for biliary injury in the open era. And, in the vast majority of BDI cases (75 %), the case was completed without recognition of the BDI. This suggests that the majority of these injuries result from a visual perceptual illusion [8]. These findings together suggest that an examination of the normal visual perception in the context of the laparoscopic environment is central to understanding these injuries.

Visual Perception

An understanding of normal visual perception is an essential starting point to understand these injuries. It is generally thought that vision is veridical (true) that "what you see is what you get." But a more accurate statement is "what you see is what you *construct*." The visual system constructs our visual world because it must. Vision is not akin to a camera that projects a complete image onto film, instead it is like a highly complex computer generating an image using photons and angular units of visual information that have to be constructed into an image [28–33]. While many think human perception is veridical (true) under most natural conditions, this is the result of visual heuristics that combine many probabilistic sources of information (optic flow, motion parallax, shading, shadows, texture gradients, binocular

disparity, etc.). Some visual information, which significantly contributes to depth perception, is only available during motion [32, 33]. Visual information is composed of angular units, visual angles, changes in these angles, and oculomotor adjustments. To derive spatial perceptions, the angular units of visual information must be transformed into spatial units and vision involves active construction of the image. There are no colors, shapes, objects, textures, motions, or depths. There is only a description that says something like, "This photoreceptor caught 5 photons, this one caught 12, this one caught 30…etc." From this array of 120 million numbers, the visual system must construct all the colors, shapes, objects, and depths that constitute our visual world. Also, the resolving power of the eye is nonuniform; outside the high-resolution fovea the retina is nearly color-blind with limited discrimination power. The two retinal images are inverted, distorted, and 2-dimensional. Vision cognitive scientists inform us that there are an *infinite number* of 3D constructions that are compatible with any given 2D image, yet visual processing constructs a 3D world [28–33]. To do this the visual system transcends the available information by implicitly (without conscious awareness) making a number of highly plausible assumptions about the nature of the environment. It uses heuristic interpretation processes to construct the image using probabilistic rules that are usually, *but not always*, true. The brain automatically chooses the most frequently used pattern for the template. It has a tremendous ability to pattern match. It fills in parts of objects that are hidden from view (visual completion); this happens automatically, effortlessly, and implicitly [29–31]. Almost *nothing* is visible in its entirety, yet almost *everything* is perceived as whole and complete. Several visual illusions occur due to visual completion (Fig. 14.3). In addition, visual perception has a temporal extent, most of what is "seen" at any time point actually resides in visual short-term memory (VSTM). Our visual experience relies on information gathered across multiple saccadic eye fixations. Since Foveal vision covers only 2° of the visual world, multiple short (300 ms) saccadic eye movements are needed to cover the scene; this short, temporally discontinuous, input is then linked with VSTM to create a rich visual scene [34–37]. But, in reality, you are only "seeing" your last glance. This temporal aspect of vision may account for such things as change blindness [38]. In fact, a number of visual cognitive scientists suggest that visual perception is a grand illusion [38].

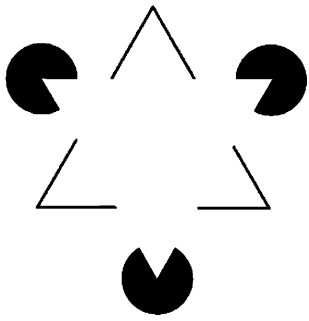

Fig. 14.3 The Kanizsa triangle. Most people see a bright white triangle occluding an *underlying triangle* and *three black circles*. The *white triangle* is a creation of visual heuristics, including "visual completion"

And finally, to achieve this amazing construction of reality, visual perception uses about 50 % of the available cerebral cortical processing power [29–31, 39, 40]. The cortical processing price of vision is important. Since natural selection rewards fecundity, not factuality; vision research experts propose that visual processing is not truly veridical but instead provides a satisficing solution sufficient for adaption in the environment [30, 39, 40].

Haptic Perception

One feature unique to the laparoscopic environment (as opposed to an open procedure) is the loss of haptic perception. Haptic perception is increasingly being appreciated as an integral part of perception, including visual perception. Haptics, a term derived from the Greek word "haptesthai" meaning "of or relating to the sense of touch," refers to the science of manual sensing, active touch exploration. Haptic perception is a complex process which occurs when one manually examines an object to discern its size, shape, texture, hardness, borders, and mobility. Haptic perception is a unique human sensory modality, in contrast with other sense modalities, because it enables bidirectional flow of energy due to the sensing and acting activities performed, as well as an exchange of information between the environment and the end user [41].

Haptic perception constitutes a form of imaging, and experiments have shown that the visual cortex is involved in processing the information; tactile perception recruits multiple visual cortical regions in a task-specific manner. Haptic and visual identification rely on distinct but overlapping neural substrates [41–46]. Haptic perception can also be fast—a brief "haptic glance" (about 200 ms) is often sufficient for haptic identification of familiar objects, whether they are geometric or material. Surgeons regularly and implicitly utilize haptic perception in the operating room, as an adjunct, to discern anatomic structures covered by connective tissue, borders, induration, masses, etc. There is recent interest in haptic perception. A number of vision scientists have shown that haptic perception not only is useful on its own but also contributes to visual perception [41–46].

Haptic perception is more accurate than vision in certain situations [47–54]. Studies suggest that the haptic system trumps the visual system in judgments of smaller-scale surface properties. The visual system may be relatively unreliable for estimation of such surface properties, so observers give greater weight to the more reliable source—haptic perception [47–49]. Haptic perception is more accurate than vision during estimates of slant [32, 33, 50, 51]. Haptic perception is crucial to depth perception [52].

Haptic perception informs visual perception. A number of vision scientists report that vision is "embodied"; the angular units of visual information are transformed into units that specify surface, extent, size, and orientation using scaling units derived from the body [32, 33, 42, 45, 51, 53–63]. Our visual perception is developed utilizing a haptic interface (our bodies, and their motion in the environment). Haptic input can be used to calibrate visual cues to improve visual estimation.

A large number of studies have shown that effort influences the *visual* perception of reaching distance, the height of hills, etc. [32, 57, 63]. Observers also recalibrate their visual percepts when visual and haptic cues are discordant—using haptic percepts as the standard to which visual percepts are recalibrated [48–54]. Haptic cues are particularly crucial in depth perception. When a haptic signal conflicts with visual cues to depth, the visual system may be recalibrated to generate depth judgments more consistent with the depth indicated by the haptic cues. When two or more noisy visual cues are present and haptic feedback is more correlated with one of these visual cues, a reweighting of visual cues occurs; increasing the weight given to the cue paired with haptic feedback [51–54]. Haptic perception informs visual perception early in life. Kittens deprived of active movement do not develop visual perception [64, 65]. Human infants first learn how to direct their movement in space using proprioceptive and haptic feedback from self-produced movement; they map visual attention onto these bodily centered experiences, not the reverse. This early visuo-motor mapping is critical for the formation of visually elicited movement control [66]. Some even suggest that elite athletes have superior visual perception because of their superior physical abilities—that motor expertise enhances visual sensitivity [61, 67].

In the laparoscopic environment, haptic processing is abolished, and with it a significant aspect of vision is eliminated. This is particularly important when viewed in the context of embodied visual perception. Haptic processing is an implicit part of our vision; its loss is not trivial. What remains is force feedback, which is an aspect of touch, but is *not* equivalent to haptic perception [41].

Visual Perception in the Laparoscopic Environment

In most situations sensory cues include input from all sensory organs (sight, sound, smell, hearing, touch or haptic), but in the surgical arena visual and haptic perception are the most important. They are both forms of "seeing" since haptic perception is processed by the visual cortex, as noted above. In the laparoscopic environment, haptic processing is nearly abolished, force feedback remains—while this is a component of touch, it is not haptic perception.

Visual imaging is also altered and it is important to understand how the changes in lighting, magnification, and vantage point interact with normal visual heuristics—possibly altering image interpretation and/or implicit construction. The laparoscopic view is a two-dimensional video screen, from a fixed vantage point, the view is from below (at the umbilicus), and it is magnified. These factors interfere with normal visual perception routines.

The fixed vantage point limits aspects of visual depth perception from motion (optic flow, motion parallax); the loss of haptic information also contributes to a loss of depth perception [29, 31, 55]. Since the camera is fixed in a port, the light source can only move in and out; illumination changes (to facilitate 3D perception) are more limited. Motion facilitates depth perception. Moving the camera in and out to get a focused and global view helps, as well as using an angled scope.

Lighting from the scope comes from a single point and it is from below, which is different from normal lighting. The view from below truncates vertical distances—causing foreshortening [29]; the CBD is closer to the umbilicus and midline so comes into view more easily. Additionally distances between the ducts would be perceived as smaller. Lighting from below also alters visual construction. In the world, lighting is normally from above. Visual heuristics assume that "lighting is from above" [29]. This is important when interpreting shadows. The box in Fig. 14.4 seems to have 5 convex circles and one concave circle when lighting is interpreted as being from above. But, if the lighting was from below, the figure would instead have 5 concave circles and one convex circle. Since laparoscopic lighting is not really "from above," interpretation of surface details can be altered [29].

Direct lighting, and lighting intensity, can also influence detection of surface detail. In normal lighting reflected light contributes to lighting and is important for detection of surface detail [31, 55]. A direct, intense, light source can mask surface detail. Figure 14.5 shows the effects of illumination changes on perception of relief magnitude [55]. The bottom portion of the figure is lit more directly than the rest; consequently this part of the image has fewer, lower-contrast shadows and perceived relief appears to be flatter.

The laparoscopic view is also magnified. In general, one would think that this is an advantage. But, magnification interferes with the visual construction of boundaries. Visual heuristics define specific rules to detect whether an image contains one structure or two structures overlapping, or connecting to, each other [29]. We divide shapes into parts along concave boundaries. The salience of a cusp increases with the acuteness of the cusp angle (Fig. 14.6) [29]. Magnification decreases the magnitude of curvature, and thus decreases the visual construction of boundaries [29]. Figure 14.7 shows how increased magnification obscures the visual boundary between the CBD and cystic duct (as the angle becomes less acute). With the upper duct (CHD) invested in connective tissue (and less visible), magnification facilitates the illusion that the CBD and cystic duct are one continuous structure.

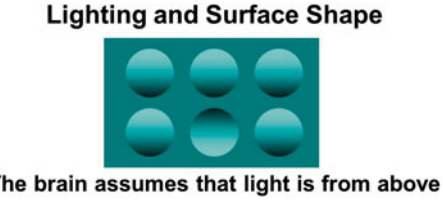

Fig. 14.4 Lighting and surface shape. The brain assumes that lighting is from above (like the sun). Note that the box in the figure seems to have 5 convex circles and one concave circle when lighting is interpreted as being from above. But, if the lighting was from below, the figure would instead have 5 concave circles and one convex circle. You may have to turn the figure upside down to appreciate how lighting looks from below

Fig. 14.5 A 3-dimensional surface showing the effects of changes in illumination and viewing geometry on relief magnitude. This image illustrates how image features (e.g., shadow and highlights) vary with changes in illumination. The bottom portion of the figure is lit more directly than the rest. As a consequence, this part of the image has fewer, lower-contrast shadows and the perceived relief appears to be flatter. (From Ho YX, Serwe Sm Trommershauser J, Maloney LT, Landy MS, The Role of Visuohaptic Experience in Visually Perceived Depth, J Neurophysiol, 2009; 101:2789–2801)

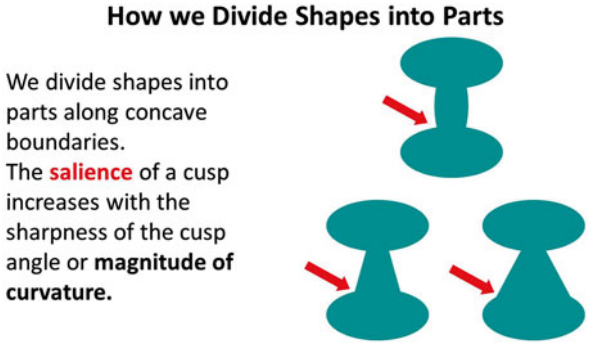

Fig. 14.6 The visual heuristics that determine how we divide shapes into parts

In summary, aspects of the laparoscopic environment interact with normal visual heuristics, altering image interpretation and/or implicit visual construction; many of them decrease the ability to judge surface detail, distances, and boundaries. Since these processes occur at an unconscious level, it is important for the surgeon to be aware of how the laparoscopic environment can change visual perception.

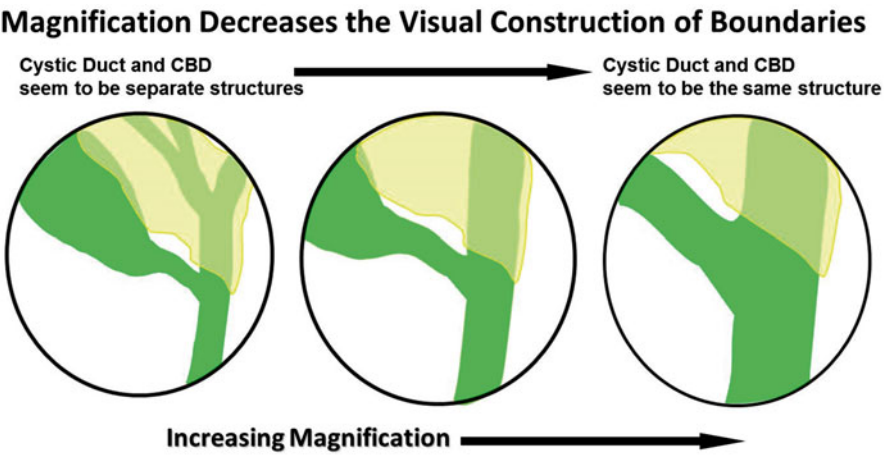

Fig. 14.7 Note that magnification makes the distinction between the two parts (cystic duct and CBD) less distinct. They look like two structures on the left, but with magnification, they seem to be one continuous structure

Perceptual Processing during Laparoscopic Cholecystectomy: Sensemaking and Situation Awareness

The literature on perception, judgment, human error, naturalistic decision making, sensemaking, and situation awareness offers a number of useful concepts for analyzing possible factors contributing to bile duct injury [69–77]. Cognitive scientists who study experts making decisions in the real world (as opposed to classroom simulations)—an area called naturalistic decision making—have found in a variety of domains that experts in the course of their work often do not go through a process that consists of choosing between options. Most often, they hold just one choice in mind, which springs intuitively from their previous extensive experience [68–76]. Even though they start with a single choice, they are also more flexible in the modification of their diagnostic assumptions [77]. All this is part of situation awareness, which is broadly—"knowing what is going on." Mica Endsley has defined the knowledge state that is achieved in situation awareness—including knowledge of current data elements, inferences drawn from these data, or predictions that can be made using these inferences [72, 73]. A closely related concept is sensemaking—making sense out of the experience in the world, a concept that includes comprehension, creation of mental models, connecting the dots, etc. Sensemaking is a motivated, continuous effort to understand connections in order to anticipate their trajectories and act effectively. Several factors contribute to situation awareness and sensemaking: sensory input (visual, haptic, auditory, olfactory, etc.), input, mental models, pattern matching, schemata, goals, expectations, and automaticity [68–77]. Input includes input from short- and long-term memory. For example, during

cholecystectomy from long-term memory and experience the surgeon has a mental model of the anatomic relationships between the gallbladder, biliary tree, and hilar structures; the patterns of these anatomic relationships; and the procedural steps involved in a cholecystectomy (schemata) [68–77]. The surgeon has the goal of cholecystectomy and a set of expectations as to what will occur during the dissection. Having performed a considerable number of these procedures, there may be some degree of automaticity incorporated into the dissection—that is pattern recognition that leads to action-sequence. These features of situation awareness and sensemaking contribute to the development of expertise; they facilitate efficiency and ease of operation.

The sensory input during laparoscopic cholecystectomy is predominantly visual. As noted above, visual perception is constructed from visual cues. Like the surgeon's long-term memory and experience, the visual cortex draws from visual memory to match the most frequent pattern to the cues. If the structure is incomplete, such as a duct invested with connective tissue, the brain fills in or completes the missing aspects of the structure in order to identify it [29, 31]. This is an automatic implicit process, and we are not aware of it; the normal visual process filters out the noise to create our perception of the true signal. As Reason stated about heuristic problem-solving "The price we pay for this automatic processing of information is that perceptions, memories, thoughts, and actions have a tendency to err in the direction of the familiar and the expected" [77]. The same is true of visual construction; the brain uses the most frequent pattern as the template [29]. During cognitive processing in the operating room a similar process occurs. In order to identify an anatomic structure, it (the signal) has to be seen among the noise of the connective tissue. Surgical dissection involves a certain degree of cognitive filtering; the surgeon matches what is perceived with the most frequently encountered template for the situation. This ability is crucial to developing the skill of surgical dissection. But, since the cystic duct is the most commonly encountered duct during cholecystectomy, if the CBD is instead encountered, normal visual processing might match it as the cystic duct.

In detailed analyses of bile duct injuries, utilizing this human factors perspective, we noted that the mistakes conformed to two tight patterns of injury, both resulting from misperception of the anatomy, not technical issues. The first was an active error, whereby the visual illusion that the CBD is the cystic duct (facilitated by aspects of the laparoscopic environment) led to misidentification of a major bile duct for the cystic duct. The second was a passive error, where the ducts were injured because the surgeon did not realize they were working in close proximity to them [8–11]. These errors stemmed from illusions of object form due to a specific uncommon configuration of the structures and the heuristic nature of human visual perception [29, 31]. The videotapes showed the persuasiveness of the illusion, and many operative reports described the operation as routine (verifying the compelling nature of the illusion).

Irregular cues were mentioned in several of the operative reports, but in only a small percentage (25 %) did these cues lead to discovery of the BDI. In several cases, the wrong rules seemed to be applied to irregular data. For example, intraop-

erative cholangiograms that did not demonstrate filling of the proximal bile ducts were interpreted as normal since no stones were seen and the duodenum filled. Extra bile ducts (which were in reality the proximal hepatic duct) were interpreted as accessory ducts or a duct of Luschka. Additional arteries in the field (the right hepatic artery—which lies behind the CBD) were interpreted as a second cystic artery. We tabulated these irregularities and identified formal rules of thumb to assist in the prevention of laparoscopic bile duct injuries (Table 14.2). The operative approach needs to actively eliminate any possibility for misperception; all tissues along the medial gallbladder wall, infundibulum, and triangle of Calot have to be

Table 14.2 Rules of thumb to help prevent bile duct injuries

Optimize imaging
Use high-quality imaging equipment
Use an angled scope (30° or 45°)
Initial steps and objectives (also see Fig.14.8)
Start by dissecting Calot's triangle. The cystic duct will be revealed after the triangle has been completely dissected
Pull the gallbladder infundibulum laterally to open Calot's triangle
Clear the medial wall of the gallbladder infundibulum, anteriorly and posteriorly
Ensure that the cystic duct can be traced uninterrupted into the base of the gallbladder
Open any subtle tissue planes between the gallbladder and presumed cystic duct; the real cystic duct may be hidden in there
Obtain operative cholangiograms liberally
Whenever the anatomy is confusing
Whenever a biliary anomaly is suspected—assume that what appears to be anomalous anatomy is really normal and confusing until proven otherwise by cholangiograms
When inflammation and adhesions result in a difficult dissection
Avoid unintended injury to ductal structures
Only place clips on structures that are fully mobilized
The tip of a closed clip should not contain tissue
Convert to an open procedure if blood transfusion is considered necessary
Convert to an open procedure when inflammation or bleeding obscures the anatomy
The need for more than eight clips suggests that the operation may be bloody enough to warrant conversion to an open procedure
Factors that suggest the common duct is being dissected instead of the cystic duct
The duct when clipped is not fully encompassed by a standard M/L clip (9 mm)
Any duct that can be traced without interruption to course behind the duodenum is the CBD
Another unexpected ductal structure is present
There is a large artery behind the duct; the right hepatic artery lies posterior to the CBD
Extralymphatic and vascular structures are encountered in the dissection
The proximal hepatic ducts fail to opacify on operative cholangiograms
Illusions
Compelling anatomic illusions, to which everyone is susceptible, are the primary cause of bile duct injuries; experience, knowledge, and technical skill by themselves are insufficient protection against this complication

Fig. 14.8 The view that needs to be obtained before completing a cholecystectomy. Note that the entire lower aspect of the gallbladder infundibulum has been dissected free, completing freeing the medial wall of the gallbladder (anteriorly and posteriorly) and taking all tissue in the triangle of Calot, only two structures enter the gallbladder (cystic duct, cystic artery), and the liver can be seen posterior to the dissection

removed, completely mobilizing this area to obtain a clear view of the anatomy (Fig. 14.8).

Seeking to understand the nature of operative reports, we compared operative reports from uncomplicated laparoscopic cholecystectomy cases and those with BDI to determine whether there were differences in the descriptions [12]. We used cognitive task analysis to elucidate the key steps in the procedure, and compared our model operative report with actual operative reports. We noted that in both uncomplicated and complicated cases, the operative reports were often missing descriptions of key procedural details. But, descriptions with more details in certain areas were more commonly associated with uncomplicated cases. These included detailed descriptions of dissection of Calot's triangle, identification of the cystic duct–infundibulum junction, and lateral retraction of the infundibulum. But, a *lack* of detailed descriptions did not correlate with the presence of a BDI [12]. There were more irregular cues reported in cases with BDI, but many similar irregular cues were also seen in uncomplicated cases (Table 14.3).

Another approach to sensemaking utilizes frames. Klein, Moon, and Hoffman have described an approach to understanding sensemaking utilizing a Data-Frame model of sensemaking [75, 76]. Frames shape and define the relevant data, and orient the observer's perspective. A common example of a frame in medicine is "rule out MI." Framing chest pain as a possible myocardial infarction (rather than reflux esophagitis, for example) facilitates recognition of a potentially life-threatening problem. We spontaneously use frames to categorize incoming data and structure to our thoughts. We reach conclusions based on the "framework" in which the situation is presented and can reach alternative conclusions about the same data if it is framed differently. Depending on how the situation is framed, data may be deemed

Table 14.3 Anatomic abnormalities described during laparoscopic cholecystectomy

Anatomic irregularities described by the surgeon		BDI cases recognized intra-op	BDI cases recognized post-op	Uncomplicated cases
Extra duct	Transected hepatic duct	X		
	Accessory duct/second duct Tubular/ductal structure Second cystic duct Duct of Luschka		X	X
Ductal abnormality	Injured bile duct	X		
	Wide/short cystic duct Abnormal ducts Abnormal biliary anatomy	X	X	X
Biliary abnormality	Redundant GB infundibulum Intrahepatic GB Fibrous liver bed	X	X	X
Bile	Bile in field (not from GB)	X	X	X
Abnormal routine IOC	Imaging of proximal bile ducts not described	X	X	X
Vascular abnormality	Additional/large arteries Additional vessels, lymphatics	X	X	X

BDI bile duct injury, *GB* gallbladder

relevant or irrelevant to the situation being analyzed. Research on expert's decision making suggests that they quickly frame contextual data and cues [75–79]. The Data-Frame theory regards early consideration of a hypothesis as advantageous. Rapid recognition of a frame permits efficient information gathering and categorization of input. Once the frame has been created, sensemaking can involve elaborating the frame (adding more details to fill out the frame), questioning the frame (when additional data seem contradictory), or re-framing—coming up with a new explanation for the data (Fig. 14.9).

We analyzed cases with bile duct injuries using the data-frame model of sensemaking to determine how surgeons used the available cues—notably irregular cues—to detect the presence of a BDI. We noted that description of irregular cues, or conversion to an open procedure, rarely led to detection of the BDI. But, when the surgeon used the irregular cues to re-frame, and consider the possibility of a BDI, then BDI detection was high (95 %) [10]. In these cases, the surgeon actively searched for a BDI using additional cholangiography, specimen exam, etc. We noted that not all operative irregularities encountered carried the same weight or led to the realization that the anatomy appeared atypical. Irregularities framed from the vantage point of a possible biliary injury often led to the injury being diagnosed. But when the irregularities were perceived (or framed) as additional "structures" or

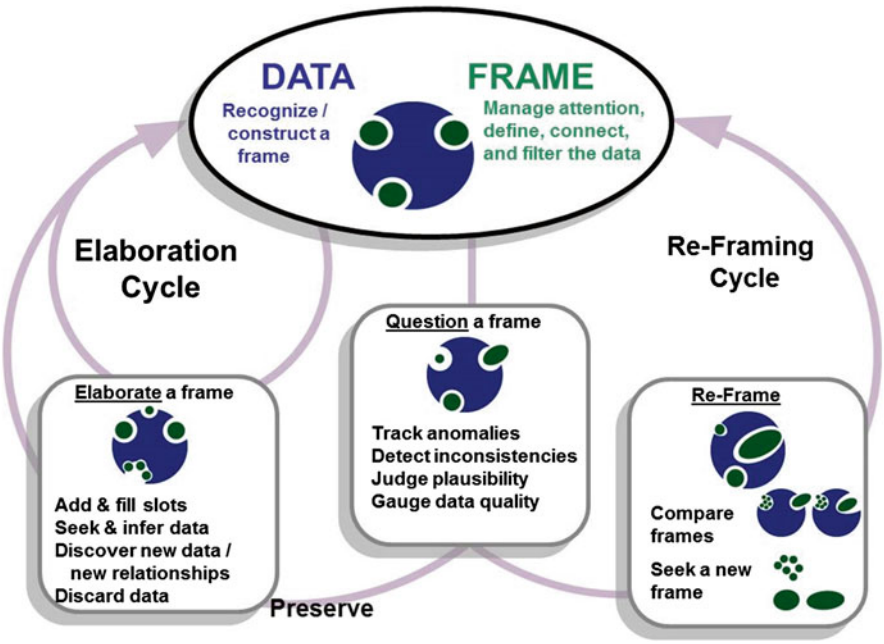

Fig. 14.9 The data-frame model of Sensemaking. Note that to elaborate the current frame, any anomalies and inconsistencies have to be discarded, but inconsistencies can also lead to re-framing (from Klein G, Moon B, Hoffman RR, Making sense of sensemaking 2: A macrocognitive model. IEEE Intelligent Systems, 2006; 21: 88–92)

"abnormalities of biliary anatomy," or "vascular abnormalities" the injury was less likely to be identified. The framing of certain cues also correlated with BDI detection; for example, when an additional ductal structure was framed as a proximal hepatic duct, BDI detection was high. But, when the additional ductal structure was framed as an accessory duct, duct of Luschka, second cystic duct, or "ductal structure," this was not the case (Table 14.3). Certain irregular cues were described in both BDI cases and uncomplicated cases [10], and these cues were less likely to lead to re-framing (Table 14.3); that is these cues were discarded as relevant and the current frame was maintained (Fig. 14.9). Since anatomic variation does occur, surgeons may not frame such a finding as abnormal. But, understanding these phenomena can facilitate an approach to BDI prevention, that is, to frame irregular cues (or a constellation of irregular cues) as a possible BDI requiring the elaboration of additional information to disprove the frame. Certainly, any additional "ductal structure" has to be framed as an injured bile duct, or proximal hepatic duct, with the requirement to disprove it using cholangiography; and, classifying a ductal structure as a duct of Luschka has to be considered with caution.

One question that arises in this analysis of laparoscopic bile duct injury is the possibility of confirmation bias, which is the tendency to seek cues that confirm the current belief and to discount cues that might disconfirm the belief. This may be an

explanation for some of the findings we have encountered in our analysis of BDI. But, the tight coupling of framing irregular cues as a possible BDI and BDI detection is less consistent with this. Research has shown that decision makers must be committed to a frame in order to be able to test it effectively and learn from its potential inadequacies, so what might look like confirmation bias might be simply using a frame to guide information seeking [75, 76].

Decision makers are sometimes advised that they can reduce the likelihood of a fixation error by avoiding early consideration of a hypothesis. But this is not always correct. Rudolph [79] studied Anesthesiologists given a "garden path" problem—an initial setup that suggests one hypothesis, followed by more subtle contradictory cues indicating a different hypothesis. Anesthesiologists who jumped to an early conclusion and fixated on it showed the worst performance (as expected); but this was a less common pattern. A more common pattern was participants who kept an open mind and refused to commit; their performance was mediocre at best. The best decision makers jumped to an early hypothesis and then deliberately tested it. Their initial hypothesis gave them a basis for seeking data that would be diagnostic [79]. This approach was more useful than the "open mind" passive approach. Other studies comparing high-domain knowledge experts and novices demonstrated that high-domain knowledge experts identified an early hypothesis, but modified their diagnostic assumptions earlier. Because of this, the high-domain knowledge experts had less evidence of confirmation bias than intermediates or novices [77]. Surgeons should not avoid framing, or hypotheses; but they should remain facile, be on the lookout for irregular cues, and be prepared to re-frame if needed.

Working Memory

A number of recent studies have correlated inflammation with a higher incidence of BDI [22–25]. Cognitive science research into working memory and attention may explain some of these observations [80–84]. Working memory, the cognitive system that stores and manages information for the task at hand, is capacity limited [80–84]. Working memory has been found to require the simultaneous storage and processing of information. It has three subcomponents: (1) the central executive, an attentional-controlling system, (2) the visuospatial processing, which manipulates visual images, and (3) the phonological loop, which stores and rehearses speech-based information [80–84]. Measures of working memory capacity have been found to predict performance in numerous cognitive tasks, including reasoning, problem-solving, reading comprehension, complex learning, and procedural skills. It is well-recognized that there is wide individual variation in working memory capacity [80–84]. Not only this, but working memory impairments and attentional narrowing have been observed during stressful conditions [81, 83], or conditions associated with high working memory load [84]. This can be even associated with inattentional blindness [84, 85]. This is in contrast to situation with high perceptual load where distractors have less effect on task performance [84]. Stressful conditions have been associated with an enhanced focus on the local features of visual stimuli and reduced

attention to how these features are globally configured, a tendency to "miss the forest for the trees" [80–84]. If a surgeon's attention is directed towards visibility issues, this may effectively mask the proximity to the bile duct. Stress tends to focus the surgeon's attention even more tightly to the bleeding or inflammation, not to the global visual field. Understanding the concepts of working memory and the cognitive approach to stress gives an additional resource for bile duct injury prevention.

Since working memory is part of visual perception, a high working memory load may actually impair visual processing [84].

Hindsight Bias

In any consideration of error one has to be aware of possible hindsight bias. David Woods, a leading expert in human factors, has delineated a clear description of this [86]. Hindsight bias is the tendency to exaggerate what could have been anticipated in foresight. After the fact the answer is known (e.g., there was a bile duct injury), so there is a tendency to view the available data assuming that it could have been used to anticipate the problem, or even prevent it. Studies have consistently shown that people have a tendency to judge the quality of a process by its outcome. Information about outcomes biases evaluations of the process. Also, decisions and actions followed by a negative outcome are judged more harshly than if the *same* decisions resulted in a neutral or positive outcome. In fact, this effect is present even when those making the judgments have been warned about the hindsight bias and advised to avoid it. The hindsight bias leads us to "construct… a map that shows only those forks in the road that we decided to take, where we see the view from one side of a fork in the road, looking back" [86]. Given knowledge of outcome, reviewers tend to *simplify* the problem-solving situation that was actually faced by the practitioner. The dilemmas, uncertainties, trade-offs, attentional demands, and issues faced by practitioners are missed or underemphasized when an incident is viewed in hindsight. Typically, hindsight bias makes it seem that participants failed to account for information or conditions that should have been obvious or behaved in ways that were inconsistent with the (now known to be) significant information. Possessing knowledge of the outcome, hindsight bias, trivializes the situation confronting the practitioner and makes the correct choice seem crystal clear [86]. Our analysis of BDI may suffer from hindsight bias. But, it is hoped that drawing attention to the possible mechanisms, the possible irregular cues, and the factors facilitating these injuries can help prevent them in the future.

Conclusion

Bile duct injuries during laparoscopic procedures are different from those that occur in open procedures, and many result from deliberate transection of a misidentified duct. Analysis of these cases revealed that many surgeons completed the operation

without recognizing that there was anything unusual about the case. The injury was only detected in about 25 % of cases—documenting the compelling nature of the visual illusion contributing to these cases. Review of operative reports and other records revealed the presence of irregular cues in many of these cases. But, when disconfirmatory evidence was available, it was often interpreted using rules more applicable to open operations, or the irregular cues were classified in ways that were less likely to result in appreciation of the error. The additional information present was often ignored because its relevance to the dissection during a laparoscopic approach was not appreciated. Since, in many cases, the same or similar irregular cues were present in uncomplicated BDI cases, this may represent normal neuro processing. But, when the surgeon framed the irregular findings as a possible BDI, injury detection was almost absolute. This shows the power of vantage point, which can be taught.

Analysis of normal visual perception, normal visual heuristics, the contribution of haptic perception to visual perception, the loss of haptic perception in the laparoscopic environment, and alterations in normal visual perception within the laparoscopic environment, provides insight into how these misperception injuries occur. An understanding of the process of sensemaking and situation awareness clarifies how experts make decisions, and an awareness of issues surrounding working memory can be useful during complex surgical dissections. Utilization of these perspectives may be useful to prevent future bile duct injuries.

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Chapter 15
Commentary: Perceptual Errors Leading to Bile Duct Injury During Laparoscopic Cholecystectomy

Nathaniel J. Soper

Despite the passage of more than 25 years since the introduction of laparoscopic cholecystectomy, the incidence of bile duct injury (BDI) continues to be higher than that associated with open cholecystectomy [1]. Laparoscopic surgery is very different than an operation performed by open laparotomy. These differences relate to the mode of access to the operative field, the different degrees of freedom of motion of the instruments, the "fulcrum effect" of laparoscopic ports (leading to reversed motion of instruments), and the reduced haptic sense that the surgeon has of the operative field. (It should be noted that surgeons' tactile sense is not changed, but their ability to discriminate palpable details of the operative field is significantly reduced.) Compared to open surgery, probably the biggest difference when performing a laparoscopic cholecystectomy is the imaging of the operative field. The image is two dimensional, magnified, directed by an individual other than the surgeon, and oriented from a relatively fixed point originating caudad to the operative field [2].

These visual and haptic differences lead to the significant perceptual errors that have been well described by Dr. Stewart in this very engaging chapter. Dr. Stewart has reviewed the neurologic and psychologic basis of the surgeon's perception of the operative field during laparoscopic cholecystectomies. These neurocognitive principles have been related to biliary injuries by reviewing operative reports and videotapes of both uncomplicated laparoscopic cholecystectomies and those resulting in BDI. Because of the perceptual limitations while performing laparoscopic cholecystectomy, Dr. Stewart has listed several "rules of thumb" that may decrease the incidence of BDI, which I will expand upon.

Given the perceptual errors inherent in the performance of laparoscopic cholecystectomy, surgeons must develop systematic safety maneuvers to overcome these

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shortcomings in an attempt to minimize the incidence of BDI. Although some cases of bile duct injury occur passively during dissection, the vast majority are purposeful, direct injuries of the bile duct caused by a misidentification of a bile duct (common bile duct, common hepatic duct or hepatic duct) for the cystic duct. Several strategies and tactics can be used to decrease the likelihood of BDI. A basic strategy is to utilize tactics which increase the anatomical information available to the surgeon. One would be the use of an angled scope that, when used correctly, can render alternative views of the operative field despite the fixed origin of the laparoscope at the umbilicus. In addition to the other perceptual limitations of laparoscopy, this mode of imaging is capable of viewing only the visible surface of the operative field, and haptics are limited, as noted above. The French have a saying, "la main voit," meaning the hand sees. During laparoscopy, the long rigid instruments can only transmit limited information regarding force feedback, so the operative field is largely experienced visually. Thus, we have found it helpful to utilize ultrasound during laparoscopic operations to see beyond the visible surface [3]. Laparoscopic ultrasound specifically allows the operator to image the location and size of the main bile ducts. The ultrasound imaging can be repeated as many times as desired, and unlike cholangiography, does not require either ionizing radiation or incision of a ductal structure which may, in so doing, result in a common bile injury. In particularly difficult cases, we will often perform the ultrasound early in the operation to locate the common bile duct in relation to where we suspect the correct dissection plane to be.

Dr. Stewart's discussion of framing the situation during performance of laparoscopic cholecystectomies is a very important concept. It is easy for a surgeon to frame atypical anatomy as a variant of normal that can be ignored. The most common type of biliary anatomy is present in less than half of all patients, so the surgeon must be mindful of the many patterns of aberrant anatomy. The discovery of an abnormally large cystic duct, accessory bile duct(s) or a duct of Luschka, or an unusual location or size of the cystic artery should stimulate surgeons to re-frame the operative situation and pause before proceeding. It is extremely important that, should a surgeon have any doubt about the anatomy he has exposed during a laparoscopic cholecystectomy, another surgeon be asked to view the operative field. The second individual will come to the situation with a completely different frame of reference and thus help clarify and potentially redirect the dissection.

Given the neurocognitive aspects of normal visual and haptic perception that can lead to error, Dr. Steven Strasberg and I described a strategy to help prevent common bile duct injury during laparoscopic cholecystectomy more than two decades ago [4]. We advocated performing a dissection that results in displaying the so-called critical view of safety. This involves dissecting all of the connective tissue away from the posterior aspect of the lower part of the gallbladder to elevate it away from the cystic plate until two, and only two, structures are seen entering the gallbladder. This involves a complete dissection of the upper boundary of the "hepatocystic triangle." Many surgical textbooks recommend dissecting Calot's triangle. Calot's triangle was described in the 19th century by an anatomist, with the base of the triangle being the hepatic duct and the two sides of the triangle being the cystic duct and the cystic artery. In real life, these structures generally do not converge on

the gallbladder wall to form a triangle, and the boundaries represent a very small area. Rather, we attempt to dissect out the ventral portion of the hepatocystic triangle—formed by the posterior wall of the gallbladder, the cystic duct, and the liver edge extending down to the hepatic ducts. The upper border of this triangle, along the gallbladder wall, is dissected beginning well away from the infundibulum; all of the fat and fibrous tissue is removed, separating the gallbladder from the cystic plate.

When beginning the dissection well up on the gallbladder, a virtual "top down" dissection is performed, minimizing the risk of BDI during the early part of the dissection. (A true top down approach beginning at the fundus of the gallbladder is difficult during laparoscopic cholecystectomy due to the need to elevate the right lobe of the liver for exposure, which is challenging after separating the fundus from the gallbladder bed. Furthermore, the laparoscopic top down approach has been reported to cause devastating vasculobiliary injuries, so should be applied cautiously [5].) When the critical view of safety is demonstrated, it should be safe to proceed with ligation and division of the cystic structures.

Severe acute and chronic inflammation of the gallbladder both can distort the anatomy and increase the risk of BDI. Early acute cholecystitis, characterized by edema, may actually simplify the operation because of tissue fluid delineating the dissection planes. Subacute cholecystitis, that occurring between 3 or 4 days and several weeks after the onset of inflammation, can lead to a very difficult and bloody dissection. Scleroatrophic cholecystitis can lead to the most difficult dissections of all, where the gallbladder is "shrink wrapped" to a very small size and may be difficult to even find, let alone dissect. Abnormalities of anatomy or difficult dissection in a zone of danger should lead the operating team to question whether to proceed. Surgeons should know their limitations, realize that in the vast majority of the cases gallbladder removal is done for elective reasons, and understand techniques by which they may "bail out" of the acute situation.

Sometimes adding an additional laparoscopic port, for instance a 10 mm port to place a large grasping instrument, may improve retraction of the difficult gallbladder. Performing an ultrasound examination to locate the bile duct may be of help. Although frequently unsuccessful due to obstructing cystic duct stones, performing a cholangiogram through the gallbladder itself may allow identification of the biliary structures. Performing a partial cholecystectomy, whereby the posterior wall of the gallbladder is left in place while removing all of the anterior wall and gallstones, and leaving a drain in the right upper quadrant, may be appropriate. Laparoscopically placing a cholecystostomy tube may be a good way of getting out of trouble when a surgeon realizes he or she is in over his/her head early in the operation. Finally, converting to an open operation may be the ultimate step in enhancing one's appreciation of the anatomy by increasing the haptic sense of the operative field. There is concern that younger surgeons trained in the era of laparoscopic cholecystectomy may not be able to perform a technically better open cholecystectomy than laparoscopic cholecystectomy, and thus this strategy of conversion may not be appropriate for all individuals. The same is true if a bile duct injury occurs and is recognized. Given the emotional strain resulting from a bile duct injury, the surgeon should not

attempt a repair himself. If an experienced hepatobiliary surgeon is immediately available, that individual should be asked to perform the reconstruction. If there is no such personnel, the operating surgeon should not feel obliged to convert to a laparotomy, but instead leave drains in the operative field and refer the patient directly to a tertiary center from the operating room.

In summary, laparoscopic cholecystectomy continues to be associated with a higher rate of bile duct injury than open cholecystectomy. As Dr. Stewart has identified, many injuries are due to the neurocognitive perceptual errors caused by laparoscopic instrumentation and techniques. Understanding those limitations and attempting to combat them by recruiting additional sensory information and tactics that minimize the chance of BDI is particularly relevant. Perhaps most important is to develop a strategy of routinely dissecting to display the critical view of safety, a technique that we believe does decrease the risk of bile duct injuries.

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Chapter 16
The Heuristics and Psychology of Bile Duct Injuries

Francis Sutherland and Chad G. Ball

Bile duct injuries (BDI) occurring during the course of a cholecystectomy is as much a problem now as it was when the British Prime Minister Anthony Eden suffered this devastating injury more than 50 years ago. Hundreds of studies have documented this complication; classification systems and safety dictums have been devised [1, 2]. However, the incidence of BDI does not appear to be changing. This has occurred despite documentation of the devastating health and financial effect on patients. The effect on the surgeon making the injury is no less profound. Shame, guilt, and loss of confidence can affect the lives of even the best surgeons. Professional misconduct and outright dismissal can occur to more marginal players.

To move towards reducing this problem we need to recognize that the causes are not simple and really involve many different facets. Clearly the bile duct is an "at-risk" structure anatomically but this does not ever justify injury. No gallbladder absolutely has to be removed! Cholecystitis can be effectively treated with partial removal [3] or drainage and antibiotics.

Like airline accidents most surgical errors are mistakes in operator cognition [4].

To understand how bile duct injuries occur we must understand how surgeons' think. Modern cognitive theory gives us this insight. The three facets of bile duct injury are, first, the "at-risk" situation. What is it about the bile duct that makes it easy to damage? The second facet is an error in perception. Why do we see what we see and what is the role of technology? The last facet of BDI is an error of correction and deals with the role of cognitive biases. How the human brain deals with ambiguity is central.

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Modern Cognitive Theory

Decades or research have resulted in a new understanding of how we perceive our world and how we think. Rather than relying on the inefficiency of just moving from one conscious thought to another we have developed a system of rapid unconscious processing and shortcuts [5]. The tremendous redundancies of our world make this possible. A door does not require any deep thought for us to open it. Turning the handle and pulling happens automatically. Indeed, if we had to think about everything that we do it would be paralyzing. These "automatics" that we use everyday are called heuristics. Daniel Kahneman [5] called this system 1 thinking. Fully formed thoughts or actions come streaming forward into our conscious. Fast think is uncontrolled, rapid, and usually correct.

A second system 2 form of thinking is necessary for situations were things are not so obvious [5]. Sometimes we have to modify or reject system one thoughts, perceptions or actions. This requires slow deliberate effortful thinking. The doorknob is missing and we have to figure out another way of opening the door. This is slow thinking and is necessary in new situations. To solve problems or be creative we have to slow think. We are all lazy and like to avoid this work of thinking; system two is only engaged when forced.

Most of our lives are spent in system one automatic thought. As we grow and learn an increasing wealth of experience about the world is stored in our "ready" memory. We use it every minute of every day as we move through our environment. Mistakes our recorded and most often not repeated. Practice makes it possible to do complex tasks effortlessly. Individuals can race a Formula 1 car, play tennis at the US open or perform complex surgery.

The "At-Risk" Situation

Proximity is the major reason the bile duct is at risk of injury. Anatomically the cystic duct comes directly off the bile duct. The cystic duct may be very short or nonexistent. A small common bile duct can look just like the cystic duct. Traction on the gallbladder base can even make it angle in the same direction. The second proximity issue is the gallbladder wall can be adjacent the common hepatic duct. Inflammation closes the space between the gallbladder and bile duct. In extreme cases they can become fused. When this happens the gallbladder and the bile duct move as a single unit.

There are two important anatomic spaces just below the liver in the area of the porta hepatis that can also have a similar appearance. The hepatobiliary triangle is the space between the gallbladder wall and the hepatic duct. It is the key dissection plane for cholecystectomies. An artery and lymph node are usually in this space. If one moves medially the second space between the bile duct and the hepatic artery can appear the same. It contains fibro fatty tissue, an artery (right hepatic or branch there of) and a lymph node. It has a "strong" well-defined lateral border (common hepatic duct) just like the hepatobiliary triangle (gallbladder wall).

Todays' "modern general surgeon" may also be considered "at risk." First, with the development of ERCP the need for a general surgeon to dissect the bile duct in the ports has been reduced. Further, the development of hepatobiliary surgery as a subspecialty has virtually eliminated the general surgeon's exposure to the porta. A familiarity with the hepatobiliary triangle anatomy belies a lack of understanding of the porta hepatis anatomy and the bile duct hepatic artery space, as a whole. The structures and their relationship to each other are invisible to most general surgeons'.

Technology can also put the bile duct "at risk." Removal of a gallbladder at laparotomy has certain advantages. An open operation gives the operator a certain perspective over the anatomy of the operative field. The field of view is wide. The relationship between the gallbladder and the porta hepatis is clear. Traction on the duodenum also pulls the bile duct "straight" more clearly demonstrating the anatomy.

A lack of spatial awareness by the laparoscopic surgeon may be a byproduct of the technology [6]. The laparoscope gets the surgeon close and limits the field of view. The more difficult the dissection the more there is a tendency to move closer. Normal cues to operative position are not seen as the surgeon focuses in on the perceived correct dissection plan. When the key landmark of the cystic duct gallbladder angle is uncertain the surrounding landmarks can orient the surgeon as to its likely position in space or alert the surgeon he is in the wrong space. The bile duct proper, sulcus of Rouviere, hepatic artery, umbilical fissure, and stomach/duodenum allow the surgeon to check his position but they are often not in the field of view.

Another attribute of this "at-risk" situation is anatomic variability. "Normal" bile duct anatomy exists in only 50 % of situations [7]. Sectoral ducts to the right liver can come off anywhere along the bile duct and be easily misinterpreted as a cystic duct. Even more, the size shape and configuration of the subhepatic structures is widely variable. The gallbladder also can vary from button size to filling the right upper quadrant. The duodenum may be fused to the gallbladder wall or the whole subhepatic space may be cocooned in fibrous tissue.

The operating room environment may contribute to risk. As the number of people in the room increases, the noise and activity levels also increase. Distractions are numerous. Surgeons may also be expected to juggle multiple tasks at the same time. Additional demands on the surgeons' attention are legion. Pagers bring the problems of the ward and emergency into the operating room. Attention to the participation level of multiple learners in the OR is a hazard of teaching hospitals that may distract the surgeon away from the task at hand. Basic human interactions carry a certain amount of distracting conflict. Surgeon fatigue is an increasingly recognized problem that may limit attention capacity.

The surgeon in the operating room is usually a "lone wolf." There is no pilot copilot relationship. Assistants, residents and nurses rarely have the skill to redirect a misplaced dissection or recognize when it is time to stop. Asking for help is often perceived as a sign of weakness and is very dependent on the culture of the institution. The surgeon himself may be an "at-risk" operator. He may be overconfident in his abilities and operate carelessly. Operating repeatedly with no oversight may facilitate the development of bad habits. Heuristics can be taken too far and move into realm of dangerous shortcuts. The speed of automatic operating with little system 2 oversight can be risky.

Failure of Perception

When we humans interact with the environment our senses interpret the information received to the best of our abilities. Our interpretations have varying degrees of accuracy but are always just an estimate [8]. The information we are receiving is always incomplete and we are forced to fill in the gaps. It is like highway driving at night. Further, sometimes the information is ambiguous, meaning that a number of different interpretations are possible. How we deal with this uncertainty is unique to ourselves. We all have different degrees of ambiguity aversion and varying degrees of ability to assimilate information.

Operating surgeons' interpret anatomy based on key landmarks. Indeed, so much information is received upon opening an abdomen as to be overwhelming. Focusing on key anatomic landmarks and the "filling" in the rest of the scenario happens automatically in the surgeons' mind and saves time. A lack of recognizable landmarks is disorienting and initiates a search for them. A surgeon that is "lost in space" is the same as the spatial disorientation that an airplane pilot may experience [4]. Patience and confidence that the landmarks will be found is an attribute of an experienced surgeon.

A cognitive map may be one way a surgeon orients herself to the anatomy [6, 9] As a surgeon gains experience the memory of multiple anatomic examples builds a cognitive map of the area. The associative memory can then recall the map and place it on key anatomic landmarks to fill in the picture and allow rapid dissection. In the normal course of an operation this may occur multiple times. The map may also have to be altered based on new information or moved if it is misplaced (wrong map or wrong placement).

With gallbladder surgery the key landmark is the angle between the cystic duct and the gallbladder. Early dissection of the hepatobiliary triangle is largely done to identify this landmark. Once it has been found the surgeons' cognitive map can be placed accurately. This then allows the operation to rapidly progress with dissection under the gallbladder, clipping of the cystic artery and cystic duct, and then removal of the gallbladder from the liver. Very little non-directed dissection needs to be done after the map is set. Efficient surgeons set their map quickly and progress without meticulous dissection of all the anatomy. Most of this is done with heuristics or in other words on "automatic." Only when there is significant ambiguity does the surgeon have to slow down into system 2 effortful cognition to work out the anatomy and surgical moves.

Using the cognitive map works fine unless the initial placement is wrong. Illusions are a situation where our interpretation of reality is universally wrong [5]. Here system 1 and system 2 interpretations of reality are equally false. The "bile duct" illusion occurs when traction on the gallbladder and cystic duct kinks the bile duct. This kink creates an angle between the common hepatic duct and the common bile duct that looks like the gallbladder cystic duct angle (key landmark). Misplacement of the surgeons' cognitive map based on this landmark illusion is the failure of perception that results in a "classic" bile duct injury. The lower common bile duct is interpreted as the cystic duct and the medial side of the common hepatic

duct in interpreted as the gallbladder wall. The operation then proceeds as the bile duct is clipped and divided. A surgeons' attention is always drawn to clean dissection planes. If there is inflammation and closure of the hepatobiliary triangle, attention is directed medially to the bile duct hepatic artery space. As discussed, these two spaces are similar in appearance and dissection.

A second illusion occurs as the dissection mistakenly proceeds up the medial side of the common hepatic duct as if it were the gallbladder wall. When the level of the liver is reached the map dictates a lateral move to begin taking the gallbladder off the liver. A normal gallbladder is fused to the liver and needs cautery to separate the tissues. Now this same move divides the bile duct for a second time at or above the hilum. It is surprising how small the duct can be and how easily it is divided with hook cautery. Further, the cautery may seal off any bile leakage. Once the surgeon is through the hilum the dissection plane becomes correct and the operation proceeds along the normal plane.

One can see that the surgeon has spatial disorientation. His dissection is based on the assumption that map placement is correct. Like playing the piano after misplacing the start point for the fingers the result is noise not music. The problem for the surgeon is that he cannot hear the "noise" to signify the mistake.

One must recognize here that the mistake is not the division of the bile duct but rather the misinterpretation of the anatomy and the misplacement of the cognitive map.

Failure of Correction (Cognition Biases)

Errors are a normal part of any operation. How we avoid, recognize and correct these errors are key to safe surgery. Small errors require limited cognition and may be corrected automatically in system 1. Major errors like misplacement of the cognitive map are more complex to correct as we have a number of cognitive biases that prevent their correction. These cognitive biases are mistakes in our thinking patterns where we tend to make the same error repeatedly.

As human beings we strive to perform tasks with the least amount of stress. In situations of ambiguity where anatomy is unclear there is a certain amount of discomfort experienced by the surgeon. The trait of aversion to ambiguity may also be more prevalent in physicians that chose surgery as a profession [10]. There is always pressure to move the operation along. Indecisiveness and spending time contemplating anatomy is very un-surgeon-like. Action in the face of ambiguity, at least temporarily, solves the problem. So when the map is misplaced the division of the presenting duct makes the surgeon feel better as a decision has been made. The opportunity to correct the mistake before it happens is lost by this bias to action. Plane old careless "wishful thinking" may play a role here.

Other cognitive biases may also prevent correction of the mistaken map placement. In the face of uncertainty alternatives may simply not come to mind (availability bias) [11]. Having a store of experience is of no value if it cannot be

retrieved from the memory bank at the critical moment. When things do not appear quite right the option of just backing up the camera to identify surrounding landmarks does not come to mind. Other options such as dissecting the gallbladder off the liver or switching to an open approach do not occur. The surgeon becomes "blind" to the alternatives.

Once a decision has been made the surgeon invests a certain amount of his ego in this decision. Everything from this point on tends to confirm the original decision. The surgeons' perception interprets all subsequent anatomy that is dissected to confirm the initial decision (confirmation bias) [5]. He is following the map and the map simply "cannot be wrong". Clues that would, by themselves, prompt a reevaluation of assumptions do not trigger a response. The bile duct is cut twice to make the anatomy conform to the surgeons' misperception.

One must also recognize that we have an innate tendency to believe what we see. We also have a tendency to believe our first impression. It takes effortful thought to move beyond our initial interpretation [12]. Hence we suffer cognitive fixation and error continuation. For many reasons failure of correction takes what should be a "near miss" into a complicated injury.

The Interplay of Causation

One can see that causation of bile duct injuries is complex and multifactorial. There are a number of anatomic, pathologic, technologic, environmental, and human reasons that the bile ducts are injured during the course of cholecystectomy. Proximity of the gallbladder to the bile duct is central. The similarity of two different dissection zones and inflammation may redirect the surgeon to the wrong zone. Traction on the gallbladder creates a kink in the bile duct that looks just like the key landmark cystic duct gallbladder angle (bile duct illusion). This enables the failure of perception and then the misplacement of the cognitive map in the wrong space medial and inferior to its proper location. A whole series of cognitive biases prevent correction of the mistake and force the operation along the path that results in the removal of the common hepatic duct along with the gallbladder. The surgeon, perhaps tired and distracted, follows the misplaced map along a path that divides the bile duct twice. At any time the surgeon may recognize his error and limit the damage. Unfortunately, cognitive fixation and error continuation often takes this injury to the end. The mistake may not be recognized until the patient becomes ill in the postoperative period.

Solutions

Proper surgical technique in creating the "critical view" [1] can certainly help in reducing the incidence of bile duct injury. To move further surgeons' must understand the multitude of reasons the bile duct is at risk, how our perception of reality can be wrong, and why the way we think can prevent us from correcting the problem.

Comprehensive cholecystectomy education needs development at all teaching centres. The first order is to teach the complete anatomy of the porta hepatis and not just the hepatobiliary triangle. It is important to understand both spaces of dissection including their very real similarities and how to recognize the differences. Residents need to dissect both spaces in cadaver and animal labs to understand the subtleties of the anatomy. Because we cannot bring real time porta hepatis dissection to all learners simulations need to be developed. Allowing residents to gain the experience before being involved in an "at-risk" situation is the goal. Residents must also understand the variable anatomy of the subhepatic ducts, especially the anterior and posterior sectoral ducts.

How to recognize the bile duct illusion needs to be taught. The very definition of an illusion means that our senses cannot be trusted. First impressions must be overridden so that more dissection can uncover the real anatomy. A video library of the illusion in all its different forms will allow learning to occur prior to trail and error operating.

Students need to understand the pathology of severe chronic cholecystitis and how it is different from milder forms of the disease. The inflammation closes the hepatobiliary triangle and fuses the gallbladder and bile duct walls. Chronic inflammation also can causes contraction of the gallbladder and stone erosion into surrounding structures (duodenum and colon). Operative strategies to deal with these difficult situations and not damage the bile duct need to be taught.

All surgeons need to have training in cognitive psychology and error avoidance, recognition and correction. Surgeons need a basic understanding of how they think during an operation and how their cognitive biases can put their operation at risk. Knowing how we make mistakes allows us to take steps in avoidance. Regular review and coaching of surgeons needs to be a part of quality assurance no matter how senior or expert the surgeon may be. Skills deteriorate with time and with no oversight bad habits may become ingrained. Surgeons must be taught to be circumspect of their judgments and always question assumptions. Slowing down to back up the thought process may avoid making an error or allow early correction.

We need to design our systems with the operator in mind. The operating room environment needs to be cognizant of who controls the tip of the scalpel and stressors facing that individual. Limiting noise and distractions are important. Adding stressors through the operative day should be avoided. The problems of the outside hospital and administration of the OR should not invade the room. They should be dealt with between or after the cases are completed. The role and number of learners in the OR needs to be defined and controlled to improve safety and the quality of the learning experience.

How the surgeon interfaces with laparoscopic technology is important. The real advantages of the laparoscope and its limiting factors need to be taught. Strategies that make up for the lack of field include backing the camera to broaden the field. Specifically, the surgeon should take a "bile duct time-out" before moving into detailed dissection. The camera is backed out to identify the landmarks around the gallbladder so that the surgeon can fix her spatial orientation (position in space). Five surrounding landmarks can usually be seen. First, segment 4 can be lifted and

the bile duct proper can be viewed. Surrounding structures of the sulcus of Rouviere, umbilical fissure, and stomach/duodenum can be seen. Careful observation can site the hepatic artery by viewing its pulsations. These five structures expose the anatomy and allow the cognitive map and disection to be placed in the correct location. A map misplaced in the bile duct hepatic artery triangle is medial and inferior to the hepatobiliary triangle. A pneumonic to remember this "bile duct time out" is B SAFE (B-bile duct, S-sulcus of Rouviere, A-hepatic artery, F-umbilical fissure, E-enteric). A time-out should be taken at the start of the dissection, whenever there is ambiguity and before a structure is clipped. It takes seconds.

Stopping rules need to be taught and encouraged in a supportive collegial atmosphere. Hepatobiliary services with special expertise in this area need to be available in support of general surgeons. A mistaken map placement then can turn into a "near miss" and not a bile duct injury proper. It becomes a learning experience and not a catastrophe.

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Chapter 17
Commentary: The Heuristics and Psychology of Bile Duct Injuries

John G. Hunter

The Heuristics and Psychology of Bile Duct Injuries: Commentary

During cholecystectomy, laparoscopic or open, common bile duct injury (CBD) is never part of the operative plan. Of the tens of thousands of surgeons who have cut the CBD during cholecystectomy, not a single one intended it. Additionally, injury to the CBD is rarely an accident, a slip of the scalpel at an inopportune time. No, most common bile ducts are cut quite deliberately, by a surgeon who thinks that he/she is "miles away" from the bile duct, separating an inflamed GB from the liver … until bile gushes out of the common hepatic duct (CHD) laceration. Alternatively, he/she is sure that they have clipped and transected the cystic duct, and leave the OR with no idea that the operation was anything unusual … until the patient becomes ill, postoperatively with a clipped, transected, and (often) excised CBD.

So how could talented surgeons, most of whom have done hundreds if not thousands of gallbladder operations get so lost? How could they become so "faked out" by anatomy that they see so frequently? The answer to these questions is well addressed in Dr Sutherland's chapter and in work performed over two decades by Drs Way, Stewart, myself, and many others [1]. A surgeon performing a cholecystectomy creates a "map" of the anatomy in his/her brain, a cognitive map that guides dissection. But, if the cognitive map is frame shifted by as little as several millimeters from actual anatomy, by a misinterpretation of the visual cues or loss of cues resulting from inflammation, disaster awaits. As Dr. Sutherland puts it:

> One must recognize here that the mistake is not the division of the bile duct but rather the misinterpretation of the anatomy and the misplacement of the cognitive map.

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Then things get worse:

> When things do not appear quite right the option of just backing up the camera to identify surrounding landmarks does not come to mind. Other options such as dissecting the gallbladder off the liver or switching to an open approach do not occur. The surgeon becomes "blind" to the alternatives … Once a decision has been made the surgeon invests a certain amount of his ego in this decision. Everything from this point on tends to confirm the original decision. The surgeons' perception interprets all subsequent anatomy that is dissected to confirm the initial decision. He is following the map and the map simply "cannot be wrong." Clues that would by themselves prompt a reevaluation of assumptions do not trigger a response. The bile duct is cut twice to make the anatomy conform to the surgeons' misperception.

So this sounds pretty bad. How do we prevent ourselves from getting "trapped" in this fashion? It is clear that our cognitive map is correct most of the time, or CBD injuries would be much more common. Nonetheless, error rates, leading to CBD injury 1 in 500 operations (a conservative estimate of the true incidence rate) results in >1000 CBD injuries in the US every year. Most industrial processes seek to drive error rates to 3.4 in 1,000,000, the so called 6 sigma error rate. If we could achieve this level of reliability in gallbladder surgery, we would see two or three CBD injuries/year in the USA. Is it wishful thinking to imagine that we now know enough to strive for reducing CBD injury rates 500-fold? While such a lofty goal would require a "paradigm shift" of some sort, is there any reason that we should not get started down this road? Dr. Sutherland has suggested several things that we could all do to drive injury rates to an all-time low. Read his chapter a second, and a third time, and as many subsequent times as is needed to cement these concepts in your automatic surgical self.

I have a few additional thoughts:

The frequency of CBD injuries is not random. We surgeons—alas—are not all created and trained equally. We are not robots, attaching a differential to an automotive transmission, over and over again. Certain surgeons cut more bile ducts than others, even when corrected for cholecystectomy volume. The attributes of those who perform a lot of cholecystectomies and have few (or no) injuries to their record can be studied. They are more meticulous, perhaps a little slower, they perform cholangiograms more commonly and they are much more likely to question the cognitive map when it deviates, even a little, from the map they have come to rely on [2–4]. As Dr. Sutherland suggests, if we were just a little more cognizant of these deviations we might enact an alternate strategy (backing the camera up, "rebooting" the cognitive map, calling for another surgeon to help us sort out the anatomy, adding another trocar to gain additional exposure, converting the operation to open, etc.). Good surgeons slow down and constantly seek confirmation that their cognitive map is correct. High risk surgeons plow ahead in the face of uncertainty. In this era, when all complications are so transparent and few so transparent as CBD injury, high-risk surgeons rarely have a chance to cut more than 2–3 ducts in their career before their privileges are revoked … but this is still 2–3 too many.

What about dissection strategy? If every surgeon were forced to obtain and document (with a photo) "the critical view of saftety" (CVS) would bile duct

injuries decline by 500-fold, or even twofold? This experiment has been done in the Netherlands. So far, the jury is out, as 98 % of Dutch surgeons report the routine use of the CVS, but bile duct injury rates in the Netherlands have not dropped over the last decade [5]. Additionally, the CVS was documented in the op note in only 17 % of all operations, and 75 % of operations were completed without a documented concern over operative difficulty or concern for BDI. One would hope that the rate of intraoperative identification of injury would increase over time, but these findings are no different from those we published 12 years ago [1]. I have seen a beautifully photodocumented CVS in a patient about to have his common hepatic duct (CHD) cut, which was hidden behind the "presumed" junction of the GB and cystic duct (Fig. 17.1). The truth, once the map was correctly interpreted (too late), was that the tented CBD (misinterpreted as the cystic duct) was attached to an extremely short cystic duct. Perhaps critics would suggest that the surgeon had not really obtained the "critical view," but the surgeon was sure enough to snap a photo before he cut the common hepatic duct!

Here's the problem with the concept of the CVS. It describes nothing that a surgeon can hang on to. Ten surgeons will describe the "critical view" in ten different ways. If we are going to resort to imagery, to help the surgeon latch on to an image that will help him know when he/she has done a complete and safe dissection, the image is that of making the gallbladder look like a polyp on a stalk, including the requirement to look behind the gallbladder—cystic duct junction (360°) using an angled scope and "flag waving" the infundibulum up and down as the camera angle is adjusted (Fig. 17.2).

Alas, perfect dissection, whether employing the CVS strategy or making the gallbladder look like a polyp on a stalk, may not get us to 6 sigma error rates, as neither of these dissection strategies is always achievable. Dense inflammation in the hepatobiliary triangle with fusion of the gallbladder fundus to the common

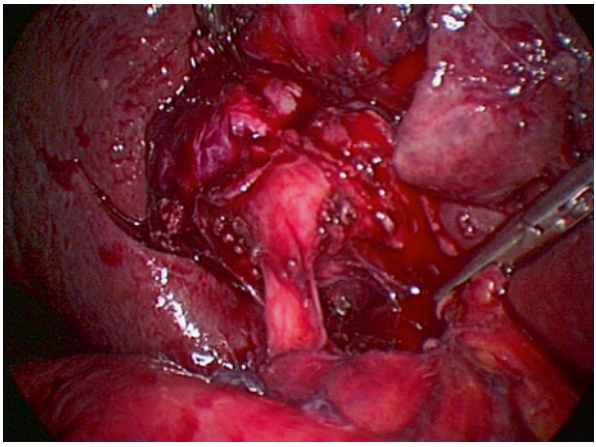

Fig. 17.1 The "critical view" misinterpreted. The duct being exposed is the CBD, prior to division

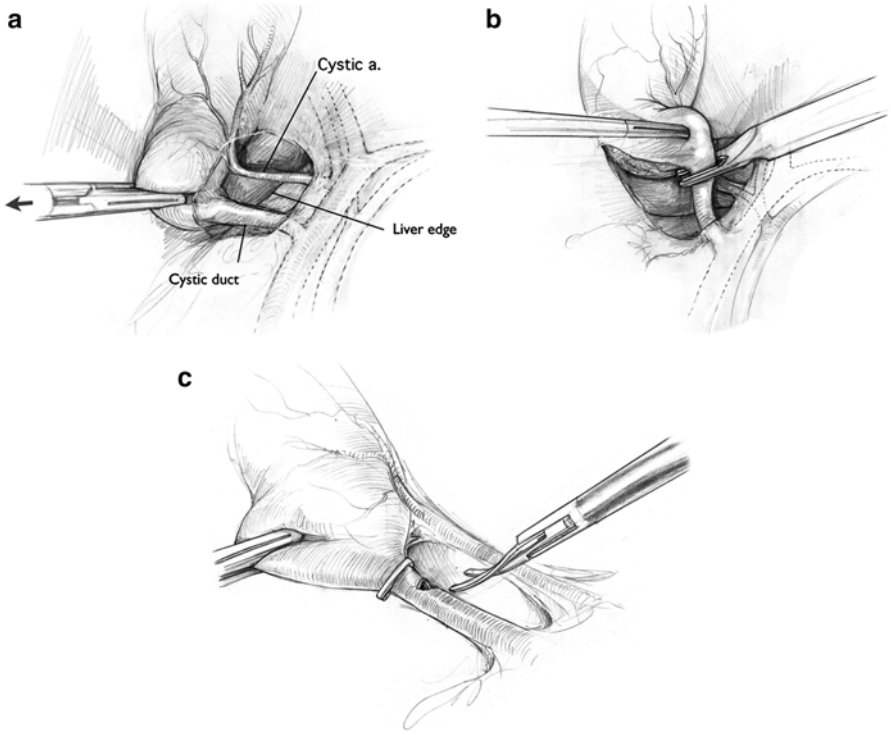

Fig. 17.2 The gallbladder is made to look like a polyp on a stalk before clips are applied. The critical view of safety (**a**) is the best single view of anatomy in the hepatobiliary triangle, but before the clip is applied, the GB infundibulum must be rotated to obtain a posterior view (**b**), confirming the impression reached by the CVS. A cholangiogram is performed through a cystic ductotomy (**c**). (Reproduced with permission from: *The Atlas of Minimally Invasive Surgical Operations*. Hunter, Sandone, Spight, Fairman, McGraw-Hill, Inc. New York (in press))

hepatic duct (with or without Mirrizi's syndrome) is a formidable challenge for even the most accomplished laparoscopic surgeon. The hepatobiliary triangle cannot be easily opened if the gallbladder is attached to the CHD with dense scar. Conversion to open surgery is a safe strategy, but not sufficient to eliminate bile duct injury in the face of dense inflammation. In these settings, the prudent surgeon working down the gallbladder from above leaves a portion of the gallbladder wall fused to the liver bed, CHD, right hepatic artery, and other portal structures involved in the inflammatory process. This operation may be accomplished open or laparoscopically with good results if the field is kept clean and exposure is not compromised by imaging or inflammation. It is not even essential to control the cystic duct orifice if this cannot be identified. Drop a drain, get out, and accept that a biliary fistula might develop. The management of a biliary fistula with endoscopic or transhepatic biliary drainage is a simple management problem when compared to bile duct injury.

Can imaging or robotic technologies bring greater safety to laparoscopic cholecystectomy? Before pulse oximetry and capnography, general anesthesia was

pretty dangerous, nearly as dangerous as laparoscopic cholecystectomy. After these two technologies became standard in most ORs, the safety of general anesthesia approached the 6 sigma level. Is it possible to create a "no fly" zone around the CBD, with alarms that sound in the OR when the surgeon is within a few millimeters of the CBD? Several technologies have been suggested to solve this problem including ultrasonography and fluorescent injectable vital dyes. The concept with ultrasound involves laparoscopic 3D ultrasound mapping of the biliary anatomy at the beginning of operation. The map of the vital structures (CBD, CHD, common hepatic duct, etc.) as determined sonographically are then overlayed (registered) in the video imaging system with 3D coordinates. As the video laparoscope moves through this 3D space, the overlaid map of the CBD/CHD location is refreshed according to the location of the tip of the laparoscopic relative to the CBD/CHD. Laparoscopic instruments with 3D fiducials attached could trigger an alarm when they were brought too close to the CBD. Currently, it appears that such a complex imaging and alarm system would add too much time (mapping) and too much expense (3D ultrasound, 3D spatial registration system) to make this approach more than a curiosity or a concept piece.

More practical and in clinical use is a system of injectable fluorescent dyes, such as indocyanine green, that allow the surgeon to toggle from white light to near infrared (NIR) light, inducing fluorescence of the biliary system, to as they dissect in the hepatobiliary triangle. Frequent anatomic confirmation of biliary anatomy, by toggling between NIR and white light as the dissection proceeds may provide confirmation to the surgeon that the map from which the surgeon is working is the correct map [6]. My fear, with this technology is twofold: First, will the fluorescence be visible when there is a thick CBD encased in dense scar? Second, I fear the second (fluorescent) map will be used by surgeons to confirm the (erroneous) cognitive map that a surgeon makes when they are about to cut the CHD or CBD. There are no alarms ringing when the surgeon is about to clip the wrong fluorescent duct, as the cystic and CBD may well fluoresce equivalently.

While a pessimistic conclusion is generally discouraged, it is hard to be optimistic that we will, anytime soon achieve a 500-fold reduction in CBD injury. However, maybe if surgeons better understand why they get lost in the video image and utilize some of the strategies in Dr. Sutherland's article and this commentary, we might be able to spare many individuals around the world the serious morbidity and mortality associated with a CBD injury.

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Chapter 18
The Classification and Injury Patterns of Iatrogenic Bile Duct Injury During Laparoscopic Cholecystectomy

Edmund K. Bartlett and Charles M. Vollmer Jr.

Introduction

Cholecystectomy is one of the most frequently performed general surgical operations in the world. Understanding of the injury patterns and classification of iatrogenic bile duct injuries is critically important not just for hepatobiliary surgeons, but all general surgeons who perform cholecystectomy. Given the limited experience that most surgeons have in dealing with these injuries, an adequate classification system is all the more important. Classification allows for consistent and reproducible study of these injuries, as well as the development of prognostic and treatment algorithms associated with specific injury patterns. Furthermore, an understanding of the common injury patterns may help to avoid complications. When injuries do occur, appropriate and rapid diagnosis and treatment may prevent progression of a complication that can lead to decreased quality of life, multiple operative interventions, biliary cirrhosis, liver failure, and even death [1, 2].

Since the rapid adoption of the laparoscopic cholecystectomy in the early 1990s, numerous classification systems have been proposed. Many of the systems take disparate approaches to classification. Some attempt to exhaustively capture and describe each possible injury, while others have sought to increase their ease of use and therefore clinical utility by simplifying injury patterns. To date, surgeons and other practitioners involved with the management of this problem have not widely accepted one system as the gold standard. This chapter reviews many of the proposed classification systems and discusses the strengths and weaknesses associated with each.

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Historical Perspective

The first cholecystectomy was performed in 1882 by Carl Langenbuch, and by 1897 nearly 100 cases were reported in the literature [3]. The first report of associated biliary injury followed not long after, when the Mayo Clinic published a report of two cases of biliary stricture following cholecystectomy in 1905 [4]. By the 1990s, approximately 750,000 cholecystectomies were performed each year in the United States, making it the most common elective abdominal operation [5].

The performance of the first laparoscopic cholecystectomy in 1985 by Erich Muhe substantially altered the practice of cholecystectomy [6]. Despite initial skepticism, the technique was rapidly and widely adopted, initially with little formal education or certification. Currently, laparoscopic cholecystectomy is estimated to account for as many as 90 % of all cholecystectomies in the USA [7].

The implications of this change on the incidence of iatrogenic biliary injury were substantial. Biliary injury following laparoscopic cholecystectomy is approximately twice as common as injury following open cholecystectomy [8–10]. The rate of biliary injury following laparoscopic cholecystectomy was higher early in the laparoscopic experience, but appears to now have stabilized at approximately 0.4 % [8–10]. Although this absolute rate of injury is low, the frequency of the operation is such that this translates into nearly 3000 iatrogenic biliary injuries in the USA each year. Interestingly, the surgical experience with open and laparoscopic cholecystectomy has now shifted so dramatically toward the laparoscopic operation that concern has arisen that conversion to an open procedure may not indeed be a safer option under all circumstances. Booij et al. describe three major biliary injuries in patients converted to open during laparoscopic cholecystectomy and advocate consideration of percutaneous drainage rather than conversion to open in appropriate circumstances [11]. Decreased training experience with open cholecystectomy may contribute to this phenomenon.

Causes of Iatrogenic Biliary Injury

Risk factors for biliary injury during cholecystectomy fall into three categories: patient factors, operative considerations, and surgeon effects. Patient factors that increase the risk of biliary injury include male gender, increased age, and increased comorbidity. Operative considerations include the complexity of the operation, presence of hemorrhage, and aberrant anatomy. The most commonly indicted surgeon factors are inadequate equipment as well as limited surgical experience [5, 12, 13].

Although a variety of surgical techniques have been advocated in an effort to avoid biliary injury, in fact, only 3 % of injuries are attributable exclusively to technical error [14, 15]. Rather, the vast majority of injuries are failures of perception due to misidentification of the common bile duct, the common hepatic duct, or an aberrant duct (most commonly right sided). It has been estimated that clear and correct identification of the cystic duct and cystic artery prior to their division would avoid 70 % of biliary injuries [15].

Outcomes Following Iatrogenic Biliary Injuries

Certainly prevention is the ideal method of addressing the iatrogenic biliary injury problem. When injuries do occur, however, rapid recognition and appropriate treatment are tantamount to successful recovery. Iatrogenic bile duct injury has been associated with increased short-term mortality compared to cholecystectomy without injury (3.9 % vs. 1.1 % at 1 year) [16]. Additionally in a study of Medicare patients after laparoscopic cholecystectomy, Flum et al. found a significantly decreased survival in patients following bile duct injury that persisted up to 9 years [8]. The majority of the survival difference was observed in the first 2 years following injury, but after 9 years of follow-up 55 % of non-injured patients remained alive, compared to only 20 % of patients experiencing a bile duct injury.

Furthermore, there appears to be a detrimental effect on quality of life that persists for many years. Multiple studies have found that although patients recover from the pain of the injury, the psychological effects of a bile duct injury lead to a diminished quality of life even after 5 years of follow-up [2, 17–19]. In the study by de Reuver et al. a subset of patients had sequential evaluation of their quality of life at a mean of 5 and 11 years. In this group, no significant improvement was observed in the quality of life over that time [18]. Hogan et al. published one of the few studies suggesting an equivalent quality of life following iatrogenic biliary injury [20]. The median follow up in this study, however, was over 12 years, suggesting that the quality of life may eventually return to baseline, but may require over a decade to do so.

In order to facilitate a more uniform approach to the study and treatment of these complications, numerous classification systems have been proposed. The remainder of this chapter will describe the most commonly utilized classification methods and compare and contrast the relative strengths and weaknesses associated with each.

Bismuth Classification of Biliary Strictures

The Bismuth classification was devised in the pre-laparoscopic era (1982) originally as system to classify biliary strictures [21]. In this system, strictures are grouped based upon the level at which healthy biliary tissue is available for surgical repair [22]. Type I strictures occur in the common bile or hepatic duct at least 2 cm distal to the hilum. Type II strictures occur in the common hepatic duct within 2 cm of the hilum. Type III strictures extend to the hilum but the right and left ducts are intact. Type IV strictures involve the confluence of the right and left hepatic duct. Finally, Type V strictures include a Types I–III stricture as well as an isolated stricture of the right hepatic duct (Fig. 18.1). This classification system has been found to correlate with the outcome of patients following surgical repair [22]. Although initially intended for the classification of strictures, the system was analogously adopted for use in the classification of biliary injury and served as the basis for the widely used Strasberg classification (below).

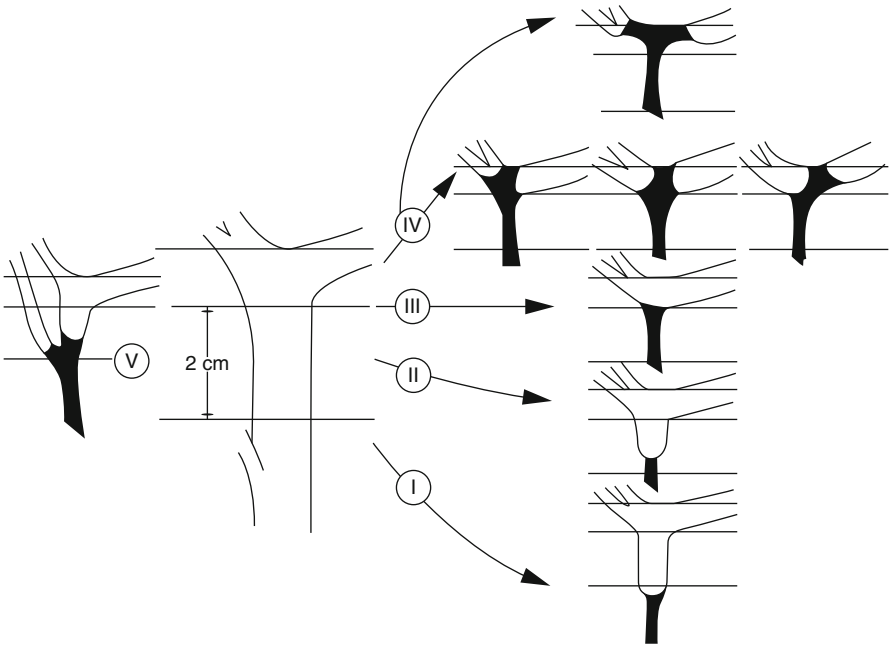

Fig. 18.1 Bismuth classification of biliary stricture. Classified into Types I–V based upon the repair techniques (reproduced from Bismuth H, Majno PE. Biliary strictures: classification based on the principles of surgical treatment. World J Surg 25:1241-4, 2001; with kind permission from Springer Science and Business Media)

Strasberg Classification

As the use of laparoscopic cholecystectomy became more ubiquitous, bile duct injuries (when compared to those following open cholecystectomy) were noted to be more complex, more proximal, and to include biliary leaks as well as strictures. Thus, in 1995 Strasberg et al. proposed one of the first systems to classify these new patterns observed following laparoscopic cholecystectomy [23]. Bismuth's work on strictures served as the template for this approach.

In the Strasberg system, Type A injuries include cystic duct leaks or leaks from small ducts in the liver bed. Type B injuries are occlusions of part of the biliary tree. This typically occurs in the setting of an aberrant right hepatic duct, which is present in approximately 2 % of the population [24, 25]. Type C injuries are a leak from a duct not in communication with the common bile duct, typically from transection without ligation of an aberrant right hepatic duct. Type D injuries are injuries to less than 50 % of the diameter of the lateral common or hepatic bile ducts. Type E injuries are circumferential injuries to the common hepatic duct and further divided into Types E1–E5 to parallel the Bismuth classification. E1 are injuries to the common hepatic duct with a proximal stump of greater than 2 cm from the hilum, and E2 injuries have a stump less than 2 cm. E3 are hilar injuries where the confluence is

preserved but no residual common hepatic duct remains. E4 injuries involve the confluence of hepatic ducts and disrupt the communication between the right and left ducts, and E5 injuries disrupt the hilum as well as an aberrant right hepatic duct (Fig. 18.2).

Like the Bismuth system, the Strasberg system is classified based upon grouping injuries with a similar approach necessary for their repair. Typically, Type A injuries can be managed endoscopically, Type B and C require drainage of the right liver, Type D can be repaired primarily, and Type E require more extensive reconstruction, typically with hepaticojejunostomy.

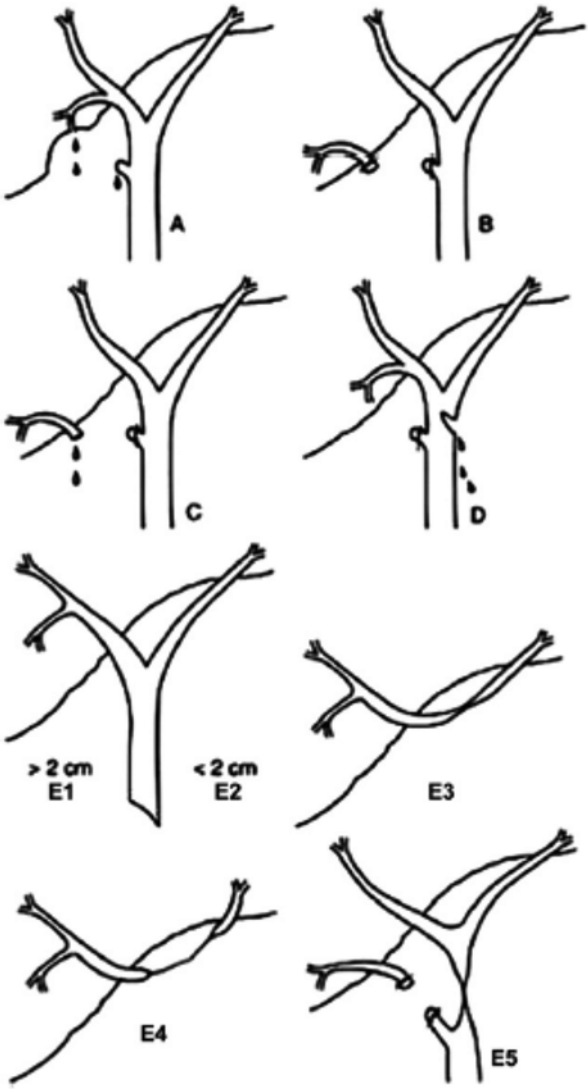

Fig. 18.2 Strasberg classification System. Injuries are classified as A–E, with E Type injuries subdivided into E1–E5 according to the Bismuth system (reproduced from Strasberg SM, Hertl M, Soper NJ. An analysis of the problem of biliary injury during laparoscopic cholecystectomy. J Am Coll Surg 180:101-25, 1995, with kind permission from Elsevier)

The true incidence of the various types of injuries is poorly described in the literature. In the development of their classification system, Strasberg et al. performed a literature search which identified 270 reported iatrogenic biliary injuries with enough information to classify. Of these there were 62 Type A (23 %), one Type B (0.4 %), eight Type C (3 %), 24 Type D (9 %), and 175 Type E (65 %). Ninety-seven of the Type E injuries could be subclassified and these were distributed evenly among Types E1–4, with only two Type E5 injuries identified [23]. These numbers are clearly influenced by the focus of the individually published series. Large series using national or state wide data typically have been unable to classify injuries and, as such, studies with an accurate denominator are uncommon. In general, most surgical series report on Type E injuries, as these most frequently require surgical intervention. Importantly though, the interventional radiology and endoscopic literature has a predominance of Type A injuries [26–28]. Recently, Pitt et al. published their series which included all patients treated by endoscopists, radiologists, or surgeons at a single institution [29]. In this study, 45 % of injuries were Type A injuries, Types B–D comprised less than 5 % of the series, and Type E injuries represented the remaining 50 %, with E1 (15 %) and E2 (19 %) being the most common Type E injuries.

Amsterdam Academic Medical Center Classification

Shortly after the publication of the Strasberg classification, Bergman et al. from the Netherlands published in 1996 their series of injuries with a proposed classification system that was not based upon the Bismuth system [30]. Their system, which was based upon their institutional series of 53 patients, divided injuries into four types. Minor bile duct leaks from the cystic duct or peripheral/aberrant hepatic radicles define type A injuries. Type B injuries are major bile duct injuries with or without associated stricture. Type C injuries are strictures without bile leakage, and type D injuries involve complete transection of the bile duct with or without associated excision of a portion of the biliary tree. Similar to the Strasberg system, this classification system is based upon treatment required for repair. Type A injuries are typically treated endoscopically. Type B and C injuries can initially be addressed endoscopically, but frequently require longer term stenting and potentially surgical reconstruction. Type D injuries require initial percutaneous drainage and hepaticojejunostomy for definitive repair.

Neuhaus Classification

In 2000, Neuhaus et al. described a classification system that built upon the Strasberg approach [31]. In this system, Neuhaus et al. sought to improve upon the Strasberg system by better capturing full range of observed injury patterns. The organization of the Strasberg system was largely maintained but certain injuries are further

segregated. Type A leaks are divided into A1 (cystic duct stump leaks) and A2 (liver bed leaks). Type B obstructions are divided into partial (B1) or complete (B2) obstructions. Type C injuries are defined as lateral injuries to the common bile duct, and are further divided into those <5 mm in diameter (C1) and those >5 mm (C2). Finally, transections of the common bile duct (and aberrant right hepatic ducts are included here) are subdivided into those without structural defect (D1) and those with (D2). The remainder of the system, including all Type E injuries, is unaltered from the Strasberg classification.

Stewart-Way Classification

Introduced in 2003, the Stewart-Way system classifies injuries based upon anatomic basis and the mechanism of the injury [15, 32]. At the time, this was a unique approach designed to focus on the prevention of these injuries rather than classification by mechanism of repair. In their study of 252 patients with iatrogenic biliary injury following laparoscopic cholecystectomy, Way et al. defined four classes of injury.

Class I injuries involve an incision into the common bile duct but no excision of duct tissue. These injuries comprise just 7 % of all injuries. Two injury mechanisms are described: either a common bile duct was mistakenly divided but recognized prior to complete transection, or a cystic duct incision at the time of cholangiography was inadvertently extended into the common bile duct. Class II injuries represent 22 % of all injuries and are defined as lateral damage to the common hepatic duct leading to stricture and/or bile leak. These injuries were most frequently due to poor exposure but were also associated with cautery or clipping injuries to the duct. Class III injuries are the most frequent (61 % of injuries) and involve excision of a variable length of the common duct that includes the cystic-common duct junction. Class III injuries could all be attributed to mistakenly identifying the common duct as the cystic duct. Class II and III injuries are further divided based upon the proximal extent of injury or resection. A healthy remnant of the common hepatic duct is present in II/IIIA injuries; the common hepatic duct is injured at the bifurcation in II/IIIB injuries; in II/IIIC injuries the bifurcation is involved; and in II/IIID the injury extends proximally beyond the bifurcation of at least one of the lobar ducts. Finally, isolated injuries to the right hepatic duct are considered Class IV injuries. These occur either from mistakenly interpreting the right hepatic duct as the cystic duct or from an unseen right hepatic duct that was injured during dissection (Table 18.1).

Although the Stewart-Way system does not specifically incorporate associated vascular injuries into the classification, they later described that each class is associated with a progressively increasing incidence of right hepatic artery injury. Overall, the right hepatic artery was injured in 32 % of cases. Of these, 6 % were associated with Class I injuries, 17 % with Class II, 35 % with Class III, and 64 % with Class IV [32].

Table 18.1 The Stewart-Way classification system [15]

Type	Injury	Mechanism	Incidence
I	Partial CBD injury	Mistaken incision into CBD or extension of ductotomy at time of cholangiogram	7 %
II	Lateral injury to CHD	Inadvertent cautery or clipping, associated with poor exposure	22 %
III	Excision of CBD/CHD	Mistaken identification of CBD as cystic duct	61 %
IV	Isolated injury to RHD	Mistaken identification of RHD or artery as cystic duct or artery; inadvertent cautery or clipping injury	10 %

Abbreviations: *CBD* common bile duct, *CHD* common hepatic duct, *RHD* right hepatic duct

The Hannover Classification

In 2007, Bektas et al. proposed the Hannover classification system as the most comprehensive system to-date [33]. The authors sought to distinctly classify all the possible injury patterns. This system expands primarily on the Neuhaus system to further define the level of injury as well as to incorporate concomitant vascular injury. Type A and B injuries are equivalent to the Neuhaus system. Type C injuries are tangential injuries to the common bile duct, further defined such that the width of the C1 injury is small (<5 mm) regardless of location, C2 injuries are large (>5 mm) but entirely below the bifurcation, C3 lesions are large and at the level of the bifurcation, and C4 lesions are large and above the level of the bifurcation. Similarly, Type D injuries are complete transections of the bile duct. D1 injuries are below the bifurcation and without a defect in the biliary anatomy. D2 injuries have a tissue defect but are below the bifurcation. D3 injuries are at the bifurcation, and D4 injuries are above the bifurcation (with or without defect). Strictures are classified as Type E lesions in the Hannover system in the same manner as the Neuhaus system.

In addition to the biliary injuries described, the Hannover classification also allows for classification of concomitant vascular injuries for Type C and D lesions. The anatomic distribution of vascular injuries are noted as follows: d, right hepatic artery; s, left hepatic artery; p, proper hepatic artery; com, common hepatic artery; c, cystic artery; pv, portal vein. For example, a complete transection of the bile duct below the bifurcation but without an anatomic defect that was also associated with a right hepatic artery injury would be classified as D1d.

Lau Classification

Also in 2007, Lau et al. published a novel classification system [34]. Rather than expanding on prior classification systems, the Lau system attempts to uniquely consolidate and group injuries into five types. Type 1 injuries are leaks from the liver

bed or from the cystic duct stump. Type 2 injuries are partial common bile duct or common hepatic duct injuries without (2A) or with (2B) tissue loss at the site of injury. A complete transection of the common bile duct or common hepatic duct is considered a Type 3 injury, without (3A) or with (3B) tissue loss. Type 4 injuries are those above the bifurcation to the right or left hepatic ducts or a sectoral duct, again without (4A) or with (4B) tissue loss. Type 5 injuries represent any ductal injury with an associated vascular injury. The authors propose that this classification system adds to prior systems in that each type is associated with both an injury pattern in ascending severity as well as a distinct mechanism of injury. As such, each injury type is associated with specific preventative measures as well as treatments once the injury has occurred.

Other Classification Systems

Numerous other systems have been described and are listed chronologically in Table 18.2. Most of these systems were developed to define the anatomy of the injury and therefore to potentially correlate with the approach to treatment. Alternatively, Sandha et al. focused specifically on the subset of patients undergoing endoscopic treatment of a leak; they used the radiographic appearance of the leak at the time of endoscopic retrograde cholangiography to classify injuries [28]. Injuries were defined as low grade if the leak could only be identified after intrahepatic opacification, or high grade if the leak was observed before intrahepatic opacification. They propose sphincterotomy alone may treat low grade leaks, whereas endoscopic stenting is necessary in high grade injuries. Because this system was designed for endoscopists, it does not capture any of the injury patterns that were not thought to be amenable to endoscopic treatment.

Table 18.2 Published classification systems for bile duct injury

Name	Year
Bismuth classification [21]	1982
Siewert classification [43]	1994
McMahon classification [44]	1995
Strasberg classification [23]	1995
Amsterdam classification [30]	1996
Neuhaus classification [31]	2000
Csendes classification [45]	2001
Stewart-Way classification [15]	2004
Sandha classification [28]	2004
Lau classification [34]	2007
Hannover classification [33]	2007
Kapoor classification [46]	2008
Li classification [47]	2010
Cannon classification [35]	2011
ATOM [42]	2013

Cannon et al. describe a more simplistic system to classify injuries based upon the financial burden of the injury [35]. They define three grades associated with increasing cost with higher grades of injury. Grade I injuries were those to accessory right hepatic ducts or the duct Luschka. Grade II injuries were all other isolated biliary injuries, and grade III injuries were vasculobiliary injuries. These grades were also found to correlate with mortality and need for operative intervention.

Comparison of Classification Systems

To date, none of the above classification systems has been universally adopted. All have associated strengths and weaknesses. As such, when comparing the systems, the goals for use of the system must be considered.

Inclusivity

Designed before the era of laparoscopic cholecystectomy, the Bismuth classification clearly is inadequate to capture the current extent and variety of injuries encountered. However, since the Strasberg system expanded on the Bismuth themes, the majority of biliary injuries have been classifiable. In their description of the Hannover system, Bektas et al. analyze their series of 74 patients utilizing a number of the different classification systems. [33] The Strasberg, Siewert, Neuhaus, and Hannover systems could correctly classify all 74 biliary injuries. The Stewart-Way system, however, could not capture 26 of the patients (35 %). In their study, Bektas et al. furthermore provide a succinct outline of specific biliary injuries and the ability of each system to describe them [33].

An additional substantial divide among the classification systems is the inclusion (or not) of concomitant vascular injuries. Of the classification systems described above, the Bismuth, Strasberg, and Neuhaus systems do not specifically account for vascular injury. The incidence of vascular injury is not insignificant, with series reporting a concomitant vascular injury in 7–35 % of biliary injuries [15, 33, 36, 37]. Stewart et al. were the first to describe the significance of this problem [32]. In their study, they found that patients with concomitant right hepatic artery injury had a significantly higher rate of morbidity associated with their biliary complication. However, the ultimate success of biliary repair and the mortality rate was unchanged from patients without vascular injury. Thus, accounting for vascular injury is important in the counselling and management of the patient immediately following injury, but may be less of a consideration when repair is not performed immediately. To date, the studies of patients with vascular injury have been limited to relatively small sample sizes due to the rarity of the injury, and this may influence the findings regarding the impact of these injuries.

Although Stewart et al. were the first to define the significance of vascular injury, the Stewart-Way system does not actually specify the particular vessel injured in the

classification system. The injury types are associated with increasing rates of right hepatic artery injury, but injury to other vessels is not described. The Hannover system is the lone system to individually classify all the potentially injured vessels along with biliary injury. Vascular injuries are also included in the Lau system, but are included as a group (Type 5), without differentiation by the individual vessels involved.

Ease of Use

The ability to precisely classify each injury must be weighed against the complexity, and therefore utility, of a given system. In their series of patients with biliary injury, Bektas et al. found that the Stewart-Way and Lau classifications described four injury patterns, the Strasberg system described eight, the Neuhaus classification described nine, and the Hannover classification contained 21 different injuries. Interestingly, despite this wide variation in complexity, all of the systems significantly correlated with the surgical treatment received by the patients in the study [33]. Thus, if the intent in classification is simply to determine the appropriate treatment algorithm, then the highly complex classification systems may prove unduly cumbersome without any added benefit.

Prognosis

Another potentially important reason to classify the injury patterns is to define a prognosis associated with each injury. Standardization of injuries is required for accurate and reproducible research to determine the severity of each injury. Consistent classification further allows for accurate counselling of patients following injury, as well as anticipation of both short and long term complications.

As mentioned above, both short and long-term survival appears to be significantly reduced following a common bile duct injury at the time of laparoscopic cholecystectomy [8, 16]. These studies, however, have required a massive numbers of patients to establish that fact, and therefore have been limited to administrative databases. There are no studies with data granular enough to classify the injuries and numbers large enough to segregate long-term survival by injury pattern. Similarly, the studies on quality of life following bile duct injury have not been able to differentiate by type of injury.

Bektas et al. did compare the systems on a number of surrogate markers of successful recovery [33]. The injury classifications by Siewart, Stewart-Way, and Hannover were all significantly associated with the need for liver resection. Injury types in classification systems that did not account for vascular injury (the Strasberg and Neuhaus systems) did not correlate with the need for liver resection. Additional studies, however, have found that specific Strasberg classified injuries (most fre-

quently E4–5) do predict the need for liver resection [38, 39]. In the Bektas study, only the Neuhaus system correlated with the long term risk of cholangitis.

Interestingly, Cannon et al. found that the Hannover system could predict patients at risk for restenosis after surgical management. They found that patients with vasculobiliary injuries to the proper hepatic artery had a 100 % rate of restenosis compared to 5.9 % in patients with other vasculobiliary injuries [35]. Findings such as this demonstrate the utility of a more comprehensive classification system, as other systems would not be able to differentiate the clinical importance of injury to the proper hepatic artery specifically. Should the findings by Cannon et al. be confirmed, a future classification system might then be able to group vascular injuries into those to the proper hepatic artery and all others, thereby simplifying the system without losing the clinical utility of the more comprehensive systems.

Treatment

One of the major challenges in applying the current classification systems is the heterogeneity of injury included. Most systems attempt to classify the full spectrum of injury and as such include complications ranging from low output cystic duct stump leaks to major resections and stenoses of the biliary tree. The grouping of the more minor injuries with the major ones may actually serve to complicate the classification system. Endoscopic treatment with sphincterotomy and stenting has proven to be highly successful in the treatment of cystic duct and accessory duct stump leaks [40, 41]. As such, any analysis that includes these complications with the other major biliary injuries may report results that are not reflective of the outcomes after major injury.

A number of the systems, beginning with the Strasberg system, classify injuries into groups that require similar treatment strategies. This is a clinically useful way to group injuries that can help to avoid the comparison of injuries with widely disparate severity. Any analysis of outcomes following bile duct injury should clearly incorporate one of these systems to classify the injury and stratify their analyses accordingly. Sandha et al. addressed this by developing a classification system specifically to correlate with treatment of a small subset of biliary injuries—those that could be treated endoscopically [28]. This may be a practical approach that is clinically applicable and focused, rather than attempting to classify all injuries in a single system.

The ATOM Classification

In response to the myriad of classification systems presented in the literature, the European Association for Endoscopic Surgery held a consensus conference on iatrogenic bile duct injury in 2011. The goal of the meeting was to devise a comprehensive system to be used as the universally accepted classification. Their system

was based upon a literature search whereby every injury patterns described in all previous classification systems were combined. The result was organized into three categories: *a*natomic, *t*ime *o*f injury, and *m*echanism (ATOM) [42].

The anatomic category is divided into main bile duct and non-main bile duct injuries. Main bile duct injuries are further divided by location. Type 1 injuries are ≥2 cm distal to the inferior border of the hepatic confluence; Type 2 are <2 cm; type 3 involve the hepatic confluence but the communication between the left and right ducts is preserved; Type 4 interrupt the right and left communication at the hepatic confluence; Type 5 are injuries to the right or left hepatic ducts but without confluence involvement; and Type 6 are isolated segmental hepatic duct injuries. The injuries are further classified based upon whether the duct was initially occluded or divided and whether this was partial (with the percent of circumference indicated) or complete. If loss of the substance of the bile duct also occurred, this is included with the length of the tissue defect. Additionally, vascular injuries are indicated with the specific artery involved denoted when known. Time of injury identification is split into three categories, early intraoperative, early postoperative (within 1 week), and late. Finally, the mechanism of injury is classified as mechanical or energy driven (e.g., cautery). Table 18.3 displays all the classification systems with inclusion criteria compared.

Although perhaps the most complex of any system to date, the ATOM classification has the benefit of capturing all injuries such that they can be translated from other systems. Therefore, a series of patients that previously had been aggregated and classified according to the Strasberg system could be directly transposed into the ATOM classification, and the additional data could be added if available. This allows for the potential aggregation of multiple large series and may add significant power to future analyses utilizing this system. As noted earlier, once the significance of specific injuries has been established, a simpler system that aggregates injuries of similar importance may be proposed.

Conclusions

Iatrogenic injury to the common bile duct following laparoscopic cholecystectomy is a rare but devastating complication of one of the most common surgical procedures. Since the mid-1990s, many groups have taken an interest in the treatment and classification of these injuries. As a result, the past 20 years have seen 15 different classification systems proposed. These systems range from the very simple to the highly complex. Yet despite this interest in classification, very little data exists on the predictive ability of these classifications with regard to management or prognosis. While certainly the possible types of injuries are vast, the difference in prognostic significance among similar injuries remains to be defined. Further research is needed to determine how best to cluster these injuries into prognostic groups, and such research may help to ultimately determine which classification system is adopted as the universal system going forward. More consistent adoption of a single "gold-standard" classification will greatly promote future comparative research.

Table 18.3 Summary of iatrogenic bile duct injury classification systems

	Anatomical characteristic								Time of detection			Mechanism of injury
			Type and extent of injury of bile ducts									
			Oc		D (leak)		LS					
Study	MBD/NMBD	Level of injury	c	p	c	p		VBI	Ei	Ep	L	Me/ED
Bismuth [21]	+	+	d	d	d	d	–	–	–	–	+	I
Strasberg et al. [23]	+	+	a	d	+	+	a	a	a	a	+	±I, k
McMahon et al. [44]	+	a	a	–	+	+	a	–	a	a	+	A
AMA [30]	+	a	e	e	d	d	a	–	a	a	+	–
Neuhaus et al. [31]	+	+	+	+	d	+	f, g	a	±	–	+	J
Csendes et al. [45]	–	b	–	–	d	d	+	+h	–	–	+	K
Stewart et al. [32]	–	b	d	d	+	+	+	+h	–	–	k	+
Hannover [33]	+	+	+	+	+	+	g	+	a	a	+	±j
Lau and Lai [34]	+	+	d	d	+	+	+	+h	+	+	–	–
Siewert et al. [43]	+	±a, b	d	d	+	+	g	a	–	+	+	–
Cannon et al. [35]	+	c	–	–	–	–	–	+h	–	–	–	–
Kapoor [46]	+	b	+	+	+	+	+	+h	j		–	–
Sandha et al. [28]	a	b	–	–	–	–	–	–	–	–	–	–
EAES [42]	+	+	+	+	+	+	+	+	+	+	+	+

(Reproduced from Fingerhut A, Dziri C, Garden OJ, et al. ATOM, the all-inclusive, nominal EAES classification of bile duct injuries during cholecystectomy. *Surgical endoscopy.* Dec 2013;27(12):4608-4619, with permission from Springer Science and Business Media)

a discussed but no clear explanation of how to include it in the classification; b no clear discriminator of level of injury; c Hanover classification for level of injury, but only for one category (III) of lesions (but also refers to Bismuth); d no distinction between partial (P) and complete (C) or this distinction is not indicted for all types or localizations; e no distinction between division left open (leak) and occlusion; f distinguishes between longitudinal partial lesions less than or more than 5 mm; g not clear what is meant by "defect" or "structural defect" (loss of substance?); h no indication of which vessel; i energy driven injury recognized but not indicated in the classification; j injury by clip recognized but no differentiation between mechanical and energy-driven injury; k recognizes mechanical and electric injury but no distinction between the 2 in the classification; l distinguishes between division left open (bile leak) and occlusion. EAES European Association for Endoscopic Surgery, + yes, – not included or discussed

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Chapter 19
Commentary: The Classification and Injury Patterns of Iatrogenic Bile Duct Injury During Laparoscopic Cholecystectomy

Dirk J. Gouma

A bile duct injury (BDI) is one of the most dramatic complications during cholecystectomy. The incidence increased twofold after the introduction of the laparoscopic procedure (0.2–0.6 %) compared with open cholecystectomy (0.1–0.2 %). It has been shown that the incidence might be higher (0.7 %) for the single port laparoscopic procedure. The socioeconomic impact of BDI has been shown in many studies. There is also a relation with increased rates of malpractice litigation. BDI during cholecystectomy remains an area of extensive discussion in the literature including different opinions on incidence, prevention, and classification. There is a wide variety treatment options with ongoing controversy. The (long term) outcome of treatment of BDI is reported with different endpoints ranging from complications or mortality after surgery to normal liver function tests during follow up or no strictures/reoperations, and quality of life. The diversity in outcome in studies on patients suffering from a BDI is partly due to the fact that there is a wide variety on the definition of BDI. Another factor is the selection of patients with BDI in a study; for example: a cohort study at a primary institute or a selected group of patients from a referral center or a survey about BDI. Subsequently different classification systems have been used. Classification should be the first principal step in the management of patients suffering from a BDI. The wide variety in classification systems is one of the most important problems for comparison of studies on BDI. In the Chapter on the Classification and Injury patterns of BDI by E. K. Bartlett and Ch. M. Vollmer the 14 existing classification systems and differences between these systems have extensively been described. This is an elegant overview of different components in patients with a BDI which can be included in a classification system, as well as highlighting some of the shortcomings within these systems.

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First of all there is no uniformity about the terminology used for "intraoperative damage of the biliary system during cholecystectomy". This is currently ranging from: a bile duct injury which might be interpreted as an injury of the "major" (common extra hepatic) bile duct; or a biliary injury which might be interpreted as any injury of the biliary system; or bile leakage after cholecystectomy to be interpreted as a leakage from the ductal system probably without an injury of the duct. More recently a new description was added the so-called vasculobiliary injury the combination of a bile duct injury with a vascular injury. The vascular injury here is also not well defined; it is still within the range from an injury of the marginal 6 and 12 o'clock artery, the (right) hepatic artery or the (right) portal vein.

Considering the enormous lack of uniformity between the different classification systems the first most important question should be: What is the aim of the classification system? How do you want to use it in daily practice. It might be used as an aid to identify the mechanism of the injury or by some others as a guide for a treatment and/or referral pattern. It could also be used to identify the severity of the bile duct lesion, the proximal extent of the bile duct lesion, or even more extensively the overall injury pattern. The description of injury pattern might range from transection to tangential duct lesions with or without information of lesions of the vascular system. Other classifications describe all aspects of injury of the entire anatomy within the ligament. The classifications have frequently been used to compare the outcome of different studies but therefore we might need more details of patient characteristics (for adequate case-mix control).

Looking at the well-established classification systems described in the chapter one could indeed distinguish classification systems according to the mechanism (Stewart-Way), the anatomy of the bile duct (Bismuth); the level of the duct, or the biliary system = including leakage of cystic duct (Strasberg/Neuhaus); and more advanced anatomic classification systems including the vasculobiliary system (Hannover). Some systems prefer to restrict the classification mainly to facilitate selection of referral or treatment (Mc Mahon, Amsterdam, Sandha). On the opposite there was recently an initiative to include more clinical aspects such as the time of detection; early versus delayed postoperative, frequently associated with ongoing biliary sepsis or obstructive jaundice or even secondary biliary cirrhosis. These aspects should be included, being of importance for better guidance of therapy and comparison of outcome. The latest developed ATOM classification is combining all previous classification items including these clinical aspects [1].

Remarkably I was personally involved in the development of two different classification systems, the restricted Amsterdam classification [2] and the recent published extended ATOM classification [1]. There might be a certain confusion why to be involved in both or probably a change using another classification. It is due to the increasing understanding of the difficulty using the current classification systems and realizing shortcomings not only in the Amsterdam but also other classifications. It might be helpful to discuss these problems from daily practice using a few studies we performed recently in an attempt to analyze different aspects of outcome in our patient cohort. In the period 1992 up to 2012 a consecutive series of 800 patients (721 patents after laparoscopic cholecystectomy and 79 after open cholecystectomy)

was referred to the Academic Medical Center, Amsterdam, for treatment of a BDI. Centralization of a large cohort of patients with BDI in the Netherlands, a relative small country with a well-defined referral pattern, enabled us to analyze different aspects of diagnostic work-up, management and outcome for all different types of BDI. Results of such a group of patients with BDI "at large" including all types of injury and different endoscopic, radiological and surgical treatment facilities treated are scarcely available.

Registration was according to the Amsterdam classification system adapted officially in the past in this country. During the development of this classification system in 1996 we intended to prepare a simplified classification as a guide for the general surgeon who could link the type of injury directly to the diagnostic work-up and treatment of the BDI. This was in order to facilitate the surgeons to refer patients with a BDI directly to different specialists (gastroenterologist, radiologists, surgeons) in those days working in separate referral units. Therefore only basic aspects of potential treatment in the future were included ranging from short term drainage of the duct (type A: cystic duct leakage), to (endoscopic) stenting (type B: bile duct leakage,), long-term endoscopic/percutaneous stenting and dilatation (type C: bile duct stricture,) and surgery (type D: bile duct transection). Considering the cohort of 800 patients subdivided within the Amsterdam classification and the final treatment as summarized in Table 19.1, it might be clear that this concept was not working adequately. In particular patients classified with a type B, C, and D injury group underwent total different endoscopic, radiological or rendezvous procedures and surgical interventions. Furthermore it is established nowadays in the Netherlands that these patients should preferably be referred to a multidisciplinary team discussing the therapeutic approach together and independent of the specialism. This problem will be the same using other classifications since the overlap of therapeutic possibilities increased during the past years. Even for patients with total transection (type D) a nonsurgical approach by the Rendezvous technique can be employed in selected cases.

Table 19.1 Patients ($n=800$) referred to AMC, Amsterdam, for treatment of a bile duct injury: Type of injury according to Amsterdam Classification and the different treatments after referral

Period 1992–2012	$n=800$	%
Type of injury:		
A, cystic duct leakage	216	27
B, common bile duct leakage	139	17.4
C, common bile duct stricture	90	11.2
D, bile duct transection/segm	355	44.4
Treatment after referral:		
ERCP and stent	396	49.5
Radiology PTD	96	12
Rendezvous	25	3.1
Hepaticojejunostomy	265	33
Liver resection	11	1.4
Others	9	1.1

Secondly the Amsterdam classification also included a certain connotation of severity of the injury: a minor injury (type A) and major injury (type B–D) as also implied in the Mc Mahon classification. This might also suggest already a potential difference in outcome. Others even adapted the words as "significant" injury versus "insignificant" injury. Analyzing again the AMC study cohort, the in hospital mortality and long term BDI related mortality after treatment for type A injury was resp. 3/216 (2.8 %) and 9/216 (4.2 %) versus after the type D injury treated by hepaticojejunostomy resp. 2/265 (0.8 %) and 6/265 (2 %) [3]. So the initial hospital mortality of the minor (insignificant) type A lesions after endoscopic drainage was relative high compared with the major (significant) type D lesion after surgery. The higher in-hospital mortality for a relative simple injury and endoscopic treatment (a normal biliary ductal system) was not due to failure of the endoscopic procedure but the patient selection/condition at referral. This could not to be recognized in the classification we used. Patients with type A lesions had a delayed referral pattern (median period of 10 days) most suffering from biliary peritonitis, sepsis and 25 % of these patients also underwent a re-laparotomy before referral. A high ASA classification (III–IV) was another independent risk factor for mortality. All patients died due to ongoing biliary sepsis in combination with high ASA score. So there is an enormous bias in selection. This is another shortcoming of the classification to facilitate comparison of outcome. In order to compare these results with other studies we need more clinical information at the time of referral/detection of the injury. This is not found in any of the classifications except for ATOM.

The clinical information as for example provided by the ATOM classification is also of crucial importance for the ongoing discussion about early versus delayed surgical treatment of type D injury. In our series of 265 patients with a hepaticojejunostomy (HJ) we found the clinical pattern at referral, mostly delayed presentation with ongoing biliary peritonitis and sepsis, by far the most important factor for the choice of early versus delayed surgery strategy. These factors of the patient population should be included in outcome studies addressing this ongoing topic about timing of intervention.

We also recently evaluated patients (11/800, 1.4 %) who underwent a liver resection after BDI [4]. These patients had an Amsterdam classification type C: $n=1$ and type D: $n=10$ and the Strasberg classification was type C: $n=2$, type D: $n=2$, and type E: $n=7$. For adequate description of these injuries/patients however we also needed addition information about the vascular injury including: right hepatic art: $n=3$ and proper hepatic artery: $n=1$ and portal vein: $n=2$ and portal vein and right hepatic artery: $n=1$. Fortunately this is already included in the Hannover classification which might be helpful to provide more details about the injury status. In the study we also included information about the timing of resection (acute resection: $n=2$ delayed: $n=9$). Recurrent biliary sepsis and atrophy during the disease progression was crucial to understand the mechanism and planning the extent of resection and reconstruction. In a recent review of hepatic resection for post-cholecystectomy BDI it was shown that an isolated Strasberg E4–5 injury with concomitant hepatic artery injury was an independent predictor for liver resection and outcome [5]. So additional information on vascular injury during classification might be helpful.

Reporting the problems of the "extreme" vasculobiliary injuries together with Steven Strasberg [6] and discussing the association with fundus-down cholecystectomy in severely inflamed gallbladders we also realized that more details about the clinical setting are needed to clarify the mechanism and potential outcome. An improved detailed classification could also be helpful here. Realizing that the incidence of vascular injury is not insignificant, reported up to 7–35 % of the biliary injuries as mentioned in the chapter by Bartlett and Vollmer, more detailed information on vascular injury in a classification might be the minimum for the future.

In summary: The extensive number of classifications of BDI available nowadays might be a prediction that the ultimate classification was not yet identified. So far the Strasberg classification has been used most frequently and was a major step forward to compare adequately the outcome of BDI in the literature. However realizing the shortcomings of all classifications as mentioned above the new ATOM classification system might fill the gap but it is a slightly complicated, time-consuming system. The ability of an extensive complex time consuming classification system such as ATOM should be weighed against advantages in reporting and comparing management and outcome studies on bile duct injury in the future.

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Chapter 20
Bile Duct Injuries and the Law

Steven E. Raper

Bile duct injury during laparoscopic cholecystectomy has led to numerous malpractice claims; many more than in the era of open cholecystectomy [1]. For the patient and family, bile duct damage sustained during surgery is a potentially devastating injury with lifelong consequences. Surgeons must be aware of the legal issues surrounding cholecystectomy. The possibility of bile duct injury should be a part of the informed consent process. The operating surgeon may be obligated to disclose the facts of such injuries. Lastly, the surgeon may be legally liable to the patient and family for damages caused by bile duct injury.

The Necessity of Informed Consent

For a definition of informed consent, the US Supreme Court held the following:

> We are content to accept, as the meaning, the giving of information to the patient as to just what would be done and as to its consequences [2]

Surgeons have a duty to discuss with patients the risks of the planned operation so that the patient can give informed consent. Individual autonomy when making a decision on health-care treatment has been a priority of the law. Requirements for consent have been codified in statutes of most states and litigated in the common

The information contained in this chapter is not legal advice. Due to the complexity and variability of federal, state, and local statutes and regulations, as well as case law, consult attorneys licensed in your jurisdiction for specific questions or in response to complaints.

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law. National accrediting bodies and most if not all professional societies also require written, signed informed consent of the patient prior to performance of a variety of medical procedures, but particularly surgery (Table 20.1).

Informed consent should be thought of as an event and a process [3]. Informed consent is documentation that permission is obtained usually by a patient's signature on a consent form (the event). However informed consent is also a process by which, through a variety of means, information is imparted to patients which allows them to give an informed consent (the process). Both are necessary from a legal standpoint. In addition to being a legal requirement, informed consent should also be considered a good opportunity for strengthening the physician-patient relationship through communication. Where studied, poor communication between physicians and patients is a common source of malpractice claims [4]. Poor communication skills increase the likelihood of lawsuits after medical injury whether or not due to error [5].

Table 20.1 Elements of informed consent

The Joint Commission [10]
1. The nature of the proposed care, treatment, services, medications, interventions, or procedures
2. Potential benefits, risks, or side effects, including potential problems related to recuperation
3. The likelihood of achieving care, treatment and service goals
4. Reasonable alternatives to the proposed care, treatment, and service goals
5. The relevant risks, benefits, and side effects related to alternatives, including the possible results of not receiving care, treatment, and services
6. When indicated, any limitations on the confidentiality of information learned from or about the patient
American College of Surgeons [44]
1. The nature of the illness and the natural consequences of no treatment.
2. The nature of the proposed operation, including the estimated risks of mortality and morbidity.
3. The more common known complications, which should be described and discussed. The patient should understand the risks as well as the benefits of the proposed operation. The discussion should include a description of what to expect during the hospitalization and post hospital convalescence.
4. Alternative forms of treatment, including non-operative techniques.
American Medical Association [45]
1. The patient's diagnosis, if known.
2. The nature and purpose of a proposed treatment or procedure.
3. The risks and benefits of a proposed treatment or procedure.
4. Alternatives (regardless of their cost or the extent to which the treatment options are covered by health insurance).
5. The risks and benefits of the alternative treatment or procedure.
6. The risks and benefits of not receiving or undergoing a treatment or procedure.

When informed consent has not been given the physician may be open to the tort of battery or unauthorized, unwanted touching. In battery, proof of damages is not necessary, but recovery is limited. The majority of cases involving informed consent issues have also alleged negligence which will be discussed in detail below. One analysis of negligence claims against doctors showed that disputes over informed consent involved allegations that particular complications were not fully discussed [6]. A full consent discussion lets the patient appreciate the fact that their physician has thought carefully through the proposed procedure, will take the necessary steps for the patient's safety and can also enhance the patient's sense of well-being. Patients who receive thorough informed consent understand the reasons for treatment more completely, are alerted to potential complications, and can notify health-care providers when more can be done to mitigate injury [7].

With respect to laparoscopic cholecystectomy, the need to fully disclose the procedure, alternatives, anticipated benefits and possible risks is especially important. Standardized, printed consent forms have been advocated [8]. In addition to the laparoscopic cholecystectomy and possible conversion to an open cholecystectomy, tube cholecystostomy and intraoperative cholangiogram should be added when appropriate. The inclusion of such material imparts to the patient the possible need for these adjuncts and further, should the case proceed to litigation, that such maneuvers were considered. The possibility of bile duct injury in its several forms should be explicit. Given the deficiencies in recall, it is helpful to the patient to receive a copy of the consent form after signing has occurred.

Disclosure of Bile Duct Injuries

How, when, and what to disclose about medical injuries—such as bile duct damage—has become complicated and requires conscientious deliberation. Essentially all ethicists and policy makers encourage disclosure of medical injury whether or not due to error [9]. The Joint Commission requires physicians to inform patients about unanticipated outcomes related to certain *sentinel* events [10]. Although not binding, a number of organizations also advocate disclosure. The National Quality Forum has identified timely, transparent, clear communication of serious unanticipated outcomes as a safe practice [11]. The Institute of Medicine has also framed disclosure as a patient safety concern [12]. Malpractice insurers have begun to appreciate that proper disclosure of medical injuries may also reduce claims.

Disclosure may also be a legal requirement; some states require disclosure of medical injuries to patients and families. As one example, the Pennsylvania legislature enacted the Medical Care Availability and Reduction of Error (MCARE) Act that requires health-care providers to send written reports of *serious events* (death or unanticipated injury requiring incremental health-care services) to the patient or family [13]. Finally, just as proper processes of informed consent may improve communication between patient and surgeon, proper disclosure may also have a positive impact in terms of trust, satisfaction, and whether to switch physicians [14, 15].

But policy mandates do not provide guidance to surgeons on how or when to disclose injuries such as those of the bile duct. Such disclosures must be carefully considered; apologies, or statements like "I made a mistake," are not a good idea. There is empirical support in some circles for apology as a possible way to decrease the number and size of settlements in malpractice cases [16, 17]. The law is not so forgiving; an apology is a statement of remorse, regret, and responsibility, and essentially proves a case for medical negligence [18]. Physicians who must disclose bad outcomes—such as bile duct injuries—need to know how to conduct themselves, and generally would be advised to contact risk management and seek legal advice. Statements constituting admission of liability also open the healthcare organization to possible vicarious liability and may void malpractice insurance contracts.

Reduction of medical liability claims and costs by implementation of a carefully constructed disclosure program has growing support. Several institutions have reported a reduction of claims and costs with implementation of robust communication and resolution programs (CRP). However, early adoption successes required strong health-care system champions, clinician communication to break down resistance to cultural change, and persistent patience during implementation [19]. Further, CRPs require that liability insurers must agree, leadership must advocate that disclosure will occur for all adverse events, disclosure protocols must be easy to understand, and opportunities should be provided for physicians to practice what to say to patients.

Significant infrastructure investments are also required, a system for rapid adverse event reporting, causation analysis teams, and coordinators for the disclosure. Lastly, consideration of what other members of a team might disclose should be managed. A recent study showed that 25 % of residents who disclosed a medical error made an admission of negligence and were told in debrief that general expressions of empathy or support are about as far as they should go [20]. In short, surgeons are at the "sharp" end of injuries such as might happen to patients' bile ducts but are necessarily only one of many individuals involved in managing proper disclosure.

Bile Duct Injury and Malpractice Claims

Introduction

Medical malpractice is a specialized form of the tort (injury) of negligence. "[I]njury alone is insufficient to prove negligence in medical malpractice cases" [21]. Surgeons cannot guarantee the outcome of a patient's condition, and, medical injuries occur without fault. But surgeons have a duty to their patients to apply knowledge, skill, and care possessed and used by their peers under like circumstances and conditions. If patients are injured and the surgeon fails to meet (breaches) a professional standard of surgical care, the surgeon may be liable to the patient in a court

of law. There are four elements required to prove a case of negligence: a duty of the defendant to the plaintiff; a breach of that duty; a finding that the breach of duty was an actual and proximate cause of the injury; and that the plaintiff suffered damages that can be monetary or non-monetary. In a medical malpractice action, the second element—breach—is defined as a deviation or departure from an accepted standard of care.

As applied to the special case of bile duct injury, the element of duty is generally clear; a surgeon who operates on a patient has a duty to meet the professional standard of care. Similarly, the question of causation—did the bile duct injury cause the damages for which the patient has sued—is generally not at issue. The two main points that are litigated are whether the standard of care was breached, and the magnitude of the damages for which the surgeon is liable.

Medical Malpractice: The Scope of the Problem

Physicians have compared medical malpractice lawsuits to Ahab's nemesis; "… evil, ubiquitous, and seemingly immortal" [22]. But from a patient's perspective, when a medical injury occurs, someone should be held accountable and the injured patient may seek legal counsel. Although not directly relevant to bile duct injuries, a short review of the literature of medical malpractice claims is instructive. Negligent medical injury has been considered morally wrong, but if such negligence does not result in a claim and compensation the malpractice system has failed [23]. In one study of malpractice claims, 97 % of patients felt to be victims of negligence did not file claims and conversely a high rate of claims were filed for non-negligent injuries [24].

Two basic strategies have been used to analyze malpractice claims; patient chart reviews and closed claims reviews. The California Medical Association reviewed over 20,000 medical charts and showed that 17 % of patients sustaining medical injury would be eligible for compensation [25]. The Harvard Medical Practice Study (HMPS) of over 30,000 charts noted 28 % of injuries were due to negligence [26]. A similar study in Utah and Colorado validated the HMPS; the rates of negligent contributing injuries were 38 % and 28 % respectively [27]. A sample taken from some 31,000 medical charts and statewide data on medical malpractice claims found a ratio of negligence to malpractice claims of about 8 to 1 [28]. The negligent adverse event to claims ratio was 5.1:1 and 6.7:1 in Utah and Colorado, respectively [24]. The data are clear; most individuals who suffer negligent medical injury do not sue.

Closed claims analyses have several advantages compared to chart reviews; physician fears of disclosure and subsequent litigation are past, most of the claims involve serious injuries, and more detailed information about the injury exists. Smaller in scope, surgery closed claims data are similarly useful. A follow-up to the Utah and Colorado study showed that 66 % of all injuries were surgical [29].

Two research groups have analyzed surgery closed claims data from different vantage points; Harvard-affiliated Departments of Surgery, and the American College of Surgeons' (ACS) Committee on Patient Safety and Professional Liability [30, 31]. The Harvard group looked at contributions of human and systems factors to errors in surgical care [32]. The ACS group asked whether injuries by individual surgeons were preventable [33].

The Harvard group reviewed 444 closed surgery claims, 422 involved injuries, 61 % were attributed to error, and 39 % were error-free [30]. Errors were found to occur most often in commonly performed operations by experienced surgeons where system failures or patient complexity were also present [34]. The ACS study collected data from five malpractice insurance companies; a total of 460 closed surgical claims; injuries thought to have met standard of care (no negligence) were present in 36 % of cases, care that fell below the standard were present in 50 % of claims [31]. Thus, the incidence of closed claims in which no breach of the standard of care was identified was remarkably similar between the Harvard and ACS studies (39 % and 36 %, respectively). A separate study of over 1400 closed claims showed that 40 % of claims were for non-negligent or no medical injury and accounted for 10 % of total liability costs in the system [35]. In summary, the available data suggest that meeting the standard of care will not prevent a claim from being filed. In the studies cited, serious injuries were present in the vast majority of cases and bad outcomes—not negligence—are more likely to predict lawsuits.

The data for bile duct injury-related claims are not as robust as for surgical malpractice claims in general, but are nonetheless useful. Since laparoscopic cholecystectomy was widely adopted in the late 1980s, litigation claims resulting from injuries to the bile ducts surpassed by 20 times that of similar litigation for open cholecystectomy. A 20-state survey from national jury verdict reporting services identified 44 cases of laparoscopic cholecystectomy injury, 21 settled out of court for a mean payment of $469,711 [36]. Twenty-three cases went to trial, with 19 verdicts for the defendant, and 4 for plaintiffs with a mean payment of $188,772 [36]. Biliary injury is reputed to be the most common cause for litigation in gastrointestinal surgery; bile duct injury represents 20 % of all general surgery claims, 50 % of laparoscopic claims and about 15 % of total general surgery indemnity (the dollars paid by insurers) is for biliary injuries [37].

One study of 46 closed bile duct injury claims documented that 72 % of injuries occurred in elective cases without acute inflammation. Eleven of 16 cholangiograms, when done, were misinterpreted. With 86 % of cases resolved at the time the study was published, the plaintiff won 21 settlements and 5 jury verdicts with mean awards of $221,000 and $214,000, respectively [38]. In a second study, 324 claims were collected by the Physician Insurers Association of America (PIAA) encompassing more than 50 malpractice insurance companies providing coverage for 60 % of physicians, 67 % of the claims filed after laparoscopic cholecystectomy involved an injury to the biliary tree and 83 % of the injuries were not recognized during the operation. Further, 50 % of the claims were settled for the plaintiff with an average of $236,384 [1]. A literature review of 122 laparoscopic cholecystec-

tomy claims involved injuries to the bile ducts in 78 % that were missed 86 % of the time. Fifteen percent of cases were converted to open but in just over half, conversion was required to repair an injury [1].

Breach of the Professional Standard

In malpractice cases involving bile duct injuries, the question of whether or not the standard of care was breached is usually determinative. Plaintiff's attorneys will argue that common bile duct injury is entirely preventable if proper surgical technique is used. Said another way, the question often put before the court is: if the operation had been performed competently would the patient's injury have occurred? The standard of care for surgeons in in most states is said to be objective, centering on professional care, skill, and knowledge usually exercised and possessed. In determining whether the standard of care was breached, what the surgeon actually did or did not do is the relevant issue; not what the surgeon may have been thinking (the subjective standard).

Ultimately, whether the standard of care was breached is a matter for the finder of fact—usually a jury but sometimes a judge—in a civil trial. The fact finder usually hears testimony from expert witnesses employed by the plaintiff or the defendant. Specifically, bile duct injury malpractice cases usually require testimony from expert witnesses to establish whether the standard of care for cholecystectomy was breached. Courts generally have decided that medical malpractice facts are too technical for juries to understand without help.

The rules regarding who may qualify as an expert witness are complex. Presiding judges allow experts to testify depending on qualifications offered by the attorney. Qualifications of expertise might include the necessary experience and training, academic as well as practical experience, and board certification. In some states, an expert witness' opinion is required to initiate a lawsuit; in others, a peer specialist may be required for specialized medical disciplines; expert's opinion might be needed to initiate a lawsuit; lastly, there may be rules designed to prevent "career" experts. Juries are not required to adopt expert opinions, but may be required to use them to consider the facts.

Elements that may be considered—and put forth by expert witnesses—have been the subject of various commentators over the years. One comprehensive report suggests nine important considerations [39]. Position the gallbladder with maximum cephalic traction. Obtain lateral and inferior retraction of Hartmann's pouch of the gallbladder. Dissect lateral to medial high in the neck of the gallbladder. Posterolaterally dissect Hartmann's pouch to identify the gallbladder neck–cystic duct junction. Free the neck of the gallbladder from the liver circumferentially. Place clips only under direct vision and as close to the gallbladder as possible. Liberally use intraoperative cholangiography to define the anatomy and mitigate severity of any injury. Dissect close to the gallbladder. Lastly, the surgeon must know when to convert to open cholecystectomy. Another commentator additionally

adds caution in interpretation of cholangiogram images and avoidance of blind attempts to control hemorrhage [40].

Notwithstanding the fact that patients give informed consent, they do not consent to negligence like a surgeon's failure to properly recognize anatomy, a decision not to convert the procedure to open, or a failure to use IOC when indicated. Lack of attention or excessive speed is an additional theory put forward in efforts to make out a negligence claim. As with any surgical procedure, there are certain risks and potential complications that are known to occur, and such complications do not necessarily constitute a deviation from the standard of care. Studies on bile duct injuries that resulted in litigation have shown that the main reasons for lawsuits are inadequate dissection of the triangle of Calot, confusion of normal anatomy, misidentification of Common Bile or Hepatic Duct (CD) as cystic duct, clips impinging on CD, blind clipping or cauterization near hilar structures, and failure to recognize a Luschka's duct [38]. If the operation was dictated as "straightforward, with minimal inflammation, easy dissection of the gallbladder, and unremarkable pathologic findings", the lack of intraoperative findings to suggest a difficult dissection might constitute a deviation from the standard of care.

The decision not to do an intraoperative cholangiogram (IOC) may also be advanced as evidence of breach. Misinterpretation of cholangiography, by not visualizing a hepatic duct, noting extravasation of uncertain origin, or not completing the procedure may also be a ground for a negligence claim. Under certain circumstances, the plaintiff may offer into evidence scholarly papers which may be offered as evidence of standard of care [41, 42]. Further, cholangiography itself does not prevent duct injuries. In litigation concerning CD injury in which an intraoperative cholangiogram was not performed, surgeons often state that there was no doubt about the anatomy. However, the plaintiff's attorney will question how the injury occurred in the first place if there was no doubt. If significant inflammation and scarring were present, an IOC should probably have been performed, or at least attempted. If the inflammation was so severe that the IOC could not be performed, but was at least attempted (and documented), it would be harder to prove a breach of the standard of care.

There are, however, times when a decision to perform the IOC becomes a judgment call of the surgeon to prevent undue risk to the patient. If the gallbladder is severely inflamed, making dissection difficult, an IOC should be attempted. If the surgeon, despite all best attempts, is unable to technically place the catheter into the cystic duct due to the inflammation, it is not below the standard of care to abort the IOC and simply remove the gallbladder, assuming the anatomy is understood. Another option would be to convert to an open procedure, although this does not necessarily protect against a CD injury. Once a bile duct is injured, improper management or delayed recognition might also breach standard of care. If the surgeon has minimal experience with bile duct reconstruction, intraoperative consultation from a colleague, a surgeon more experienced in HPB surgery, or transfer—even from operating room to operating room—might be the best option. Lastly, in a teaching hospital setting, letting an inexperienced surgical resident persist in attempting the procedure in the face of distorted anatomy, bleeding, or inflammation may be judged negligent.

Evidence

Bile duct injuries happen in the operating room, and although there may be corroborating evidence in the case of delayed diagnosis, for the bile duct injury itself, only the operative note and depositions are likely to be admitted at trial. Op notes should be concise and without speculation. They should not be retroactively changed and are best dictated, edited and signed at the time of the procedure. Relatively little has been published on how to dictate an operative note. In one report 250 actual operative notes were compared to a model note developed through cognitive task analysis. Using such an analysis, the following elements were judged to be important: (1) cephalic traction of the gallbladder, (2) dissection of the gallbladder neck bordering the triangle of Calot; (3) identification of the cystic duct–gallbladder neck junction, (4) details of ligation and division of the cystic duct and cystic artery, (5) dissection of the gallbladder from the hepatic bed, and (6) findings to include inflammation, any difficulties in dissection, bleeding, and other irregular cues. Key elements were present in 25 % of routine operative reports, but none in bile duct injury cases, respectively. Further, irregularities such as perceived anatomic or other deviations correlated with bile duct injury operative reports [43].

Depositions are question and answer sessions under oath, which result in a written and possible video transcript. In most states, the questions are generally about the surgeon's treatment of the patient but can be about any subject matter relevant to the case. In most states, deposition testimony can be read to a jury even if the physician does not take the stand. Plaintiff's counsel (representing the injured patient) hopes to get an admission of negligence (see apology discussion above), lock in statements to prevent the physician from telling a different story at trial (impeachment), or create conflicting testimony amongst treating physicians.

As the subject of a deposition, the surgeon's obligation is to answer questions accurately. The deposition is not a conversation but part of an important formal legal proceeding. Prior to sitting in a deposition, the surgeon's attorney will generally give advice on preparation. It is important to be serious, business-like, and courteous. Understand and answer only the question asked, a process that should be simple but not easy. If the question is not understood, it cannot be answered, and it is appropriate to ask that the question be repeated or even rephrased. Records should be referred to if appropriate. A general rule of thumb is that the surgeon should be able to give any answer in two sentences or less and preferably with a yes or no. Medical literature is generally not allowed at trial; however if the surgeon acknowledges a source as "authoritative," she may be questioned as to anything in that source.

Damages

Patients are more likely to sue the surgeon who performed the cholecystectomy if bile duct reconstruction results in complications and the patient's recovery is protracted. These complications include anastomotic stricture of the

hepaticojejunostomy, cholangitis, cirrhosis, or liver failure. If the patient does well for the first 5 years after reconstructive surgery, then the patient most likely will continue to do well. However, in those years of recovery, damages both monetary and non-monetary will be alleged.

To be awarded damages, the patient must show that the surgeon's malpractice caused the injury, and a price in dollars can be put on the damages. Damages can be broadly separated into monetary and non-monetary categories. Monetary damages are generally easier to quantify. Monetary damages cover expenses caused by the malpractice, including medical bills, lost time from work, and future missed work often including anticipated promotions and raises. There is inevitably guesswork involved, especially when it comes to future medical expenses. Experts are generally employed to assist in the calculation of these damages.

Non-monetary damages refer to costs of the patient's suffering that are real but do not have a definite price. Probably the most common example is pain and suffering; the physical or emotional distress resulting from the malpractice and resulting injury. The patient seeks compensation in dollars as the only viable substitute for the experiences sustained as a result of the injury. The price the defendant owes for pain and suffering is calculated separately from the amount owed for monetary expenses, such as medical bills, time lost from work, and loss of future earning capacity.

Often, relatives will also file claims for injuries such as loss of consortium and loss of services. The dollar value is generally arrived at by the fact finder—judge or jury. The patient and others will give evidence about the patient's pain and suffering, and other non-monetary damages. Experts often testify about the usual outcome of the patient's injury. Some states—California being the most prominent—place a cap on the maximum amount of non-monetary damages the patient can recover. Some states cap all damages. Some states reduce the damages the surgeon must pay by the amount the injured patient receives from insurance or other sources (the collateral source rule). Lastly, some states limit the contingency fees an attorney can charge for a malpractice representation (although the usual fee is about one-third of the award, plus expenses).

Conclusion

Should a bile duct injury occur, the likelihood of a patient's claim of malpractice against the surgeon depends on a number of factors. Good communication and a thorough informed consent process may help defuse anger, as well as insure that the patients are aware of the possibility of such injuries. Once a bile duct injury is sustained, the patient should be told the facts as known, and such disclosure must be done according to any relevant state laws and regulatory requirements. Apologies are ill-advised; such conversations are best had after deliberation with legal counsel. The documentation of the operation should be thoughtful and limited to the facts of the case.

The medical malpractice system is not efficient; many patients who are injured by negligence never file a claim. Conversely, when serious injuries occur, some claims are filed in the absence of negligence. Laparoscopic cholecystectomy cases are more likely to generate lawsuits than open procedures. Lack of timely conversion, failure to consider or misinterpretation of cholangiograms, delay in diagnosis of the injury and inadequate repair in the event of recognition are all common sources of litigation. Lastly, many lawsuits are settled out of court; those cases that go to trial are split with verdicts for both the plaintiff and defendant. The decision to go to trial is often one of the most difficult a surgeon must face in a career of difficult decisions and reinforces the need to work closely with counsel throughout what is always a harrowing experience.

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Chapter 21
Commentary: Bile Duct Injuries and the Law

Keith D. Lillemoe

Nearly 25 years since the widespread introduction of laparoscopic cholecystectomy, major bile injuries continue to occur at near the same incidence as in the mid-1990s (0.4 %) [1]. In addition to the added costs, disability, morbidity, and even rare mortality, bile duct injuries remain a major indication for medical malpractice claims against general surgeons. A study published from the United States early in the laparoscopic cholecystectomy era (1993–1996) by Kern [2] reviewed the outcomes of malpractice litigation involving laparoscopic cholecystectomy. He found 44 cases were filed with over 60 % (27 cases) associated with a bile duct injury. The care of these injuries was complex with a mean of two reoperations (range 2–9) and multiple readmissions for strictures. Fourteen of these cases were settled "out of court" with an average cost of settlement being over $506,000. However, 13 cases went to jury trial, with 12 cases having a jury verdict in favor of the defense. On the other hand, in another US series of 46 bile duct injuries, 86 % of cases were resolved in favor of the plaintiff [3]. The average award was $214,000. In a more recent study from England, the percentage of claims resolved for the plaintiff was also 86 % [4]. Finally, the most recent study, also from England, reviewing 15 years of litigation found that although the number of claims following laparoscopic cholecystectomy had fallen in recent years, their national malpractice carrier had still settled 303 of almost 418 claims between 1995 and 2009, with total cost of £20.4 million or $33.4 million. A bile duct injury was the most frequent injury resulting in litigation and the most likely injury associated with a successful claim ($P<0.001$) with the average payout for successful claim being £102,870/$168,337 [5].

This chapter by Steven Raper, an accomplished hepatobiliary surgeon and also lawyer, nicely defines the medicolegal aspects of bile duct injuries. He defines the

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value of informed consent, how to honestly disclose the nature of an injury, including the value and risks of an apology, and communication/resolution programs. All these points are valuable regardless of the type of an adverse surgical outcome that could result in a medical malpractice claim. He then describes the standard components of a malpractice case which includes the breech of the standard of care and the damages associated with an injury. He specifically addresses the issues of breech of standard of care as it relates to bile duct injuries, including the use for intraoperative cholangiogram, the extent of dissection, and the management of the injury once recognized. He discusses the nature of evidence in a medico-legal case including operative notes and medical records and the surgeon's own deposition testimony. Finally, Dr. Raper defines the various aspects of the damages that can be determined as the causal result of the injury.

In summary, he nicely provides the "facts" of a medicolegal process and how it pertains to biliary injury. I would like at this time to provide a bit more of the "nitty-gritty" of a bile duct injury from the perspective of a surgeon who has created more than one bile duct injury (and not been sued) and who has defended dozens of surgeons in bile duct injury litigation. There is essentially no published data on the subject that I will address so I hope the readers accept the following as opinion and not necessarily as fact. I will proceed to what I consider the key components of how a surgeon can best defend against or avoid malpractice claims in cases when an injury has occurred and then focus again on my opinions related to the issues that can arise when a case actually comes to trial.

Avoidance of a Malpractice Claim

Operative Consent

I do not feel that operative consent has ever been a crucial factor in the ultimate decision of a malpractice case related to bile duct injury. Despite this and having been in academic practice for almost 30 years, I almost always get my own operative consent from the patient. In doing so, I always describe that a bile duct injury *can occur* during a laparoscopic cholecystectomy, as well as the other complications of bleeding, infection, risk of anesthesia and need for open cholecystectomy. I emphasize to the patient that should an injury take place that their course will be complicated and further procedures will be necessary. In addition to the actual signed consent, I dictate in my consultation note that such a discussion has taken place and also dictate the same in the introduction of all operative notes. I thus make it clear multiple times in the medical record and hopefully in the mind of the patient that a bile duct injury, although rare, can occur and have serious ramifications.

Dictation of the Operative Note

Again, despite being in academic practice, I dictate all of my own operative notes. The proper operative note should describe what is done and, more importantly, all of the decision-making associated with the procedure. If significant inflammation is encountered during a laparoscopic cholecystectomy, don't necessary embellish the difficulty of the dissection—leading to people question why you didn't convert. Rather define that how, with careful meticulous dissection, you as a surgeon felt that you were continuing making progress in completing the procedure laparoscopically. Define your dissection technique and if you are able to demonstrate the critical view, be sure to dictate it. If you recognize an abnormal anatomy, carefully define what you think the anatomy represents and how you defined it, remembering almost all major bile duct injuries are the result of a visual perception illusion or misidentification [6]. When complications, such as bile duct injury occur, it is important that you have described your technique, what you believe you saw and then justify the decisions that you made in the operative note, to help you and your experts defend the outcome. If you recognize an injury has occurred, laparoscopically or after conversion to an open procedure, document the findings and more importantly, document the steps that you take at that time. Personally, I never record laparoscopic procedures and seldom take operative photos. They seldom help your case and if anything goes wrong it demonstrates for the jury (in hindsight) your error.

Management of Bile Duct Injury Recognized at Laparoscopic Cholecystectomy

The bile duct injuries that I caused were recognized at the time of the original laparoscopic cholecystectomy. I converted, and being an experienced biliary surgeon, I felt comfortable in doing my own repair. Nevertheless, I was "shook up" and concerned about my patients' welfare. Certainly I knew that I was at risk for a lawsuit. If you are an accomplished biliary surgeon and feel that you can do a repair, don't try to minimize the incision or the extent of the reconstruction. In most procedures, if there has been an excision of a segment of duct or if the injury is high, performing an end-to-end repair is likely to fail and lead to late complications with an anastomotic stricture [7]. Thus in almost all cases, a tension free Roux-en-Y hepaticojejunostomy is the preferred option to provide the best long term outcomes. I am also an advocate of transanastomotic stenting. Such stents allow control of any bile leaks that may occur postoperatively, as well as allowing the opportunity for postoperative cholangiography, both in the early post operative period and in the weeks after discharge. Certainly maintaining access to the biliary tree has some benefits in minimizing any postoperative complications. A perianastomatomotic drain should be placed to protect against the consequences of a bile leak, which can likely occur even in the best of hands with a small non-dilated, "normal" hepatic duct.

The real question however that most surgeons, who perform laparoscopic cholecystectomy and have created a bile duct injury, must answer is the following: Am I the right person to do this repair? My guess that in most cases, the answer is no [7]. Thus if you are at an institution where there are surgeons with hepatobiliary experience, call them into the operating room and turn the case over to them. Allow them to make the decisions and perform the reconstruction. Remember, this is not an ego thing. You want to do what's best for your patient in providing the optimal results. Furthermore, if someone else does the repair and postoperative complications occur, they cannot be directly attributed to your bad judgment in doing a procedure you're not experienced in performing. If there is no experienced help at your own hospital, simply controlling the biliary leak and transferring the patient to a tertiary care center is the best option. In most cases, you should call the surgeon to whom you wish to refer the patient from the operating room, describe your findings and do exactly what you're told to do (and dictate it into the operative note). Most surgeons will tell you to do nothing further, to avoid making the injury worse. If the gallbladder has not been removed, don't take it out. Drain the right upper quadrant so that bile peritonitis or collections do not occur. Finally, do not make an attempt to tie off or clip the proximal duct, with the hope that dilatation will occur to make the subsequent reconstruction easier. All this does is extend the injury proximally and cost you valuable length of the duct.

After the procedure, whether you have done the repair yourself, had a colleague at your own hospital complete the repair, or if you are preparing to transfer the patient, sit down immediately with the patient and their family, explain that an injury took place. (Often it is a good to call out to or visit the family in the waiting room as soon as you recognize a problem to update them, as often they were expecting a much shorter period of time for the procedure.) If there is a reasonable explanation, such as severe inflammation, for how the injury took place, be honest and offer the best explanation you can. If you or your colleague have done a satisfactory repair, and then explain that you are comfortable that a good recovery and outcome will follow. I would not apologize for any error, but find it better to explain that there are factors about the operation that led to this occurrence and that by recognition and repair; you have hopefully averted further complications. Be as optimistic as possible. Express on your confidence that the patient will do well.

If the decision is made to transfer the patient, explain that you are not "deserting" the patient, but simply transferring them into the hands of a more experienced, accomplished team to provide the most optimal results. This is generally not an urgent transfer and I would certainly recommend allowing the patient to recover from anesthesia and explain what's going on. Having accepted a number patients under similar circumstances, I can tell you that the more understanding they have of why they are being transferred, the better it is.

Recognition of an Injury in the Postoperative Period

The normal routine recovery following a laparoscopic cholecystectomy is that the patient is generally better in 1–2 days. If the patient has been discharged to home and calls you after 3–5 days saying they are having far more pain, distention, nausea, fever, vomiting, or anything atypical for the normal pathway, do not ignore their complaints, but rather have them come into the office or the emergency room to be evaluated. It is always better to be suspicious and rule out a leak or injury early, than to delay until the patient presents with sepsis or systemic inflammatory response from an ongoing bile leak. Once it is recognized that an injury may be likely, due to the presence of a bile leak or fluid collection, again it is time to make the determination where should the patient best be managed. If you are *not* at a center that offers the multidisciplinary team of interventional radiology, invasive biliary endoscopy, and experienced hepatobiliary surgeons—now is the time to transfer the patient before doing procedures which may be of no benefit, create further complications or just simply add to the expense that may be starting to accrue to the patient's care. Under no circumstances should patients be taken to the OR urgently without defining the nature of the injury. A laparotomy or even a laparoscopy to identify the injury and to attempt to do a repair or even to just wash out the abdomen seldom is of benefit and again simply adds to the potential for morbidity and cost. Finally, it has been my experience that most severe complications and even deaths after biliary injuries have been in patients in which there has been significant delays in referral and failure to control an ongoing biliary leak, often with unsuccessful attempts at operative management [8].

Remember, as soon as the patient is in the hands of the tertiary care team, you as a primary surgeon can do no further harm. Yes, you have created an injury, but you have not *personally* contributed further to the consequences or complications of the injury. Other people's complications will certainly be part of your ultimate responsibility, but yet you have no further opportunity to do anything else that might be considered negligent in the hands of a critical expert witness.

Issues at Trial

Most outcomes of medical malpractice litigation for bile duct injuries come down to the quality of the evidence presented both by the patient, the surgeon, and most importantly, the expert witnesses for both the surgeon and the patient. As a surgeon, you need to make sure that you can defend your decision-making and offer an explanation of how the injury may have taken place to the jury. At both the deposition and trial you should be prepared and knowledgeable. Present the appearance of a competent physician, who carefully thought out all of your decisions both at the

original laparoscopic cholecystectomy and in the aftercare. Certainly show compassion toward your patient who whether, it be negligence or not, has suffered to some extent with the injury.

In most cases, the plaintiff's expert will say simply that every bile duct injury is a mistake that should never happen during a laparoscopic cholecystectomy and thus it is below the standard of care and negligent. The job of the defense expert witness is to say that surgery does not always have a perfect outcome and that complications do take place despite the best intent of any surgeon. A complication or a bad outcome does not necessarily mean the surgeon was negligent. As long as you have not hurt yourself in your operative note, other medical records or at deposition, the best defense is simply that the surgeon was doing his or her best to define the anatomy and encountered factors that a reasonable prudent surgeon might make the same decisions with a similar outcome. A defense witness should make an effort to educate the jury and to convince them that negligence was not necessarily the cause of the injury. In my opinion, most juries want to believe that surgeons never intend to be negligent and will accept the fact that complications do occur. It's important that your expert is credible, knowledgeable about both your case and bile duct injuries, in general, to convince the jury that this was the case with your patient and that once the injury was recognized, you did everything possible to ensure the best of outcomes whether it be repair to the injury yourself, recruit a colleague, or transfer the patient to another hospital.

Issues that are often brought up in the opinion of the plaintiff's expert witness include that intraoperative cholangiography, obtaining the critical view, or even conversion to open cholecystectomy should have been performed and had any of these been done, the injury would have been avoided. In my opinion, there is no evidence that the standard of care requires intraoperative cholangiography and delineation of the critical view (even though I personally believe that it is the most important mechanism for preventing bile duct injuries) and that conversion is not necessary as long progress with dissection is being made in conducting the operation. In fact, the argument can be made that even more serious injuries can result when a surgeon, less experienced in open cholecystectomy, has converted to an open procedure.

Damages

The plaintiff's team not only wants to prove that you are negligent, but that the biliary injury that you caused will result in huge medical costs both in the past and even more in the future, continued long term negative effects on quality of life [9] and significant risk of further deterioration in health status. I have seen many plaintiffs' teams come in with life cost analysis, describing the frequency of follow up blood work and radiologic exams, the likely need for further endoscopic or percutaneous interventions, reoperation and even liver transplant. These total costs will oftentimes run into the millions of dollars.

One cannot deny that the cost associated with a bile duct injury can be significant both in terms of added medical costs as well as loss of income to the patient and their family. However, the projections for massive future healthcare costs and deterioration of health require that such events are 'more likely to happen than not' which in the medicolegal world means a *greater than 51 % chance* of this outcome occurring. The fact that reported outcomes for biliary reconstruction completed by experienced hepatobiliary surgeons consistently show a greater than 80 % long term success [10, 11], means the chance of reoperation, further procedures, and the extraordinarily rare occurrence of a liver transplant cannot be accepted as likely to happen, and therefore cannot contribute to future health care costs. The vast majority of patients, based on multiple reported series will have successful long-term outcomes, so these claims of millions of dollars of future medical costs cannot be accepted. Furthermore, there is plenty of evidence to show that most recurrent bile duct injuries occur within 5 years of repair [12]. Since many malpractice cases take years to come to trial, if a patient is fine 4 or 5 years after repair, it's far more likely than not that they will continue to be fine the rest of their life.

In conclusion, approximately one out of every three general surgeons performing laparoscopic cholecystectomy will injure a bile duct during the course of their career. Unfortunately, many of these individuals will be sued. I honestly believe, again having caused bile duct injuries myself, that these surgeons are not all negligent nor was the operation in which the injury took place a breach of the standard of care. Nevertheless, remembering a number of very important points, as you perform every laparoscopic cholecystectomy, but certainly in those cases where you have complications, can certainly minimize the chances of you being found guilty in a malpractice suit.

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Chapter 22
Intraoperative Management of Bile Duct Injuries by the Non-biliary Surgeon

Jeffrey Barkun and Prosanto Chaudhury

Epidemiology

The introduction of laparoscopic cholecystectomy (LC) in the late 1980s marked a revolution in general surgery. The novel technology led to the justified demise of less efficacious alternatives to treat gallstones, such as bile salt dissolution or percutaneous lithotripsy. It also led to an almost doubling of the incidence of cholecystectomy, which now stands between 750,000 and one million per year in the USA alone (Thomson Reuters estimated procedures, 2010) even though up to 20 % of patients have no clear indication for LC [1]. LC has several advantages over a conventional open cholecystectomy [2] but the risk of bile duct (BD) injury remains an Achilles' heel. The main risk of BD injury had originally been thought to be present during a surgeon's learning curve for LC [3] but later reports have confirmed that it is ever present. BD injury after LC is thought to be more common than after open cholecystectomy: 0.1–0.2 % versus 0.2–0.7 % [4, 5]. BD injuries after LC occur closer to the bifurcation, and can involve a concomitant arterial injury, especially right hepatic artery, in a significant number of cases [6] making them more complex to manage and more morbid. The consequences are devastating for the patient and include increased serious patient morbidity, up to threefold increased mortality in the first year alone [7], and severely compromised quality of life in the long term [8] though there is evidence that this may be offset by expert corrective biliary surgery [9]. BD injury after LC is also a significant source of

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medicolegal actions in many countries, with 70–86 % claims being settled successfully for the plaintiff, often out of court: http://www.cmpa-acpm.ca/-/medico-legal-problems-related-to-cholecystectomy-biliary-tract-injuries [10, 11].

Mechanisms of Injury

Risk Factors

Although bile duct injuries may be associated with an alteration or an aberrancy of local biliary anatomy, up to half may occur during a "so-called easy" LC even in the hands of an experienced laparoscopic surgeon [12].

The SAGES guidelines summarize the evidence relating to possible clinical factors associated with the development of BD injury at LC: surgeon inexperience, patient age, male sex, the presence of acute cholecystitis (level II, grade C) and the correct identification of relevant anatomy (level I, grade A): http://www.sages.org/publications/guidelines/guidelines-for-the-clinical-application-of-laparoscopic-biliary-tract-surgery/ [13].

Surgeon inexperience/Learning curve: Surgeon inexperience and a learning curve effect have been [14] associated with increased rates of CBD injury. However, a review of operative volumes of graduating chief residents has shown a steady increase in average LC experience reaching 107 [15] in 2011 and 112 in 2013 [16]. As a consequence, it is believed that other factors now account for the majority of injuries [17]. Perhaps the strongest measurable clinical predictor identified to date comes from a retrospective population-based cohort study, from the Ontario Health Insurance Plan, admitted to hospital with acute cholecystitis. A well-matched cohort of 14,220 of these allowed for a comparison of "early cholecystectomy" (operation within 7 days of the index admission) versus those in whom cholecystectomy was "delayed." The delayed group had an almost twofold greater risk of major bile duct injury (0.53 % vs. 0.28 %) compared to patients treated with early surgery [18]. These findings confirm a hypothesis that previous randomized trials had been underpowered to answer: that a policy of delaying cholecystectomy for acute cholecystitis may indeed set the conditions for an increased risk of BD injury.

Problems of Technique

1. Error traps: In a pragmatic review of possible sources of misidentification leading to biliary injury at open or LC, Strasberg has described four "error traps" which most commonly occur [19]. The first is the "infundibular view error trap" which involves concealment of the cystic duct and drawing-in of the common hepatic duct against the gallbladder. The second involves the use of a fundus-down approach in the face of severe inflammation, usually at open cholecystectomy

after conversion to LC, which can lead to a severe vasculobiliary injury and liver devascularization. The third is attributable to a failure to perceive the presence of an aberrant right hepatic duct on cholangiography, and the last involves damage through cautery, especially when there is "parallel union" of the cystic duct alongside the bile duct. Several technical areas have been incriminated with CBD injury during LC, though as accepted technique has become widely taught and standardized, some of these factors may be less important now than when the procedure was first introduced [17].

2. Improper occlusion of cystic duct

   Clips should be applied so that their tips can clearly be seen beyond the edge of the duct, or clearly locking in the case of Hem-o-lock clips. In order to achieve this, the duct must be cleared of all extraneous fibro-fatty tissue. In the setting of a thickened duct 2 pre-formed endo-loops should be applied to the cystic duct stump to decrease the chance of cystic stump leak.

3. Injury to ducts or blood vessels in the liver bed.

   An improper plane of dissection may lead to dissection in the liver rather than the plane between the liver and gallbladder. This can result in injury to superficial vessels or ducts in the gallbladder (GB) fossa. This type of injury is more prone to occur in inflamed cases where identification of the proper plane can be difficult. Meticulous dissection in a clear field and the recognition of departure from the correct plane are required.

4. Thermal Injuries

   Early or injudicious use of cautery in the triangle of Calot before clear identification of structures can lead to severe thermal injuries to the common bile duct (CBD). Such injuries also occur in the inflamed setting more commonly, possibly because higher cautery settings are often employed to control haemorrhage in this setting. To avoid these injuries, low cautery settings should be used during dissection (25 W or less), and cautery should be used sparingly until all structures are well identified.

5. Tenting injuries

   These injuries result from excessive traction on the Gallbladder during clip placement on the cystic duct "tenting" the CBD up into the clips. This does not seem to be as common an injury in the laparoscopic as the open era.

Classification

There exist a number of different classifications of biliary tract injury. An ideal system would provide relevant information regarding prognosis and management of the injury and take into account patient condition, timing of detection, and the presence and degree of sepsis. Among many different classifications that have been proposed and adopted, none take all of these conditions into consideration; a thorough discussion of these is detailed in another chapter (see Chap. 20). To date, no single classification system at this time has been universally adopted.

Table 22.1 Lau classification [5]

Type	Criteria
1	Leaks from cystic duct stump or small ducts in liver bed
2	Partial CBD/CHD wall injuries without (2A) or with (2B) tissue loss
3	CBD/CHD transection without (3A) or with (3B) tissue loss
4	Rt/Lt hepatic duct or sectorial duct injuries without (4A) or with (4B) tissue loss
5	Bile duct injuries associated with vascular injuries

CBD common bile duct; *CHD* common hepatic duct; *Rt* right; *Lt* left

The Bismuth classification of biliary strictures is a holdover from the open era of cholecystectomy [20]. This classification is based on the most distal level of healthy bile duct available for reconstruction at the time of repair and allows the surgeon to choose an appropriate technique for repair. It correlates well with outcome after repair [21]. The Bismuth classification does not take into account the full spectrum of possible bile duct injuries. Laparoscopic injuries more commonly involve transection or resection of part of the common bile duct than injuries from the open era. The likelihood of concomitant vascular injury, usually to the right hepatic artery is also greater in the laparoscopic era and not accounted for in this classification.

The Way and Stewart [22] classification proposes four grades of injury and classifies them by mechanism of injury explicitly including concomitant vascular injury. The presence of vascular injury is associated with increased morbidity and in some series with increased rates of failure of initial repair.

Most recently in 2007 [5] Lai and Lau proposed a classification that lists injuries in ascending order of magnitude (Table 22.1). The mechanism of injury for each grade differs and thus specific measures to prevent them are proposed. Additionally, the magnitude of treatment for each grade of injury also differs.

Acute Recognition and Management of BD Injury

BD injuries are only recognized at the time of surgery, in 23–32 % of cases [22–24] which points to the importance of intraoperative clues to raise the index of suspicion that "something is amiss."

(a) Suspicion that the CBD or common hepatic duct (CHD) is being dissected rather than the cystic duct:

- Placement of a 9 mm clip is insufficient to occlude a ductal structure [22]
- The ductal structure being dissected can be traced without interruption behind the duodenum [22]
- The operative field reveals the presence of another and unsuspected duct

- A large artery, the right hepatic duct, is seen coursing behind what had been presumed to be the cystic duct.
- Extra lymphatic and vascular structures are encountered during dissection

(b) Suspicion that a BD injury may have occurred:

- A feeling of "unease" during a difficult cholecystectomy, in particular when associated with very a prolonged period of dissection (see below, section "Recommendations (Top Ten)") where an unusually large number of clips (greater than 8) [22] have been used, or when there is sustained bleeding from an area medial to the GB (deep to the cystic duct node) or deep in the field of dissection.
- Unease at recognition that the presumed anatomy cannot be reconciled with what was anticipated.
- Unease with the interpretation of intraoperative cholangiography (IOC) esp. failure to visualize the proximal CHD and intrahepatic ducts.
- Unsuspected bile leakage, especially if voluminous.
- When the operator encounters an unexpected plane of dissection: deep within liver parenchyma with visualization of tubular structures [19], or when one sees a "double pulsation sign" which identifies the inferior vena cava posterior to a GB scarred onto the porta hepatis.

(c) Confirmation of the occurrence of a BD injury:

When one of the above scenarios is present, the operating surgeon must decide on possible next steps; the first of which is the decision to consult with another surgeon, ideally one who is "more senior" or has greater hepato-biliary training and experience. Next is the possible need to characterize further whether a BD injury may have occurred. A BD injury can only be confirmed by radiographic or visual demonstration of the damage to the biliary tree. This can be achieved by performance of IOC, intraoperative ultrasound (IOUS) or by conversion to an open procedure. The merits of each of these are discussed below. However, an attempt at defining the exact extent of the BD injury at LC may not be necessary. There are several reasons for this: the first is that this is usually better done by postoperative imaging which is more accurate at defining the level and extent of injury (especially if it involves a concomitant arterial injury). The second is that attempts at a better definition of the BD injury can lead to a worsening of the level or extent of the injury. There is also no absolute need to convert to an open operation strictly to assess the extent of the injury, as this maneuver and further dissection of the hilum generally only complicate subsequent definitive management and can also result in further injury [25].

(d) Immediate management of BD injury:

Any overall management strategy is best discussed as early as possible with an HPB consultation service. In many areas, HPB centers maintain a "hotline" to provide consultation over the phone, and in unusual cases may join the index surgeon to perform an immediate on-table repair [26, 27]. Until larger series describing this service are reported, it is the rare scenario where an immediate

repair may be attempted at the index LC; therefore definitive repair at this stage is not usually the goal. In the majority of cases intraoperative wide drainage of the sub-hepatic space followed by formal consultation/transfer to the HPB specialist remains the safest option for the patient. The objective is to achieve complete control of the expected biliary leak through closed suction drains. Surgeons who are not experienced in the management of bile duct injuries should not attempt primary repair, as the rate of failure in this situation is extremely high. Bile duct injury repair by the primary surgeon has been reported to be successful in only 10–17 % of cases versus over 90–94 % when performed by a specialist HPB surgeon in a dedicated center [24, 28] (see later chapters regarding acute and delayed repairs). Immediate primary duct to duct repair, which may seem attractive to some, is rarely a worthwhile option. Lack of expertise in biliary repair by non-HBP surgeons is supported by operative volume data of current graduating residents. Upon graduation, the cumulative average number of LC performed per trainee during their residency in 2013 is 112; the average number of bile duct explorations is 0.9 (with a maximum of 10), and the average number of choledocho-enteric anastomoses is 1.6 [16].

Other Immediate Management Steps

Other steps that are important in the overall management of a suspected BD injury include the need to prepare full disclosure with the patient and their family. This includes discussion of possible long-term effects of the injury. There is also need for the surgeon to contact their liability coverage insurer although thresholds will vary according to jurisdiction. Both these points are dealt with in other chapters. Universal, however, is the need for precise and timely chart documentation of the operative findings, discussion with the HBP consultant, and perioperative care plan. Lastly, the patient needs to be prepared for either consultation or transfer to a HPB service. While awaiting transfer, patient hemodynamic and fluid optimization have to be ensured, especially after extensive blood loss, in the case of a large-volume bile leak, or if an ileus develops. Prior to a transfer, management of patient expectation and timely logistics are important to optimize future care.

Avoidance of BD Injury

SAGES (Society of American Gastrointestinal and Endoscopic Surgeons) has recently introduced the Safe Cholecystectomy Program in an effort to decrease the incidence of CBD injury and to develop a culture of safety around this commonly performed laparoscopic procedure.

The following are six strategies which surgeons can employ to adopt a universal culture of safety for cholecystectomy and minimize the risk of BD injury [29].

1. Use the critical view of safety (CVS) method of identification of the cystic duct and cystic artery during LC (see below)
2. Perform an intraoperative time-out during laparoscopic cholecystectomy prior to clipping, cutting or transecting any ductal structure.
3. Understand the potential for aberrant anatomy in all cases.
4. Recognize when the dissection is approaching a zone of great danger and halt the dissection before entering the zone. Finish the operation by a safe method other than total cholecystectomy (see section "Alternatives to Conventional Cholecystectomy") if conditions around the gallbladder are too dangerous.
5. Make liberal use of IOC or other methods to image the biliary tree intraoperatively (e.g., IOUS). IOC is recommended in cases of confusing anatomy, difficult dissection from adhesions/inflammation, or when a biliary anomaly is suspected.
6. Get help from another surgeon when the dissection or conditions are difficult. There is anecdotal evidence from a single-specialty general surgery group over two time periods suggesting that a surgeon as first assistant may reduce the incidence of BD injury at LC [30].

Unfortunately no single technique has been consistently shown to decrease the occurrence of bile duct injuries and supporting evidence can be controversial, thus warranting further comment.

1. Selective versus routine IOC:

   Some surgeons have long advocated the routine use of IOC, dating back to days prior to the introduction of LC. Several publications notably by Flum et al. [14] have suggested, primarily on the basis of medico-administrative data, that the incidence of CBD injury is lower in cases where IOC has been performed. It has also been suggested that IOC may identify injuries at an earlier stage during the index operation, possibly helping to minimize their extent. However others have suggested that (1) when data are examined by stratifying for frequency of IOC use, surgeons who do not use IOC have similar rates of CBD injury whether or not they use IOC and (2) surgeons who use IOC in over 75 % of their cases have a significantly greater rate of CBD injury when they do not perform IOC. This study also points to surgeon experience as a significant factor in the development of CBD injury, and that the impact of IOC earlier in one's surgical experience seems greatest [14]. A study by Sheffiled et al. [31], using instrument variable analysis techniques, rather than multivariate analysis, demonstrated equivalent rates of CBD injury regardless of IOC use. In spite of these conflicting data, all agree that IOC is an important tool for every surgeon who performs LC, whether it is used routinely or selectively, and that IOC should remain readily available.
2. The infundibular dissection technique

   The infundibular or infundibular-cystic technique for identification of the cystic duct during LC was described early in the LC experience. The technique involves dissection on the cystic duct in the anterior and posterior surfaces of the triangle of Calot. Once the putative duct is identified it is traced back on to the

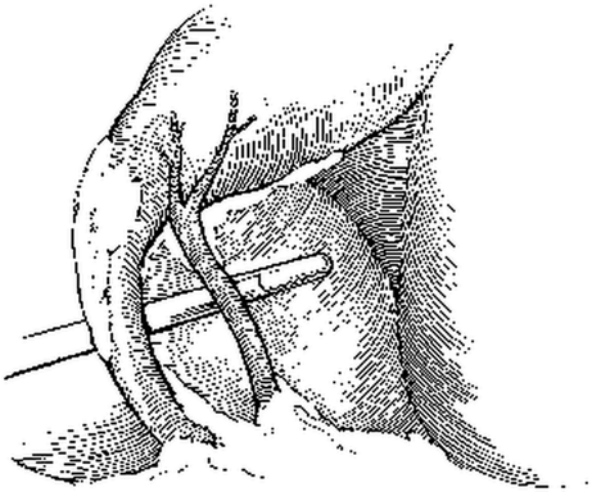

Fig. 22.1 Critical view of safety reproduced from Strasberg [33]

gallbladder. The identification of the duct is made based on the characteristic "flare" or funnel shape at the junction of cystic duct and infundibulum of the gallbladder. However, in cases of inflammation, the triangle of Calot may be obliterated, or drastically shortened. What the surgeon believes to be the cystic duct may thus actually be the CBD; Strasberg has referred to this as the hidden cystic duct and identifies it as one of the error traps leading to CBD injury [32]. Most authors agree that even when clearance of the cystic duct is performed over 360°, the infundibular technique cannot be used safely as the sole means of identification of the cystic duct.

3. The critical view of safety

   Since its publication in 1995, the critical view of safety technique of Strasberg [33] (Fig. 22.1) remains one of the most secure means of performing laparoscopic cholecystectomy. In this technique the triangle of Calot is cleared of all fat, fibrous and areolar tissue and a part of the GB beyond the infundibulum is dissected off the liver bed. When this is successfully accomplished, the only two structures remaining that enter the gallbladder are the cystic duct and the cystic artery. Only when this dissection is complete and the hepatocystic triangle is totally skeletonized, along both the anterior and posterior planes, should any structure be clipped or divided. Recently, photo documentation of the critical view of safety by doublet photography (anterior and posterior views) has been proposed as a standard means of objectively documenting that a safe dissection has been performed (Fig. 22.2) [34].

4. Low threshold for conversion

   Conversion of an LC to open cholecystectomy carries a connotation of failure for many surgeons, and often leads to persistence in the face of poor operative conditions, a situation which is not conducive to potentially preventing injuries.

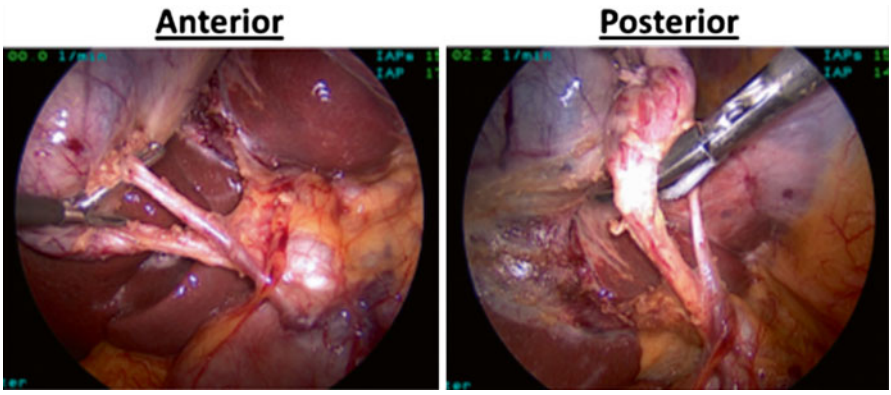

Fig. 22.2 Doublet photography reproduced from Strasberg [34]

While there are no clear rules for stopping and converting a LC, no pop-up reminders on our laparoscopic screens, there are certainly hints that arise during a LC operation that we as surgeons must be mindful of. Failure to progress in dissection, anatomic disorientation, poor visualization, and equipment problems are all conditions that could be used as stopping criteria [25] (see list above). Key considerations include the surgeons' own experience and skills. Ultimately it is important to remember that the consequences, for the patient, of a premature or unnecessary conversion pale in comparison to the morbidity of a CBD injury.

5. European technique

Early debates about laparoscopic technique at LC included a discussion about the vectors of traction on the gallbladder. The most commonly used technique in North America involves a surgeon standing to the left of the patient, and four trocars. One of these grasps the fundus, elevating it cranially, and a second grasps Hartmann's pouch and applies inferolateral traction. The "European" technique however does not support the fundal retraction and instead involves and elevation of the liver base which does not produce a "deformity" of the gallbladder [35]. It has been postulated that the latter (1) might allow for a more natural splaying of the triangle of Calot and (2) might prevent a "lining up" of a cranially pulled cystic duct with an aligned distally stretched CBD. No comparative series has ever been published.

Alternatives to Conventional Cholecystectomy

In situations in which there is severe inflammation in the triangle of Calot or neck of the gallbladder, the CVS can be difficult to achieve. This is not a failure of this technique; rather it is a key benefit since it alerts the surgeon to possible danger. In such instances, a planned LC should be replaced by consideration of a laparoscopic subtotal cholecystectomy, partial cholecystectomy, or cholecystostomy tube

placement, and/or conversion to an open procedure based on the judgment of the attending surgeon.

Though it is not well documented in the literature, one in six gallbladder operations may be deemed intra-operatively "difficult" [36]. There may be several reasons: excessive bleeding, difficult dissection, particularly in the triangle of Calot, or persistent unclear exposure or anatomy. There is a potentially different solution for each of these situations, but most important is for the surgeon to recognize the need for a change in surgical strategy because (1) a "total" cholecystectomy is becoming an unsafe option, and (2) there exist effective alternatives. Converting to an open procedure, i.e., abandoning the laparoscopic "challenge" is hardly ever an inappropriate course of action, but open total cholecystectomy may not be a safe option either. This is especially true when considering that most recent surgical graduates lack experience with open cholecystectomy. A review of operative volumes of chief residents graduating in 2011 has shown an increase in average LC to 107 but a constant drop in experience with open cholecystectomy, now numbering 11 [15]. By 2013, the number of LC had increased to 112, while the number of open cholecystectomies decreasing further to 5 [16]. Nevertheless, the alternatives to total cholecystectomy remain similar in nature whether they are performed laparoscopically or open.

1. Tube cholecystostomy:

   A scheduled intraoperative placement of a cholecystostomy tube has become unusual owing to the popularity of radiologically guided percutaneous approaches. This option nevertheless remains a viable and safe intraoperative backup strategy. Advantages include the ability to treat an acute cholecystitis and the possibility of performing postoperative trans-cystic cholangiography once gallbladder outlet edema will have resolved. The need for postoperative removal of the gallbladder after cholecystostomy is hard to quantify but data from a disparate group of patients undergoing nonoperative urgent percutaneous cholecystostomy suggest that this represents less than half of index patients [37].
2. Subtotal or partial cholecystectomy:

   Various techniques have been described all of which involve leaving some portion of the gallbladder in situ. The GB "inside" approach LC [38] involves excising most of the GB anterior wall, leaving the cauterized posteromedial wall attached to the liver, with or without stump closure, with or without drainage. Another approach involves resection of both anterior and posterior GB walls but leaving a distal stump of GB, usually through transection at its neck or Hartmann's pouch, again with or without drainage. Residual stones are removed as best possible from the stump. There have been two systematic reviews evaluating these techniques, one of which is a meta-analysis performed according to PRISMA guidelines [39, 40]. 30 studies reported 898 laparoscopic cases, 234 open, and 99 laparoscopic converted to open. Bile leak was noted postoperatively in 18 % patients, especially when no cystic duct closure had been attempted. A single patient was noted to have a CBD injury. ERCP was performed in 51 patients (4.1 %), mostly for retained bile duct stones (30 patients) or for persis-

tent bile leaks (16 patients). Reoperation was reported in 22 patients (1.8 %) (5 patients, for CBD exploration and 4 patients for completion LC in). Overall different subtotal LC techniques had similar outcomes but a laparoscopic approach appeared to have less complications than its open counterpart except for postoperative bile leaks [40]. Though these reported patients represent at best a very heterogeneous group, the results of partial cholecystectomy, performed in the most difficult cases, compare favorably to those of elective LC, supporting that this is a very good alternative for the difficult GB. Unresolved issues remain the management of the postoperative drain, when applicable, and the possibility that the underlying GB pathology is malignant.

Recommendations (Top Ten)

In a previous publication, M. Callery compiles his extensive experience and lists a number of recommendations for the performance of a safe LC by a surgeon newly entering into practice [41]. We have adapted this list and updated it according to the above discussions.

Don't start your career with a "tough" GB (e.g., a patient with acute cholecystitis who was treated with antibiotics and deferred for 6 weeks)
"20-min rule": if no progress after 20 min … OPEN
Always be mindful of the direction of traction on Hartmann's pouch (infero-lateral opens the triangle of Calot)
Dissect on the GB wall, prevention of BD injury trumps spillage of GB contents
Achieve Anterior *and* Posterior Critical View (+ count the number of "tubes")
Beware of the Infundibular View (aim for 360° at the least)
Avoid the cautery till later in the operation, and keep it low
If something is amiss, call a colleague in early (misery loves company)
Take the time to get a full consent from the patient
Beware of the "easy" gallbladder … Don't speed up, slow down …
Beware of the LC when you leave for vacation right after the operation…
Always dictate your note very soon after the operation and document measures used to "protect" the CBD at LC

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Chapter 23
Commentary: Intraoperative Management of Bile Duct Injuries by Non-biliary Surgeon

Mark Callery

Bile duct injury (BDI) causes lasting morbidity, can be fatal, increases costs, and often results in litigation. It remains the most dreaded complication worldwide of laparoscopic cholecystectomy (LC) with certain types of injury (ductal lacerations, bile leaks, aberrant duct injuries) occurring more commonly than before. Early reports suggested that injury rates reflected the "learning curve effect." Indeed, inexperience will contribute to BDI, but today, there are other explanations. After all, LC is over 25 years old for most and training and experience in laparoscopy has advanced for all. Biliary injuries today continue to occur for surgeons who are well beyond the learning curve. That BDI rates remain static is a very sad reality.

A most recent reminder of this comes from Nicolaj Stilling and colleagues from Denmark [1] in the May 2015 issue of ***HPB***. By mining 5 years of a national database, the authors identified 139 patients who suffered iatrogenic BDI for whom annotated clinical outcomes were available. The results are unsettling, but not at all unfamiliar. The median age of patients was 46 years. Nineteen percent suffered concomitant vascular injury. All were repaired at a specialty HPB center by 3 days (median) and 83 % within 2 weeks. Hospital median LOS was long (11 days), 11 % of patients required initial reoperation, 30-day morbidity was 24 %, and longer term complications would afflict 42 %. Ultimately, 4 % of these patients died because of BDI. As noted by Saxon Connor of New Zealand in his highlight, "the results make sober reading." But Sax's heart rate justifiably increases as he makes a call to action by us all against the catastrophe that is BDI. Don't wait idly for these same results to occur again and again, but rise up and truly work to improve the standards and performance of cholecystectomy.

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In a chapter rich with detail, logical advice, and useful technical options, Dr. Jeff Barkun answers this call on behalf of non-biliary surgeons. Dr. Barkun is Professor of Surgery and Head of General Surgery at McGill University in Montreal, Quebec and certainly a global figure in HPB Surgery. Dr. Barkun establishes for the reader the epidemiology of BDI, and then considers their mechanisms as related to risk factors and errors in technique, and their classification. Next, he coaches on how to recognize if a BDI has indeed occurred and what to do in that miserable acute setting. He stresses the need to recognize one's limitations, emphasizing that drainage, stabilization and referral to a specialty center is the best option. Dr. Barkun explains very clearly the technical elements and overall procedural strategies for avoidance of BDI including recognition of aberrant anatomy, the use of cholangiography, the critical view of safety, and perhaps most importantly, the purpose and honor of a low threshold for conversion to open cholecystectomy. Finally, he provides readers with a list of practical recommendations to consider before embarking on any LC.

It really is a terrific, practical and highly informative chapter. I suggest you read it start to finish once, regroup then immediately read it a second time. I got so much more during my re-read as Barkun has truly created a unifying theme of Prevention. Upon that theme, everything he says makes so much sense, and most importantly, is achievable. My commentary will begin with a fascinating vignette about a historically significant BDI, and then offer my perspectives on several aspects of prevention highlighted by Dr. Barkun. Finally, I'll hope to bring you up to speed on some contemporary paradigms of standardization and training. That's where things seem to be heading.

It was jaundice, recurrent abdominal pain, and gallstones that brought Robert Anthony Eden to the operating theatre of St. Bartholomew's Hospital on April 12, 1953. From a birth into gentry, an Eton education, service in World War I, to the position of youngest Foreign Secretary in UK history, Lord Anthony was presumed the heir apparent to Winston Churchill as Prime Minister (Fig. 23.1). But his luck and that of his surgeon Basil Hume changed that Sunday. It was a challenging cholecystectomy with considerable bleeding, a prolonged anesthetic followed by bile leakage and jaundice post-operatively. Richard Cattell of Boston's Lahey Clinic by serendipity was lecturing in London and asked to consult. He insisted reoperation was necessary for the BDI, but in Boston. Churchill resisted, mandating London. Cattell explained the enormity of the injury and re-operation required and Churchill relented. Eden would survive and recover but with complications and reoperations. History suggests his compromised health severely impacted his handling of the Suez Canal Crisis as Prime Minister in the 1950s. And so, a political luminary suffers a BDI which has geopolitical consequences felt for decades.

This historical vignette illustrates critical features of BDI discussed by Dr. Barkun which I should highlight further. Disease severity and anatomy are very important risk factors. BDI are more likely to occur during difficult LCs, no different than with open operations. When LC is performed for acute cholecystitis, BDI occur three times more often than during elective laparoscopic cases, and twice as often compared to open cholecystectomy for acute cholecystitis. Aberrant anatomy is common and indeed contributes to BDI. For example, aberrant right hepatic duct

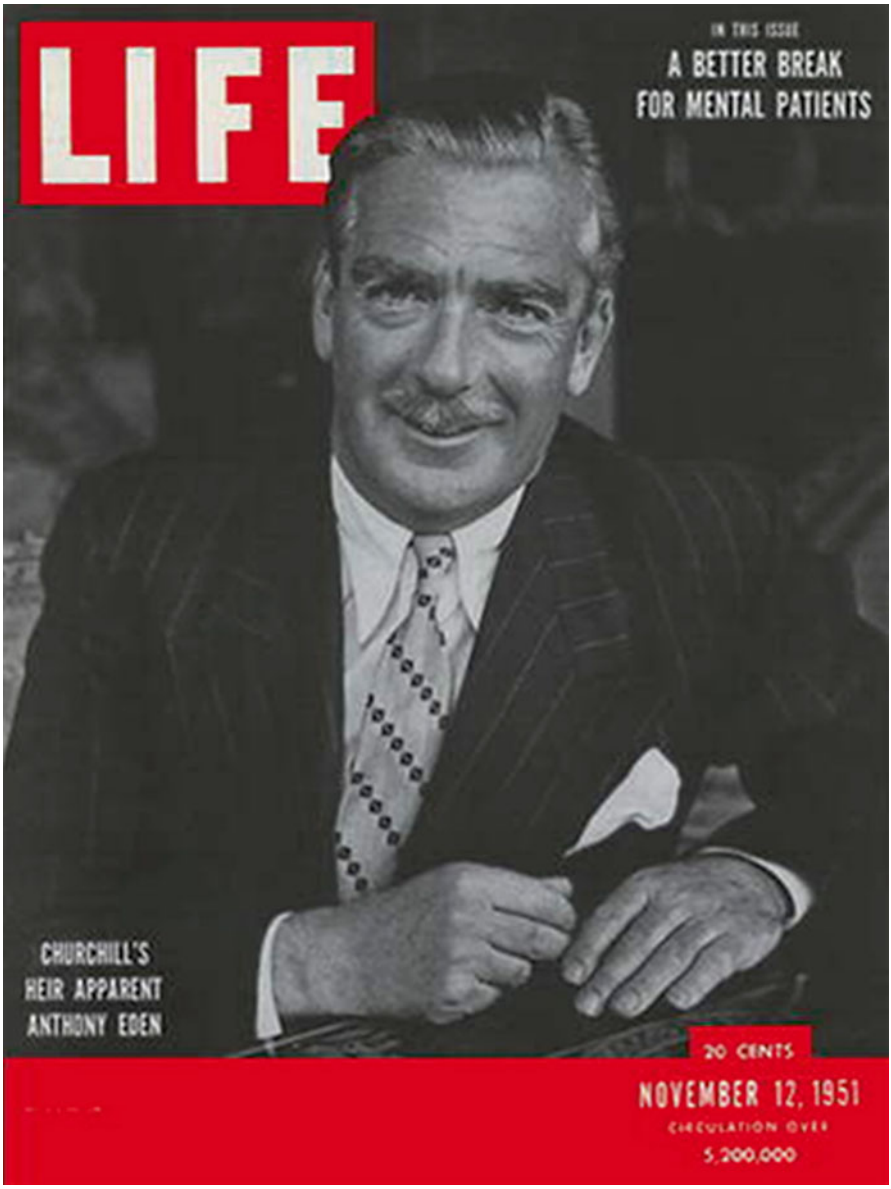

Fig. 23.1 Lord Anthony Eden before BDI catastrophe

anomalies are commonly highlighted in injury reports. Routine intraoperative cholangiography (IOC) is a valuable adjunct to dissection, and as noted (Flum) is actually associated with lower BDI rates. It can reduce the incidence of biliary injuries, or at least their severity. Nothing though replaces a meticulous dissection of anatomy to the Critical View of Safety. The infindibular technique should be avoided as noted by Dr. Barkun.

At times, the best approach is prompt conversion to open surgery. In your operative note, you can emphasize your decision in terms of judgment, prevention and safety. If you're like me, you'll depend on the "20-minute rule." With experience, you will know the progress you should be making. If you are not progressing, convert in a controlled fashion. Be sensitive to the needs of the whole OR team to optimize the open cholecystectomy, and realize what lay ahead will be difficult. Don't delay and get into bleeding, bile and stone spillage, injury to the liver or other viscera, protracted anesthesia, or worse, BDI. It simply makes no sense. Look at imaging carefully in advance, gauge the challenge, and then examine the RUQ once under anesthesia. If you palpate a big hard gallbladder, odds are very much against you for an LC. Be prepared.

Is conversion as easy as it seems? Perhaps for some, but certainly not all. The reality is that open cholecystectomy has been far less frequently performed over these past 15 years. Trainees during that period presumably received valid instruction and proctoring for LC, but rarely for open cases. Established surgeons needed to command the laparoscopic operation to compete, all the while potentially diluting their comfort with the open variant. Finally, there is the pressure and patient expectation for rapid recovery. Two very different operations lead to two scenarios which, though not proven, could subtly account in part for static biliary injury rates. Because of inexperience, the surgeon ignores or resists the sensible default option to convert, does not and incurs injury. In other instances, the surgeon overextends laparoscopic experience when disease severity warrants conversion, and incurs injury. The medico-legal consequences of surgeon experience have recently been analyzed by SAGES past-president Steve Schwaitzberg, et al. [2].

What can help prevent this? First, during informed consent, patients need be fully aware that open cholecystectomy is always a possibility. If faced with acute or chronic cholecystitis at operation, the best surgeon will seek help rather than persist on marginal laparoscopic or open cholecystectomy experience. During training, these dictums for safety will be reinforced during every gallbladder case, and if available, technical elements taught and refined through inanimate videotrainers and simulation modules before actual patient care [3].

Even more will be required, and we can look beyond surgery for guidance. Steven Strasberg, a thought-leader on biliary injury prevention strategy, recommends "changing the culture of cholecystectomy." He invokes a stopping rule mentality, something common in industry. This means that once danger arises, clearly defined rules are applied to stop a process before it enters any zone of great danger. He provides tangible examples from aviation to argue that similar safety measures are possible and warranted during cholecystectomy. He exposes common zones of danger in the difficult cholecystectomy revealing how risks can be controlled using stopping rules. After all, this is usually benign disease.

Training through formal educational programs such as Fundamentals of Laparoscopic Surgery (FLS) as offered by SAGES and the American College of Surgeons should be pursued so surgeons can optimally refine their skills. One could argue that credentialing might even pivot to some degree off such validated curricula. Beyond didactics and skill-set training, the question arises whether these truly

matter at the moment of truth—the actual operation? There is also increasing scrutiny over the value of contemporary simulation-based training models, especially in light of how expensive and resource intensive simulation can be. Dawe et al. [4] provide a comprehensive systematic review which informs this issue. Using strong data, they show that simulation-based training indeed results in skills that are transferable to the operating room for LC and endoscopy. They extend recommendations that simulation is a safe, effective, and ethical manner to get entry surgeons LC trained before that moment of truth. One can but imagine both the implications and opportunities this infers for surgical training going ahead.

SAGES convened its Safe Cholecystectomy Task Force with a charge to improve safety in LC and reduce BDI. They now provide an expert Delphi consensus [5] aimed at identifying future directions for process improvement, training and research towards this goal. They present 39 factors for safe practice in LC agreed upon through a nominal group technique process. They cover technical, nontechnical and perioperative domains and most have been highlighted by Dr. Barkun. It is an excellent paper absolutely worth your time to read.

Today, some argue convincingly for procedural standardization in performing each and every LC. In essence, the surgeon understands, accepts and follows a checklist of technical steps while performing LC. After all, checklists are common across many different industries, and all agree they can enhance complex task completion, strengthen teamwork, and reduce error rates. And we all know they exist in surgery as highlighted by the World Health Organization surgical checklist and its favorable impact on surgical outcomes worldwide across quite varied settings.

Connor et al. [6] propose a succinct, easy to remember checklist for the performance of LC that emphasizes safely and reliably obtaining the critical view. When the checklist cannot be completed, or when the surgeon for whatever reason deviates from it, then alarms should go off. The procedure may well be entering a danger zone, and everyone involved (not just the surgeon) should activate "stop mentality." While some will not agree with all the proposed steps of this particular checklist (avoidance of cautery, IOC), the message can still be embraced. There are other examples of LC procedural standardization available in the literature all with the same motive of reducing BDI and fostering a culture of safe cholecystectomy. Take a look, build a checklist like these perhaps tailored slightly to you and your team, and move ahead.

Although BDI has cast its cloud on LC, millions individually and societies worldwide have benefited from this historic advance against gallbladder disease. In fact, LC sparked the fire that today is minimally invasive surgery. We must preserve these benefits. But still, based on estimates of 800,000+ such operations in the USA next year, we can expect 3000 or so new BDI to occur. All agree that is unacceptable. We must continually assess measure and mandate clinical competency for this operation. As I've highlighted, this will necessitate new paradigms in training and procedure standardization. We will also need meaningful medical error tracking, credentialing and transparent outcome reporting, all designed to optimize patient safety. BDI is a lingering healthcare and financial disaster sorely in need of a lasting solution.

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Chapter 24
Management of Bile Duct Injuries Within the First Forty-Eight Hours

Robert H. Hollis and John D. Christein

Introduction

The reemergence of bile duct injury (BDI) in the literature has followed the rapid increase in number of a laparoscopic cholecystectomies performed. In the 1990s, rates of BDI in laparoscopic cholecystectomy were reported between 0.4 and 0.6 % vs. 0.06 % in patients undergoing open cholecystectomy [1–5]. Though rates of BDI have decreased as laparoscopy has become the standard approach for cholecystectomy, a significant rate of BDI still occurs. From years 2000 to 2009, BDI rates were estimated at 0.3 % [6, 7]. Comparison between open and laparoscopic approaches is now biased by the infrequent use of the open procedure and selection for cases not amendable to laparoscopic intervention [8]. If not managed properly following BDI, patients are at significant risk from several physiologic sequelae, including intra-abdominal fluid collections, cholangitis, and hepatic dysfunction. These complications can culminate in severe sepsis and hepatic failure that lead to excessive morbidity and mortality as well as costs [5, 9, 10].

The first step in management of BDI is early recognition of the injury, yet achieving diagnosis within the first 48 h of injury has been proven difficult. Early recognition is instrumental in minimizing the complications associated with BDI. Once diagnosis is identified, steps should then be taken to determine biliary anatomy as well as refer to a hepato-pancreato-biliary (HPB) specialist. Importantly, it is the complications and their sequelae that will determine the appropriate timing of BDI

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repair. Intra-abdominal fluid collections will need to be drained, infections will require antibiotics, malnutrition must be addressed, and intra-abdominal inflammation may often delay the appropriate timing for formal biliary reconstruction. Given these key management principles, the first 48 postoperative hours following BDI is a critical time period for physicians to attain diagnosis and begin appropriate interventions to maximize chances for a successful early repair.

Patient Presentation

It has been unlikely for BDI to be identified during the index operation; between 68 and 87 % of patients with BDI will not be diagnosed until the postoperative setting [11–18]. In one cohort of 307 patients with BDI after laparoscopic cholecystectomy, only 28.9 % of cases diagnosed postoperatively were identified within 1 week of the index surgery [12]. Many factors can contribute to the delay in diagnosis. The laparoscopic cholecystectomy has become largely an outpatient procedure associated with routine protocols [19, 20]. Operative notes, discharge medications, and discharge instructions all likely follow a standard protocol. Further, when patients contact surgeons or their staff following discharge, routine responses may be given to complaints of mild nausea and pain. Given the frequent delay in BDI diagnosis, there is a need for higher vigilance in the immediate postoperative period.

Two common clinical scenarios should raise biliary injury into the clinician's differential when the patient presents in the first two postoperative days following cholecystectomy. In the first scenario, the surgeon experiences a difficult cholecystectomy and chooses to admit the patient for further observation. The degree of operative difficulty may be related to inflammation, bleeding, or anatomical variance that distort visualization and often leads to intraoperative uncertainty. In many of the cases, the primary surgeon may have chosen to convert from laparoscopic to open or leave a drain in the gallbladder fossa. On postoperative day one or two, the patient develops nonspecific signs and symptoms of abdominal pain and nausea with mild abdominal discomfort on exam.

While nonspecific, these clinical signs should prompt the possibility of BDI and any bilious drain output should raise definite suspicion. Of 151 patients referred for BDI repair in the Netherlands, initial diagnosis occurred postoperatively but during the initial hospitalization in 41 % [21]. Others have shown that the majority of patients discharged home that were later diagnosed with BDI had reported the presence of concerning symptoms during the index hospitalization [14]. Given the lack of evidence for routine cholangiography in preventing bile duct injuries, the rare use of cholangiography may lead to recognition of BDI more often in this postoperative period [7]. Even in cases where intraoperative cholangiography was performed, videotape review has shown that BDI cannot be ruled out in the postoperative setting due to error in operator interpretation or cholangiogram catheter placement [17, 22].

The second scenario involves a patient that is discharged home following uneventful cholecystectomy and subsequently contacts the surgeon or returns to the

emergency room with nonspecific symptoms of abdominal pain, nausea, anorexia, or fatigue [23]. These patients may not have developed any overt physical exam findings of jaundice and can show only mild abdominal discomfort on exam [13]. Again, these nonspecific signs should not be disregarded as benign and should be fully evaluated with the notion that a bile duct injury is possible.

These subtle clues are sometimes the only clinical information that will trigger the workup for BDI patients. Cholangitis, severe sepsis, or signs of peritonitis are unlikely to be presenting signs of patients with BDI during the first week [12–14, 21]. The outpatient origin of BDI diagnosis may be affected by pressure from reimbursement measures that use standardized assessment of medical necessity to qualify for in-patient hospitalization. The significance of BDI diagnosis in immediate postoperative setting is highlighted by the focus in malpractice cases. Delay in diagnosis of injury or complication is one of the most common causes of litigation following cholecystectomy and can lead to significant plaintiff payouts [24, 25]. Therefore, while BDI represents a rare event post cholecystectomy, clinical suspicion should develop early when patients present with postoperative signs or symptoms outside of the normal clinical course.

Diagnostic Work-Up: Initial Laboratory and Imaging Studies

In patients with post-cholecystectomy complications, diagnostic work-up should focus not only on defining the complication but also determining the extent of physiologic sequelae that have manifested as a result of the complication. These sequelae must be addressed in order to achieve clinical improvement. Laboratory workup should cover basic metabolic abnormalities, measures of hepatic and biliary dysfunction, nutritional markers, and systemic markers of infection. Laboratory results may show beginning signs of hepatic dysfunction such as transaminitis and hyperbilirubinemia [23]. Laboratory information alone will not define the complication. Further imaging is necessary to (1) assess for intra-abdominal fluid collections, (2) define biliary anatomy and patency, and (3) in select cases rule out hepatic vascular injury.

No specific order of imaging studies has been evaluated in the workup of BDI patients, yet the procedure-based nature of cholangiography may favor initial imaging for intra-abdominal fluid collections. Post-cholecystectomy intra-abdominal fluid collections can represent biloma, abscess, or hematoma. Biloma or abscess is a herald sign that a BDI may be present. Computed tomography (CT), ultrasound, magnetic resonance cholangiography (MRCP), or cholescintigraphy (HIDA scan) have been utilized to identify bilious fistula. HIDA scans, as opposed to CT, MRCP, and ultrasound, will not be able to determine the presence of abscesses. The usefulness in HIDA scans in assessing bile duct fistula may be limited to select circumstances such as determining the persistence of bile duct leak [23]. Though associated with significant cost and radiation exposure, CT imaging is often the preferred initial imaging modality for evaluation of BDI patients [26]. CT imaging has been

shown to have superior sensitivity (96 %) compared to ultrasound (70 %) or HIDA scan (64 %) for diagnosis of bilious ascites in the postoperative period [14]. In comparison, MRCP can reveal enhanced biliary anatomy with 95 % sensitivity for BDI as well as diagnose intra-abdominal fluid collections that would need to be addressed [27]. Thus MRCP can also be considered for initial imaging in evaluation of patients with concern for BDI.

Once fluid collections are identified, pursuit of drainage procedures is a key factor associated with successful BDI repair [12, 15]. Initial CT imaging will not only provide information about the presence of intra-abdominal fluid collection, but also will deliver information regarding approaches for interventional radiology to perform percutaneous drainage procedures as well as information regarding vascular patency and hepatic perfusion if arterial phase contrast is administered. In select cases BDI patients may present with diffuse biliary ascites, and percutaneous approach will provide insufficient drainage. For this situation, laparoscopic washout with drain placement will be indicated to minimize inflammation as well as infectious sources prior to biliary reconstruction.

Diagnostic Work-Up: Cholangiography

The multidisciplinary management of BDI patients is highlighted by the frequent need for percutaneous drainage procedures and by the critical role of complete cholangiography to define biliary anatomy. Cholangiography can be performed via endoscopic retrograde cholangiopancreatography (ERCP), MRCP, or percutaneous transhepatic cholangiography (PTC). MRCP is limited by lack of therapeutic capabilities in relation to ERCP and PTC. For all BDI, HIDA cholangiography alone will not be able to deliver the anatomical specificity needed to direct management. However, in the community setting, MRCP or HIDA may be the only tools readily available to determine the presence of a BDI and should be employed if necessary. If concern persists despite these tests, transfer to a facility with ERCP and PTC capabilities should be sought. Given availability of all modalities, we recommend initial evaluation with ERCP.

ERCP performed by a skilled endoscopist for symptomatic patients post cholecystectomy can play diagnostic and therapeutic roles. ERCP can differentiate between retained gallstones, cystic duct leaks, tumors causing biliary obstruction, and bile duct transections or stricture [22]. Therapeutic sphincterotomy, gallstone retrieval, and/or stent placement may be performed for retained gallstones, stricture, and compressive tumor [28]. In the case of Strasberg level A or D injuries, which include cystic duct leaks or lateral bile duct injuries, ERCP with endoscopic stent placement will allow the injury to heal with no need for further operative intervention [23, 29]. When ERCP identifies only distal biliary anatomy, PTC must be pursued to further define the injury as illustrated by Strasberg classification. In a patient with Strasberg type E1–5 injury, or complete bile duct transection, ERCP will show a blind end of the inferior bile duct with non-opacification of intrahepatic ducts;

PTC will be necessary to delineate the proximal extent of injury and will additionally offer proximal biliary drainage.

Lack of complete cholangiography has been shown to be associated was poor long-term success rates in bile duct repair [12, 15]. The potential harm of bile duct repair without cholangiography is illustrated by the case where a hasty surgeon pursues reoperation in a post-cholecystectomy patient found to have biloma with the assumption that the bile fistula is from a cystic duct stump or accessory duct leak that is in reality a common hepatic duct injury. Over sewing of the assumed incorrect structure due to lack of cholangiography would lead to a poor postoperative course in this patient [15]. In the case of high biliary injuries, bilateral PTC may be necessary to identify the location of the injury in relation to right and left hepatic ducts as well as injuries involving small ducts such as right posterior sector duct or an aberrant caudate duct. In such cases where only one lateralized PTC was placed, biliary reconstruction may not include a high injury on the hepatic duct opposite the PTC drain and inevitably lead to persistent bile duct fistula requiring subsequent reoperation.

Diagnostic Work-Up: Arteriography

Due to the proximity of the right hepatic artery to the common bile duct and right hepatic ducts, the right hepatic artery has been subjected to significant rates of injury in patients with BDI. Studies have found between 10 and 32 % of patients with BDI will have a concomitant hepatic artery injury, with the right hepatic artery most often implicated [12, 30–33]. Patient who are referred after failed management by the primary surgeon have illustrated even higher rates of concomitant hepatic artery injury [34]. The Strasberg level of injury is associated with the rate of hepatic artery injury; in a cohort of 28 patients with right hepatic duct injury, 18 (65 %) patients also had right hepatic artery injury suggesting the right hepatic artery may have been confused for the cystic artery [30]. Because of this high rate of rate of arterial injury, the role of routine arteriography by ultrasound, arterial phase CT angiography (CTA), or catheter-based angiography has been proposed.

Patients with BDI and hepatic arterial injury have higher rates of intraoperative or postoperative bleeding, hemobilia, abscess formation, and hepatic ischemia necessitating hepatectomy compared to patients with BDI alone [30]. In addition, there is concern that hepatic artery injuries may affect the long-term success rate of biliary reconstruction repairs due to poor arterial collateralization of the supraduodenal bile duct [34, 35]. Ischemic changes could impair biliary patency through anastomotic leaks or biliary strictures. Late hepatic necrosis could lead to abscess requiring drainage following an early BDI repair [32, 34–36]. When compared to patients with BDI alone, success rates of BDI repair in patients with right hepatic injury were significantly worse when performed by the primary surgeon. However, this difference was not seen when biliary specialists performed the repair [30]. The benefit of hepatic artery reconstruction is yet to be fully determined, but delivers

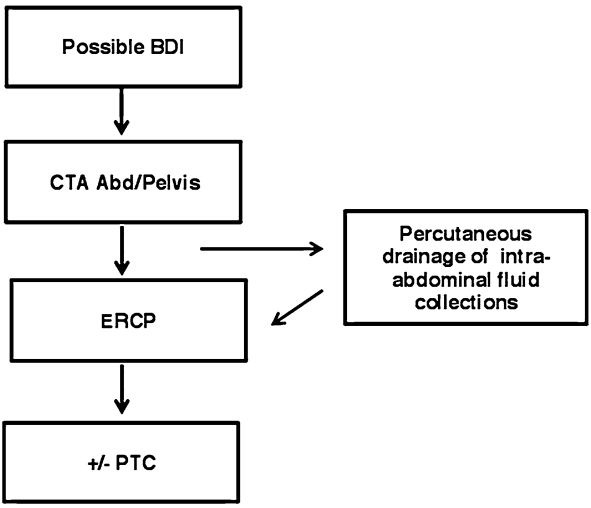

Fig. 24.1 Example of imaging sequence in work-up of patient with possible BDI

1. Pre-operative drainage of intrabdominal fluid collections
2. Complete cholangiography
3. Repair by HPB specialist
4. Surgical technique

Fig. 24.2 Key factor associated with successful BDI repair [15, 37, 38]

the most potential when the repair can occur within the first 48 h of injury [35]. Given these implications, further investigation of arterial injuries should be sought in BDI patients with high biliary injuries or when the primary surgeon conveys concern for vascular injury through anatomical uncertainty or amount of bleeding during the index operation. Use of triple-phase CTA during initial evaluation imaging of BDI patients can simultaneously diagnose this potential complication. An example of an imaging algorithm for work-up of patients with possible BDI patient is illustrated in Fig. 24.1.

Role of Early HPB Specialist Referral

Key factors shown to be associated with successful BDI repair, defined as durable restoration of biliary continuity, include preoperative biloma or abscess drainage, complete cholangiography, surgical repair technique, and repair performed by a biliary specialist (Fig. 24.2) [15, 37, 38] Success rates among 307 BDI patients undergoing initial BDI repair by biliary specialist were 91 % vs. 13 % in those

undergoing repair by the primary surgeon [12]. Patients with BDI injury repaired by the primary surgeon show higher postoperative rates of biliary stricture, cholangitis, need for subsequent intervention, as well as overall morbidity and mortality measures [5, 31]. Repair of BDI by biliary specialist has been shown to be more cost effective and associated with decreased length of patient symptoms. [10, 15]

Early referral of patients diagnosed with BDI to biliary specialist not only delivers specialized clinical expertise but also gives emotional detachment from the primary surgeon and may decrease potential litigation by avoiding association with further complications [25]. Despite these implications, review of Medicare beneficiaries from 1992 to 1999 found that 75 % of BDI repairs were performed by the primary surgeon [5]. Survey of surgeons in British Columbia in 2002 found that only 40 % sought HPB referral after a patient was diagnosed with BDI [39]. While surgeons may feel obligated to deal with the complications their patients experience, the obligation to provide the best possible outcome requires early HPB referral. The expertise of HPB specialist is now highlighted by an accredited fellowship. The correct time to arrange for transfer to biliary specialist is as soon as BDI diagnosis is made [40]. Further diagnostic or therapeutic interventions at the referring hospital should be limited to those necessary to minimize complications while awaiting transfer [18].

Early Versus Late Repair

Evidence regarding the appropriate timing for operative repair of BDI has produced controversial results. Proponents of delaying repair of BDI up to or beyond 6 weeks from the index injury procedure state that this time period is necessary for inflammation and infection to regress and is crucial for durable BDI repair. Inflammation may blur ischemic limits or impair dissection in the hilar plate necessary for high bile duct anastomosis. Delaying BDI repair may also allow for biliary dilation to make for a technically easier anastomosis and also allow for evolution of any hepatic ischemia secondary to hepatic artery injuries [13, 31]. Advocates for early repair of BDI state that that this will minimize the morbidity that patients experience while awaiting repair as well as eliminate their potential to develop new complications. Importantly, they argue that the inflammatory response around the hepatic hilum will be low enough within 72 h of the index procedure that a repair can be successfully completed with good long-term results [13].

Variations in time intervals to BDI repair across studies have explained some of the differences observed. While three studies have shown that time to BDI repair did not make a difference, one study of 151 patients with BDI found that repair undergone less than 6 weeks from injury was associated with higher major complications rates [11, 12, 16, 21]. These complications included higher rates of long-term anastomotic stricture [21]. The authors hypothesized that the complications were driven by persistent perihepatic inflammation or infection and that repairs undergone in the period within 72 h of biliary injury should be further examined. Smaller follow-up

studies confirmed that repair within 72 h post-injury was associated with improved outcomes including biliary stricture rate, extended ICU stay and intra-abdominal abscesses compared to longer delays from injury to repair [13, 18].

One important source of bias in the analysis of time to BDI repair is the delay that occurs when patients are transferred to a biliary specialist. A significant difference between biliary surgeons and primary surgeons in BDI reconstruction is that repair by biliary surgeons is associated with a longer delay from BDI diagnosis to operative repair in patients who present with severe symptoms such as cholangitis, abscess, peritonitis, or shock. This can be indicative of appropriate preoperative diagnostic and therapeutic interventions including fluid collection drainage as well as complete cholangiography, which are strongly associated with successful BDI repair. When multivariate analysis was applied, time to repair of BDI was not associated with success rates in initial BDI repair [12]. Contrarily, study of 112 BDI patients who only underwent biliary reconstruction performed by a biliary specialist found that repairs greater than 21 days from injury were associated with increased reoperations and overall morbidity [31].

Given these findings together, the timing of BDI repair must be individualized for each patient [41]. When patients are diagnosed with BDI, referral arrangements to an HPB specialist should be made immediately. The patient should be evaluated for intra-abdominal fluid collections and complete cholangiography should be performed. If fluid collections or bilious ascites are present, the patient should undergo the appropriate drainage procedures. Following drainage procedures, BDI repair should be delayed up to or beyond 6 weeks to allow inflammation and infection to regress. If the patient does not illustrate intra-abdominal fluids collections, has minimal metabolic disarrangements, and possesses the appropriate physiologic reserve, immediate repair may be undertaken by a HPB specialist.

UAB Experience

BDI referrals to the UAB HPB service come mostly from statewide community hospital settings. Referral is made largely in the postoperative period after cholecystectomy when fluid collections are found, but occasional intraoperative consults from primary surgeons do occur. Upon arrival to our institution, patients undergo laboratory work-up for metabolic abnormalities, hepatic and biliary function, as well as nutrition and infectious markers. Immediate imaging consists of triple-phase CT to identify intra-abdominal fluid collections, hepatic arterial patency, and any evidence of hepatic ischemia. Our next goal is to define biliary anatomy. Cholangiography is first performed through consultation with gastrointestinal medicine colleagues for ERCP diagnostic and potential therapeutic capabilities. For Strasberg level E injuries, where proximal biliary anatomy is incomplete, interventional radiology is consulted for PTC and drains are left in place. When drainage from bilateral hepatic ducts is unclear, bilateral PTC drains are pursued. If intra-abdominal collections are present, percutaneous drainage is performed and

antibiotics therapy initiated as appropriate. Cases that present within 72 h of injury with no need for drainage procedures and minimal complications will be considered for early biliary reconstruction. Arterial reconstruction is considered on a case by case basis. Otherwise biliary repair is delayed for 6 weeks with focus on nutritional support and antibiotic therapy during the intervening time as indicated.

Conclusions

Patients with BDI often present with only vague symptoms of nausea and abdominal discomfort in the first 48 h following injury. High clinical suspicion is necessary for early identification of injuries. Laboratory workup should assess for metabolic abnormalities, hepatic function, nutritional parameters, and signs of infection. Imaging should include evaluation for intra-abdominal fluid collections, complete cholangiography, and arteriography for select cases. All intra-abdominal biloma or abscesses should be drained to alleviate infection and inflammation prior to BDI repair. Patients should be transferred to HPB specialist as soon as BDI has been diagnosed. Immediate biliary reconstruction may be pursued if no drainage procedure is required and the patient is physiologically fit. When drainage procedures are required, infection is present, or inflammation is excessive, BDI repair should be delayed up to or beyond 6 weeks.

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Chapter 25
Commentary: Management of Bile Duct Injuries Within the First Forty-Eight Hours

Miguel Mercado

Bile duct injuries are mostly detected in the postoperative period. Only around 20% are detected intraoperatively; thus, the decision for early or late repair is a matter of concern.

One of the issues of intraoperative repair (i.e., at the operation in which the injury occurred) is related to the level of the bile duct anastomosis. Some groups advise to wait before performing the repair considering that ischemic damage to the ducts needs to fully settle [1]. At the index operation, it is also difficult to assess the circulatory status of the ducts. This is why we recommend that the repair should be done as high as possible (higher than the confluence, towards the left duct); this would allow the surgeon to do the procedure on the best-quality bile ducts available given the injury.

Another important concern is related to the injuries of the right hepatic artery [2]. Injuries to the whole right hepatic vessels are extremely rare, but isolated injuries to the right hepatic artery are not uncommon. The higher the bile duct injury takes place, the more probable it is to present a right hepatic artery injury. One of the main problems of this vascular injury is that it is not only caused by the section and/or interruption of the vessels, but also by the ablative injury, just as it occurs with the bile ducts. Repair of the artery is demanding and few procedures have been done using autologous interposition grafts and/or rotation of branches of the celiac artery.

In our experience, it is not necessary to repair the artery. Suprahiliar collaterals develop and usually the arteries have retrograde flow, favoring the development of collaterals. High repair also prevents dysfunction of the anastomosis related to late ischemic injuries of the duct [3].

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We promote the early repair of the bile duct injuries. We have previously shown that the results of early and late repair are comparable, and without doubt, early repair has several advantages for the patient, as well as economical repercussions [4]. Leaving patients with external drains for weeks or months, needing hospital care and periodic changes of the drainage, is expensive and demanding. Some of them develop cholangitis, secondary colonization of the bile, developing sludge and stones that affect the long-term results of the reconstruction.

We advise an early repair if the patients do not have systemic sepsis and/or refractory cholangitis, as well as multiorganic failure. Some of the patients need percutaneous drainage of collections and/or biliomas, limited laparotomies and, in some instances; they arrive to the hospital with severe damage to the abdominal wall. By individualizing each patient, as stated by Hollis and Christein, we promote an early repair of the injuries, performing in all cases a high repair.

One of the main concerns for HPB surgeons is to elucidate why a hepatojejunal anastomosis done with all the requirements of a high-quality bilioenteric anastomosis (nonischemic ducts selection, wide and tension-free anastomosis, usage of fine absorbable stitches (5-0) that prevent inflammatory and/or granuloma development) may have postoperative dysfunction in a minority of cases. It has to be accepted that bilioenteric anastomosis is "contra natura." The apposition of the epithelium with the mucosa causes a fibrotic ring that may suffer stenosis and/or closure. The presence of lithiasis (micro or macro) secondary to colonization of the bile, as well as other yet to explore issues (fatty infiltration of the ducts in patients with metabolic syndrome, autoimmune responses, cholangitis, etc.) are also a cause of anastomotic dysfunction. Leaks may also play a role in the late development of stenosis because of early perianastomotic inflammatory reaction. This can be prevented by adequate and symmetric placement of sutures, and in some instances this case may require a transhepatic stent to reduce bile duct pressure at the anastomotic level.

All these scenarios must be considered by the surgeon. If the surgeon has experience in bile duct injuries and feels comfortable (physically and psychologically) to do the repair at the index operation, following the rules of a high-quality bilioenteric anastomosis, this procedure is the best choice [5]. In the scenario where the surgeon chooses only to place drains and refer the patient swiftly (probably the best decision for a surgeon unfamiliar with bile duct reconstruction), arriving in the first postoperative repair, an early repair is indicated if no systemic inflammatory response is found, uncontrolled sepsis and/or multiorganic failure.

If a patient has also organ damage (duodenum, colon, etc.), generally characterized by peritonitis, we advice to place percutaneous transhepatic drains and do the repair after the duodenal, colonic, or sometimes small bowel damage has been controlled [6]. Some of these cases have also abdominal wall damage; some other ones need multistage plan for repair.

After identification of the injury, a multidisciplinary approach is advisable. Individualization of the cases, combined with the center's experience (this is why cases have to be referred), can offer the best solution for these unfortunate and complex cases [7].

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Chapter 26
Endoscopic Management of Bile Duct Injury During Laparoscopic Cholecystectomy

Guido Costamagna and Ivo Boškoski

Introduction

Every year in the USA more than 750,000 laparoscopic cholecystectomies (LC) are performed [1]. LC offers many advantages over open cholecystectomy. Among them are less pain and less wound infections, decreased activation of inflammatory mediators, improved cosmesis, and reduced hospital stay. Because of these advantages, in the past two decades LC has rapidly and largely replaced open cholecystectomy for the management of symptomatic gallstone disease. The only potential disadvantage of LC is the higher reported incidence of major bile duct injuries (BDI). It is impossible to estimate the real incidence of iatrogenic injuries of the bile ducts during LC, but it is calculated that it has increased by two to three times (between 0.2 % and 1.7 %) with its advent [2, 3].

BDI are mostly due to misidentification of anatomic structures during LC, excessive use of electrocautery, adhesions in the gallbladder fossa, inaccurate placement of sutures, ligations, and extensive placement of clips [4].

Intense inflammation has been identified as an independent risk factor for the onset of BDI, and some authors recommend conversion to open surgery when this condition is encountered [5, 6].

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Surgical repair was the treatment of choice for BDI in the past, while ERCP was limited to its diagnostic role to better understand the site and extension of the injury [7]. Obviously, after establishing of ERCP as a pure operative tool the respective roles have radically changed.

Postoperative BDI have been classified by Bergman et al. [8] in four types: *Type A* cystic duct leaks or leakage from aberrant or peripheral hepatic radicles, *Type B* major bile duct leaks with or without concomitant biliary strictures, *Type C* bile duct strictures without bile leakage, and *Type D* complete transection of the duct with or without excision of some portion of the biliary tree.

Clinical Features and Diagnosis

Early BDI are those that present within 1 week from surgery, and represent about 10 % of all post-cholecystectomy injuries [9]. The injury is frequently recognized during LC often as a result of unintentional clipping, ligation or section of the common bile duct, and may or may not be associated with biliary leaks. Patients may present with pruritus, jaundice, abdominal pain and fever, or only with alteration of liver function tests (LFT). If a biliary leak is present, bile can be found in surgical drainages or there can be evidence of biliary intra-abdominal collections.

The vast majority of BDI (70–80 %) becomes symptomatic after weeks or months after LC [10], when the injury has evolved into a stricture.

Bile duct strictures (BDS) at distance from LC typically occur at the site of unrecognized minor BDI of the ducts without an associated leak. The clinical presentation can be with pruritus, jaundice, abdominal pain, alteration of LFT, and recurrent cholangitis. If left untreated, these injuries can lead to secondary biliary cirrhosis [11].

The Bismuth classification of post-operative BDS has been described before the advent of LC. The intent of this classification was to guide surgical repair, and has been well correlated with outcome after treatment [12].

According to Bismuth [13] there are five types of BDS. *Type 1:* located at the lower common hepatic duct or bile duct (>2 cm from the hilum); *type 2:* mid-common hepatic duct (<2 cm from the hilum); type 3: stricture located at the hilum; *type 4:* destruction of the hilar confluence (separation of the right and the left hepatic ducts); and *type 5:* involvement of one right hepatic branch.

Abdominal ultrasound can detect dilation of the intrahepatic biliary tree, which associated with elevated LFT and history of LC should lead to the suspicion of biliary injury. The most accurate noninvasive examination to depict the biliary anatomy, the site, and length of the stricture is MRCP with 3D reconstruction [14].

MRCP is very useful before ERCP as a treatment planning strategy tool. It can diagnose biliary leakage from the cystic duct or intrahepatic biliary tree, strictures, or the presence of bile duct stones or other pathologies.

In some cases also CT scan can be useful, especially for the determination of residual liver parenchyma function and assessment of liver atrophy in patients with long-standing biliary injuries.

Endoscopic Management

Endoscopic management varies on the basis of the type of injury, and the presence or not of biliary leakage and the time of onset, whereas management of strictures is mostly dependent on their complexity.

Management of Bile Duct Leaks

The most frequent type of early biliary leak is the one from the cystic duct, and is due to inaccurate cystic duct closure or clip displacement [15]. Delayed leaks are usually a result of thermal or vascular injury during dissection [16]. Suture failure due to high biliary pressure secondary to retained choledocholithiasis is a less frequent cause of leak.

Another cause of bile leak is the presence of a direct communication from the gallbladder to the right hepatic ductal system through the gallbladder bed (Luschka duct) [17, 18]. The best way to prevent biliary leaks and injuries during LC is to be aware of anatomical variations [19], which have to be recognized during the dissection of the gallbladder pedicle.

The main goal of endoscopic treatment of bile leaks is to depressurize the biliary tree by lowering the pressure gradient between the bile ducts and the duodenum at the level of the sphincter of Oddi.

This can be obtained with biliary sphincterotomy, associated or not with removal of retained stones, placement of a nasobiliary drain or of a plastic stent [20].

Complex biliary leaks are associated with strictures and/or loss of substance of the bile ducts.

Management of Bile Duct Strictures

The clinical history of the patient should be carefully evaluated before endoscopic treatment. The clinical suspicion of BDS should always rise especially in patients with elevation of LFT and a history of LC. For instance, the presence of many clips in the right hypochondrion on the plain X-ray may be an indicator of a difficult LC.

The “road map” MRCP is a very useful tool before ERCP that can literally guide the endoscopist to the best biliary drainage choice.

After endoscopic sphincterotomy it is essential to perform a good-quality cholangiogram in order to establish the type and site of the stricture. Strictures can be negotiated only if there is a continuity of the biliary tree (not in case of Bergman type D).

The cholangiographic appearance of BDS is quite typical: the stenotic tract is short, often asymmetric, and angulated. Furthermore, postoperative strictures are also often rich in fibrotic tissue. These features may make the guidewire negotiation through BDS very tricky and in some instances much more difficult in comparison to malignant strictures.

The choice of the wire for stricture negotiation is very important. It is preferable to use hydrophilic wire (0.035, 0.021, or 0.018-inch in diameter) with a straight or curved (J-shaped) tip.

ERCP in these patients should be done in referral centers with experienced endoscopists and assistants. Manipulation of guidewires is generally done by assistants. It requires a lot of patience, skills and optimal fluoroscopic imaging and it should be gentle in order to avoid false routes. During guidewire manipulation, it is important to have the direction of the catheter and the wire in the same axis of the stricture. In very angled strictures, this can be achieved by straightening the common bile duct below the stricture itself by pulling an inflated stone extraction balloon just below the stricture. Some steerable catheters can also be useful in certain cases to orientate the guidewire. At the very first treatment, in most cases it is enough to place at least one large bore (10 French) plastic stent.

Before plastic stents placement, pneumatic balloon dilation of the stricture can be required in certain cases. Pneumatic dilatation alone is highly effective but has up to 47 % of restenosis rate at long term [21–23].

Pneumatic dilatation, if needed, should be preferably done only during the very first treatment, and should be avoided during further procedures, especially in plastic multistenting procedures. Actually, the forceful disruption of the stricture may add further traumatic damage to the tissue and consequential development of a new exuberant fibrotic reaction.

Stents keep the stricture opened for a prolonged period, allowing scar remodeling and consolidation. In case the stricture has not been dilated enough to place a stent, insertion of a 5 or 6 Fr nasobiliary drain for 24–48 h is important to guarantee immediate biliary drainage. The nasobiliary drain acts as a mechanical dilator and at the next ERCP, stent placement is usually possible.

The choice of the type of stent is depending mainly on the type and site of the stricture. Stents can be plastic and fully covered self-expandable metal stents (SEMS). SEMS can be used in some circumstances for BDS in selected patients. Biodegradable biliary stents until now have been experimented only in animal models [24].

Currently, plastic stents are the mostly used for this purpose. Single-plastic stents have achieved unsatisfactory long-term outcomes [25]; therefore, today, the standard endoscopic approach for post-cholecystectomy strictures is the “aggressive multistenting strategy.” This consists in temporary simultaneous placement of multiple large bore plastic stents, over a period of 1 year [26, 27]. ERCP with stents exchanges is generally done every 3 months, with progressive increment of the number of stents at each ERCP, until complete resolution of the stricture at cholangiography (Fig. 26.1). Complete stricture resolution at cholangiography is defined as absence of any significant indentation at the site of previous narrowing.

This treatment has been found to be highly successful, with low recurrence rate. Furthermore, stricture recurrences are generally endoscopically retreated with high success rate [26, 27].

This aggressive multistenting approach consists in gentle and long-term “massaging” of the stricture, allowing it to adapt to the increasing number of stents and to avoid formation of exuberant fibrous tissue.

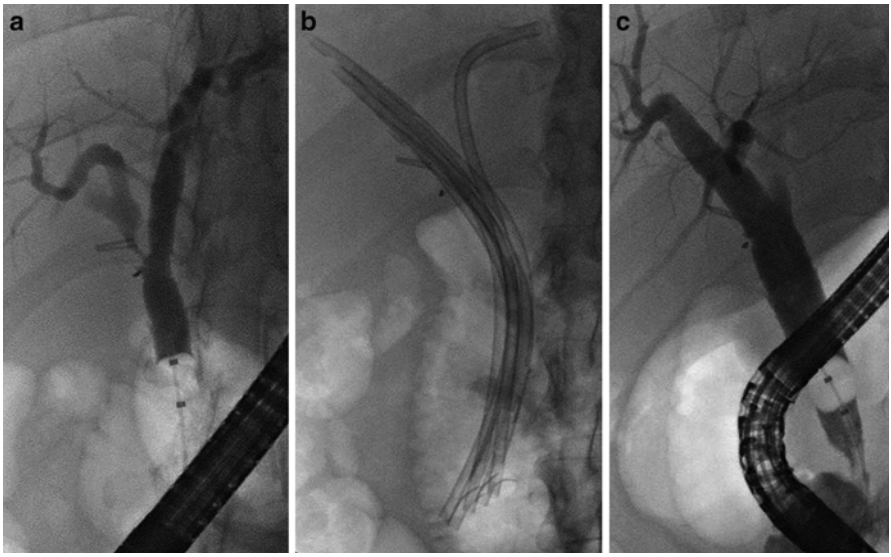

Fig. 26.1 (**a**) Bismuth type V stricture associated with biliary leak. (**b**) Stenting with multiple plastic stents (multiple sessions during 1-year period). (**c**) Final appearance after plastic stents removal

This approach is suggested also by the European Society of Gastrointestinal Endoscopy (ESGE) in the recently published clinical guidelines for endoscopic biliary drainage [20]. According to these guidelines, plastic biliary multistenting is technically feasible in >90 % of patients with highest long-term biliary patency rate in 90 % of postoperative biliary strictures [20].

Obviously, this approach is limited by the need of multiple ERCP sessions over the 1-year period, patient compliance and increased costs.

SEMS are an excellent tool for the treatment of malignant biliary strictures, and have also been increasingly used for the treatment of benign biliary strictures [28, 29].

SEMS must be fully covered and therefore removable if used in benign biliary strictures. Early dislocation and migration are the main problems related to covered SEMS. To overcome this, SEMS with flared ends have been designed [30, 31]. Another problem related to covered SEMS is that these stents can be used only in benign biliary strictures that involve the main bile duct and do not involve the hilum. In terms of costs SEMS are more expensive than plastic stents, but these costs are counterbalanced by the reduction in number of procedures required for plastic multistenting.

Outcomes of Endoscopic Treatment

More than 90 % of uncomplicated biliary leaks heal after biliary sphincterotomy or temporary drainage (nasobiliary drain or plastic stent) with removal of any potentially associated biliary stones [20]. In a limited case series Baron et al. have also

evaluated the use of covered expandable metal stents for closure of complex biliary leaks with good outcomes [32]. Hence, there is no discussion about the role of ERCP in the management of bile leaks, but there is still open debate about the optimal treatment of BDS.

Surgical repair has been the mainstay of treatment of BDS for long time. Today endoscopy is the first line treatment because its efficacy is comparable to surgery, but has lower rates of morbidity and mortality [33]. However, surgery remains available when endoscopy fails.

Good outcomes from endoscopic treatment with multiple plastic stents of BDS have been reported in many studies. In most of the studies, BDS were a consequence of different types of surgery (liver transplantation, open cholecystectomy, liver trauma, liver resections and laparoscopic cholecystectomy), with success rates ranging from 69 to 100 % (Table 26.1). Results of endotherapy are also influenced by the location of the stricture.

For instance, in the study by Draganov et al. a high success rate was achieved in patients with Bismuth type 1 or 2 strictures (80 %), and the lowest in type 3 strictures (25 %) [21].

Major complications of endoscopic multistenting are cholangitis, pancreatitis and stent migration, and are more common in patients who are non-compliant with the stent exchange protocol [20].

Stricture recurrences after endoscopic treatment do occur, however in most series the reported rate is low (Table 26.1), Tuvignon et al. [34], on the contrary reported a recurrence rate of 33.3 %. In this study, the persistence of a significant indentifica-

Table 26.1 Results of endoscopic management of postoperative bile duct strictures

Reference	Number of patients	Intervention type	Stenting duration months	Stricture recurrence %	Final success %	Length of follow-up (years)
Bergman et al. [27]	44	OC	NA	20.4	79.6	Median 9
Costamagna et al. [26]	35	MIXED	12	11.4	89	Mean 13.7
Kassab et al. [44]	65	LC	14	4.5	69	Mean 2.3
Kuzela et al. [45]	43	LC	12	0	100	Mean 1.3±0.9
De Reuver et al. [35]	110	LC, OC	11	10	74	Mean 7.6±2.9
Vitale et al. [46]	46	LC, OC	12	22	91	Mean 2.5±2.0
Tuvignon et al. [34]	96	LC, OC	12	33.3	82.3	Median 6.1

LC laparoscopic cholecystectomy, *OC* open cholecystectomy, *MIXED:*, *LC*, *OC*, liver transplantation biliary anastomosis, hepatic trauma with biliary repair, *NA* not available

tion of the bile duct on cholangiography at the time of stent removal was reported as a strong predictor factor of stricture recurrence. In a study by de Reuver et al. the independent predictors of outcome were the number of stents inserted during the first ERCP procedure, BDS classified as Bismuth III and IV, and endoscopic stenting before referral [35].

Canena et al. evaluated the cholangioscopic appearances of post-cholecystectomy BDS after endotherapy with an increasing number of plastic stents, and the predictive values of these appearances for the outcome [36]. The authors observed stricture recurrence only in patients in whom tissue hyperplasia was present at the end of a normal period of stenting with adequate calibration on cholangiography. Furthermore, after the second stenting protocol, there was resolution of epithelial hyperplasia in all cases. The authors concluded that the presence of hyperplastic tissue should be considered as a marker of instability and a logical predictor of active fibrosis of the bile duct stricture, which should lead to restricturing, despite a well-calibrated bile duct.

The main advantage of endotherapy with plastic stents is that strictures recurrences can be easily retreated endoscopically [26], and that in any case endotherapy does not preclude subsequent surgery, whereas hepaticojejunostomy, which is the classical surgical procedure, makes future endotherapy difficult, if not impossible.

As long as the use SEMS is concerned, the majority of the studies compares the outcomes of treatment with SEMS of benign biliary strictures due to various nature, including chronic pancreatitis, biliary anastomotic stricture, postoperative biliary strictures, sclerosing cholangitis, and autoimmune pancreatitis. [37–43]. Overall, results are promising but need further evaluation.

According to the ESGE guidelines, covered SEMS should be placed in selected patients with benign biliary strictures only as an investigational option [20]. Furthermore, SEMS cannot be placed in patients with post-LC BDS involving the hepatic hilum.

The role of SEMS in benign biliary strictures is not yet clearly defined due to variable results and small numbers, and is currently not recommended [20].

Conclusions

Endoscopy is in most instances the first-line treatment of injuries of the bile ducts occurring during LC. Sole biliary sphincterotomy with or without stones extraction and/or stent placement is the treatment of choice for the majority of bile leaks, whereas the “aggressive” plastic multistenting is the treatment of choice for BDS.

The use of fully covered SEMS for post-LC BDS is limited to carefully selected cases.

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Chapter 27
Role of Interventional Radiology in Managing Bile Duct Injuries

F. Edward Boas and Richard D. Shlansky-Goldberg

Introduction

Bile duct injuries occur in 0.5 % of cholecystectomies and are associated with high mortality [1]. Laparoscopic cholecystectomy is less invasive and has faster recovery than open cholecystectomy, but at the cost of more severe and frequent bile duct injuries [2, 3]. These injuries include leaks, strictures, removal of part of the duct, and arterial injury. Often, due to the reduced visualization of the laparoscopic approach, these injuries may be missed at the time of surgery, requiring the use of radiologic imaging and percutaneous techniques to diagnose and treat these injuries postoperatively. Some interventions are performed to temporize the patient to bridge them to a definitive operative procedure such a choledochojejunostomy, while many may be the definitive therapy, such as biliary drainage for cystic duct leaks.

The classic injury is misidentification of the common duct as the cystic duct, followed by transection, laceration, or clip placement in the common duct. The right and left hepatic ducts can also be injured. Bile can leak from the cystic duct, due to inadequate clip placement or laceration. Anatomic variants, such as an aberrant right hepatic duct draining into the cystic duct, may be associated with a higher rate of bile duct injury if not recognized by the surgeon [4, 5].

The right hepatic artery is close to the common hepatic duct and is also vulnerable to injury during cholecystectomy. In an otherwise normal liver, ligation of the right hepatic artery is usually asymptomatic, due to portal flow and arterial collater-

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als supplying the right hepatic lobe. Right hepatic artery pseudoaneurysm after cholecystectomy can cause hemobilia and hematemesis. This can be treated by coil embolization of the right hepatic artery both proximal and distal to the pseudoaneurysm [6].

Ideally, bile duct injury should be recognized and repaired at the time of surgery. However, most injuries are not recognized at the time of surgery [7], and they present later with biliary leaks or strictures. Biliary leaks result in fluid collections that can become infected. Biliary strictures can cause jaundice as well as cholangitis. These cases can be managed using a combination of surgery, endoscopy, and interventional radiology (Fig. 27.1).

Surgical management is preferable for immediate repair of bile duct injuries. Partial transections can be sutured, and a leaking cystic duct can be ligated. Completely transected ducts usually cannot be re-anastomosed without putting tension on the anastomosis. Therefore, a Roux-en-Y hepaticojejunostomy is typically performed to allow for a tension-free anastomosis. In some cases, complex bile duct injury can progress to biliary cirrhosis, and liver transplant might be required [8].

Endoscopy can be used to treat common duct strictures and leaks, by placing a plastic biliary stent across the injury. A retrievable covered metal stent can be placed endoscopically for cystic duct leaks [9].

Interventional radiology has a role in managing biliary injuries that are not accessible endoscopically. Endoscopic treatment may be less invasive but is limited to a single access point, the ampulla. Due to the higher complication rate and patient discomfort of percutaneous biliary drains, endoscopic stents are preferred for common duct injuries. However, high bile duct injuries (at or above the bifurcation) are difficult to reach endoscopically. Also, the bile ducts might not be endoscopically accessible in patients with altered surgical anatomy, such as choledochojejunostomy. In these patients, percutaneous biliary drainage is preferred to treat biliary strictures and leaks. Interventional techniques allow for enormous creativity, given the multitude of approaches and techniques that can be used to gain access to the biliary tree, without the need for general anesthesia or surgical morbidity. Biliary strictures can be treated with percutaneous biliary drains (which can be upsized to greater than 22 F) and cholangioplasty, leaks can be diverted, new biliary connections can be created, and "damage control" can be performed to stabilize the patient. In many cases, percutaneous and endoscopic approaches can definitively treat biliary injuries. If surgical biliary reconstruction is ultimately required, preoperative biliary drainage allows for elective repair, with superior imaging of the damaged biliary anatomy via cholangiography.

Imaging

Ultrasound is the least expensive imaging study, and it can be performed at the bedside. Ultrasound can detect biliary dilation and can also show the level of obstruction, although overlying bowel gas frequently obscures the common bile duct. The com-

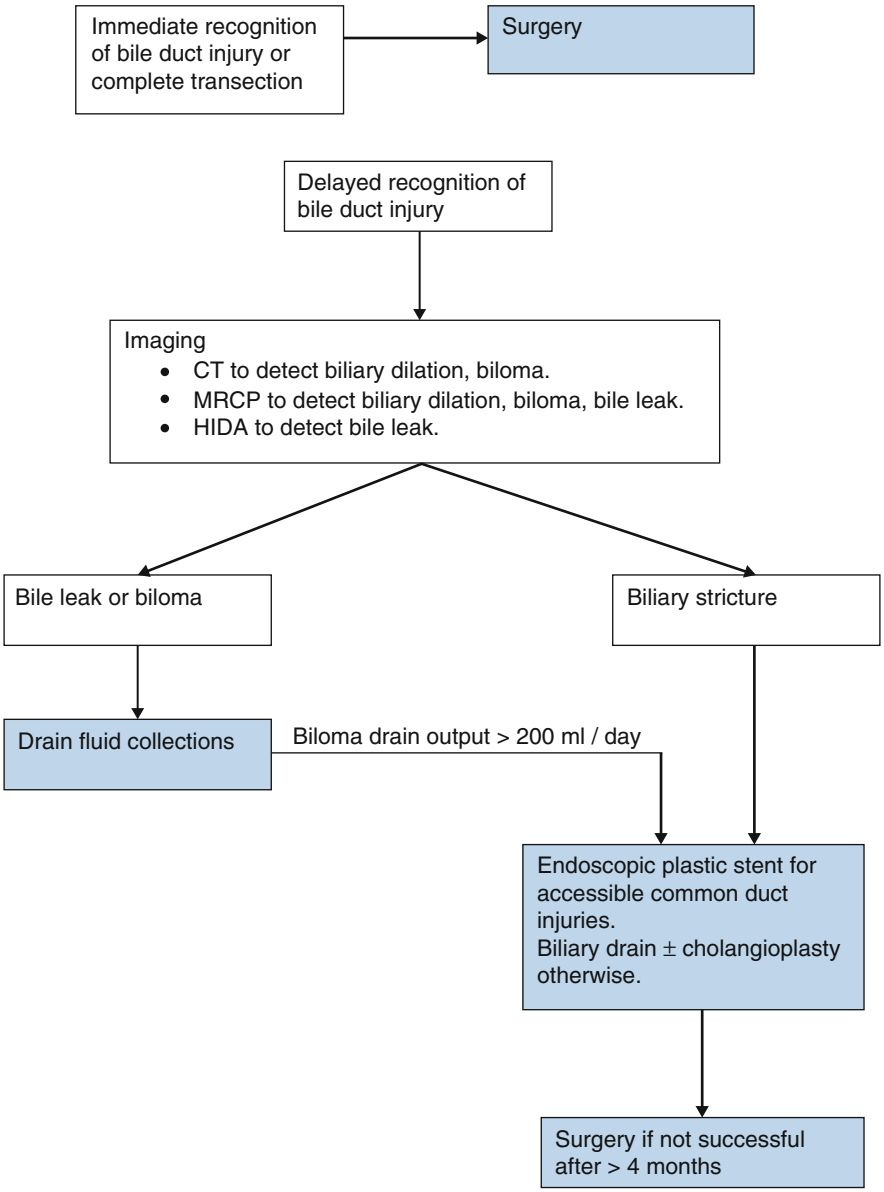

Fig. 27.1 Flow chart for management of bile duct injuries

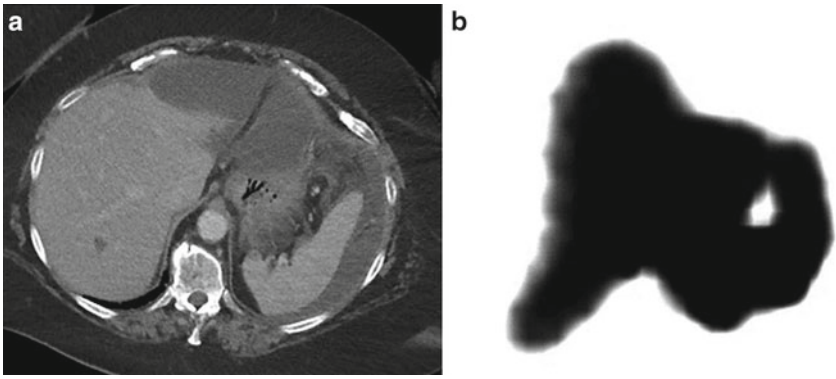

Fig. 27.2 (**a**) CT shows fluid around the liver after laparoscopic cholecystectomy. (**b**) HIDA scan performed after CT clearly demonstrates that the fluid is due to bile leak

mon bile duct normally measures less than 7 mm in inner diameter, with less than 1 mm increase in diameter with increasing age [10], or post-cholecystectomy [11].

CT is helpful for evaluation of fluid collections and biliary dilation. It is probably the most common initial imaging study in suspected biliary injury, but it cannot directly demonstrate a biliary leak (Fig. 27.2). The level of biliary obstruction can often be seen on CT as a transition from dilated to nondilated bile ducts, sometimes associated with a metal surgical clip. Leaking bile ducts are decompressed by the leak and thus typically nondilated. Bilomas measure as simple fluid density on CT, with Hounsfield units between 0 and 20.

A HIDA scan, also known as hepatobiliary scintigraphy, is a nuclear medicine scan that can show biliary leaks [12] (Fig. 27.2). Although 99Tc-HIDA has largely been replaced by other radiotracers (which have improved liver uptake), the term "HIDA scan" remains in common use. A normal HIDA scan after cholecystectomy initially shows radiotracer uptake in liver, followed by excretion of radiotracer into the bile ducts and small bowel. Pooling of tracer elsewhere—most commonly in the gallbladder fossa, perihepatic space, or paracolic gutter—indicates a bile leak.

MRCP is an MRI protocol optimized for seeing the bile ducts. It can show the anatomy of the biliary tree and any associated bilomas (Fig. 27.3). MRCP can also show a biliary leak, when it is performed using an intravenous contrast agent that is excreted into the bile ducts, such as gadoxetate (Eovist) [13], although it is typically performed without contrast, using heavy T2 (fluid-sensitive) weighting. MRCP has higher resolution than a HIDA scan and shows the biliary tree more clearly than CT.

After noninvasive imaging has demonstrated a biliary injury, ERCP or percutaneous transhepatic cholangiography can further delineate the extent of injury as well as provide access for treating the injury.

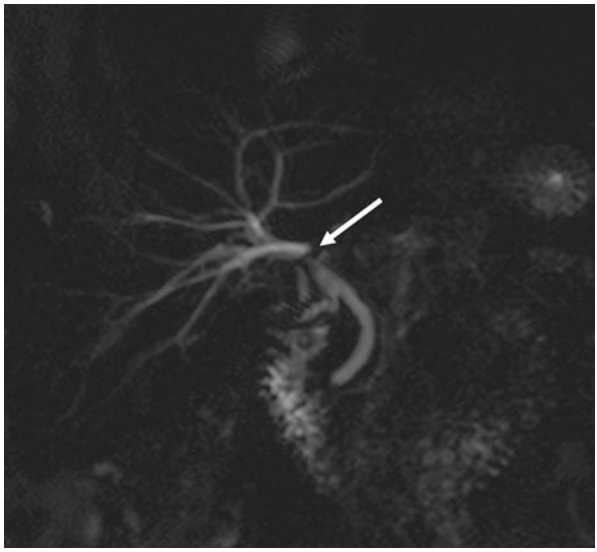

Fig. 27.3 MRCP demonstrating stricture of the common hepatic duct (*arrow*)

Percutaneous Biliary Drainage and Cholangioplasty

Indications

For biliary strictures, percutaneous biliary drains can provide external or internal/external drainage of obstructed bile ducts. For biliary leaks, percutaneous biliary drains can reduce biliary pressure and divert bile flow away from the leak to allow it to heal. ERCP should be considered first, and percutaneous biliary drainage should be performed if ERCP fails or is not possible due to choledochojejunostomy or a high bile duct injury (at or above the bifurcation). Small biliary leaks can resolve on their own [14] and might not require biliary drainage. The status of the leak can be monitored using the biloma drain output.

Biliary drainage also allows any inflammation to resolve in order to more safely perform a definitive surgical procedure such as choledochojejunostomy. More importantly, the catheter allows the duct to be more easily isolated to create the anastomosis (Fig. 27.4).

Pre-procedure Preparation

Ideally, for a new biliary drainage, INR should be less than 1.5, platelets greater than 50,000, and antiplatelet agents and blood thinners should be held [15]. A large study of 34,606 biliary drainage procedures in Japan showed that severe

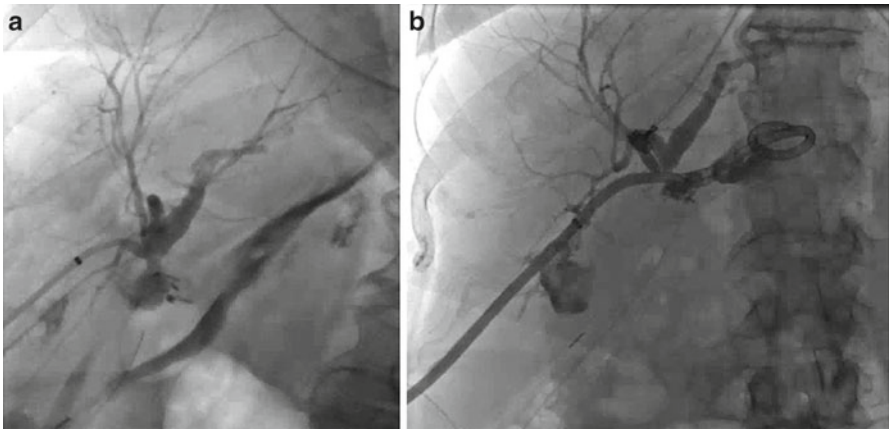

Fig. 27.4 (**a**) Bile leak from a high common duct complete disruption, with contrast pooling extrahepatically. (**b**) To improve drainage of the leak, the drain was positioned to drain the biliary tree, with the loop in the peritoneum

post-procedural bleeding was associated with continuation of antiplatelet agents, but not with continuation of anticoagulants [16]. Broad-spectrum antibiotics should be administered pre-procedure, and continued post-procedure in cases of obstruction or cholangitis [17]. Pre-procedure paracentesis may be helpful if there is large volume ascites, especially for right-sided biliary drains. Ascites is a relative contraindication for biliary drainage due to the inability to form an adequate tract. Lack of tract formation allows contaminated bile to potentially infect the ascites, causes ascites leakage from the tract, and loss of access with catheter dislodgement. Losing catheter access due to ascites can be disastrous, creating an additional site of leakage that cannot be easily diverted. Thus, bilious ascites from bile leak must be drained prior to biliary drainage, either by catheter placement or daily paracentesis. For a new biliary drainage, contrast will be introduced into the hepatic and portal veins during the attempt to find an adequate duct to drain. Therefore, creatinine should be evaluated beforehand, and steroid premedication should be given to patients with contrast allergies. New biliary drainages are typically performed using deep sedation or general anesthesia.

Biliary Drain Placement

First, a peripheral bile duct is accessed using a 21 or 22 G Chiba needle, and used to perform cholangiography. If the needle is within a central bile duct, then contrast can be injected to opacify the biliary tree, and a more peripheral bile duct can then be targeted under fluoroscopy. Placing a biliary drain into a more peripheral bile duct reduces the risk of vascular injury. This process may require multiple passes of

the needle to find a suitable duct, especially if the biliary system is decompressed due to a leak. Generally, the more dilated the biliary system, the easier the drainage. Biliary leaks are very challenging to drain, due to the small size of the decompressed bile ducts and the difficulty of maintaining adequate opacification.

Left-sided ducts are often accessed under ultrasound guidance, if they are dilated. Ideally, a segment 3 duct is targeted from a left subxiphoid approach, with the needle angled superiorly and to the right. The position of the needle within the bile duct is then confirmed by injecting contrast under fluoroscopy. One advantage of left-sided drainage is that it is generally more comfortable due to its subcostal position. Also, if there is ascites, left-sided biliary drains are less likely to leak ascites around the drain, because they enter the abdomen more anteriorly compared to right-sided biliary drains. Left-sided drainage is also preferable if cholangioscopy is to be attempted, as it provides better access to the right ducts. In the case of drainage for malignancy, left duct drainage can be preferable, because the left hepatic duct is typically longer than right hepatic duct. Thus, when there is progression of malignant bile duct obstruction centered around the confluence of the right and left ducts, the right anterior and posterior ducts typically become isolated before the left ducts become isolated. One disadvantage of left biliary drains is more radiation exposure to the hands of the operator. Also, left bile ducts are anterior, which makes them drain more rapidly due to gravity, and thus more difficult to opacify in the setting of a leak.

Right-sided ducts are often accessed under fluoroscopic guidance. The liver should be entered inferior to the tenth rib and anterior to the mid-axillary line. If possible, the liver should be entered subcostally, as intercostal drains tend to be more painful due to the catheter rubbing against a rib when the patient breathes. The process for finding the duct is that the needle is advanced towards the hilum of the liver. Contrast is then injected slowly as the needle is withdrawn, until bile ducts are seen. Bile ducts can be distinguished from blood vessels as the contrast stays within the duct and does not flow away rapidly.

An 0.018″ mandril wire is then passed through the needle, and a triaxial wire exchange set (stiffening cannula, introducer, and sheath) such as a Jeffrey set (Cook medical) is placed over the wire, which then enables placement of a 0.035″ wire and a 6 French sheath into the bile ducts. A 5 French catheter and wire are then advanced across the bile duct injury, if possible. Finally, an 8–12 French internal/external biliary drain is placed over the wire, with side holes both above and below the bile duct injury, and a locking loop formed in the bowel. For bile leaks, 12 French catheters are associated with a high cure rate [18], although we do not know of any published data comparing the effectiveness of different sized biliary drains. If the bile duct injury cannot be crossed, an external biliary drain can be placed. Typically, an external biliary drain has a smaller locking loop that can be formed within a bile duct, such as a Dawson-Mueller drain (Cook medical). The catheter can also be placed through the leak into the peritoneum to provide better stability, which allows use of a larger locking loop and helps to physically identify the leak location.

Biliary drains are typically “Cope” loop catheters, named after Constantin Cope, who invented the crossed-limb loop anchor [19]. They are also known as locking

loop or pigtail drains. The locking loop is formed by pulling on a suture that runs through the catheter, out a sidehole, to the tip of catheter. This suture must be released or cut to remove the catheter. Different manufacturers have proprietary suture locking mechanisms on the catheter.

Post-procedure Management

An uncrossable biliary obstruction results in the placement of an external biliary drain that must remain to gravity drainage, since there is no internal egress for the bile. An internal/external biliary drain should remain to external drainage in the immediate post-procedure period (usually extending for 24 h) to reduce the risk of bacteremia and sepsis. Since biliary drainage is performed by injecting the biliary tree, the increase in intrabiliary pressure can result in biliovenous reflux that can result in transient bacteremia and can progress to fulminant sepsis. Bacteremia can also result from traumatic communication of the biliary tree to the portal or hepatic vein during needle and catheter introduction. This risk is increased with the presence of ongoing cholangitis. Post-procedure gravity drainage should reduce these risks. The catheter can be capped after 24 h, if the patient is afebrile, has drainage of clear bile without significant blood, and there is no biliary leak. This will prevent dehydration and electrolyte loss. If there is an associated bile leak, the catheter should be kept open to gravity drainage to maximize diversion from the leaking duct. Output from nearby drains should be monitored. If drains associated with a bile leak continue to output bile, the biliary catheter should be upsized until all bile is diverted and there is no drainage from the biloma drains. This will allow the leak to heal. All biliary tubes should be flushed daily with 5–10 ml normal saline without aspiration to maintain patency. Aspirating biliary drains may draw debris from the duodenum, which may lead to catheter failure. Due to the high morbidity of initial biliary drainage, overnight observation should be performed, while biliary exchanges can be done as outpatient.

High output biliary drains can cause dehydration and electrolyte abnormalities. For inpatients, this can be managed by replacing biliary drain outputs with Lactated Ringer's solution intravenously. For outpatients, this can be managed by replacing biliary drain outputs with an oral electrolyte solution, such as Gatorade. If the patient has a feeding tube, bile can be given back to the patient through the feeding tube to limit electrolyte loss.

Biliary drains are typically exchanged every 3 months to prevent clogging, but are exchanged more frequently if cholangioplasty or other interventions are planned. Total biliary drainage time greater than 4 months is associated with a higher success rate for resolving bile duct injuries [20]. An over-the-wire cholangiogram can be performed to evaluate for persistent leak or stenosis. For biliary leaks, cholangiogram and biloma drain check should be performed when the biloma drains have minimal output, in order to confirm that the leak has healed and decreased drainage is not due to catheter dysfunction. The over-the-wire cholangiogram is performed

through a sheath that does not cross the bile duct injury. If the bile duct injury has resolved on the cholangiogram, then an external biliary drain can be placed to maintain access to the bile ducts. This external drain should be capped for 2 weeks without flushing. If the patient passes the capping trial (no fever, no significant leakage around the tube, no rise in bilirubin), then the drain can be safely removed. If a biliary drain is removed less than 2 weeks after placement, some interventional radiologists will embolize the tract with gelatin foam pledgets, in an attempt to reduce the probability of bleeding or bile leak.

Cholangioplasty

Although there is wide variation in protocols for managing biliary strictures, the basic concept is to open the stricture with either repeated balloon dilation or a large bore drain.

During a biliary drain exchange, cholangioplasty can be performed using a high-pressure balloon. High pressures and prolonged cholangioplasty (up to 15 min) are typically required to overcome the dense fibrous tissue around biliary strictures. An 8 mm balloon can be used for intrahepatic strictures, and a 10–12 mm balloon for common duct strictures. Cholangioplasty can be repeated at 2–14 day intervals [21, 22].

Our benign stricture treatment protocol [23] is to initially place a 12–14 F internal/external biliary drain, then upsize every 2 weeks until the patient has a 16–18 F Heyer-Schulte silicone drain. Cholangioplasty to 8–10 mm is performed at the final upsizing. The large bore drain is exchanged every 3 months. After 6 months, an over-the-wire cholangiogram is performed to evaluate the stricture. If the stricture resolved, an external biliary drain is placed above the stricture and capped for 2 weeks. At the end of the capping trial, liver function tests are checked prior to biliary drain removal. If the stricture is recalcitrant as demonstrated by the over-the-wire cholangiogram, or recurs during the capping trial, the stricture usually undergoes repeat cholangioplasty and stenting for another 6-month period. Failure after the next 6 months of drainage may lead to surgical revision or chronic biliary drainage.

Outcomes

The technical success rate for bile duct cannulation should be >70 % for nondilated ducts, and >95 % for dilated ducts [24].

For benign biliary strictures, our success rate using large bore silicone biliary drains is 84 % at 1 year and 67 % at 10 years [23]. Repeated cholangioplasty and internal/external biliary drainage have a primary success rate of 59 % and a secondary success rate of 80 % at 25 years [21]. For postoperative biliary leaks, percutaneous

biliary drainage (12 French) was able to heal the leak in 10 out of 10 patients after an average of 2–3 months [18]. However, there is a great deal of variation in reported success rates for nonsurgical treatment of bile duct injuries. In one study, definitive treatment of surgical bile duct injuries was achieved using endoscopic or percutaneous plastic biliary stents in up to 36 % of cases, after an average of 11 months of stenting [7]. The other 64 % of patients were treated surgically. Total biliary drainage time greater than 4 months is associated with a higher success rate [20].

Complications

Biliary drain placement has a major complication rate of 8 %, including hemorrhage, sepsis, and bile leak [24].

Hemorrhage into the biliary drain can be due to a sidehole against a portal or hepatic vein branch. This can be diagnosed by performing a tractogram by exchanging the biliary drain for a sheath over a wire, and injecting contrast into the sheath in order to opacify any veins traversed by the drain. Venous bleeding can typically be fixed by upsizing the drain and adjusting the drain position to tamponade the bleeding vein. Arterial injury during biliary drain placement may require an angiogram and embolization. If the angiogram is negative with the drain in place, the angiogram should be repeated after the drain has been removed over a wire, in order to reveal any arterial injury that was tamponaded by the catheter.

Sepsis occurs after 2.5 % of biliary drainages [24], and requires continued broad-spectrum intravenous antibiotics and ICU admission. Vigorous contrast injection should be avoided during biliary procedures to reduce the likelihood of developing sepsis (see earlier discussion). If capped, the biliary drain should be placed back to gravity drainage. If the tube is clogged and the patient has cholangitis, the tube should be exchanged and possibly upsized.

Bile leakage around a biliary drain occurs when the drainage pathway inside the catheter has higher resistance than drainage around the catheter. This can occur if the catheter is clogged, if a sidehole is too close to the skin, or if the sideholes are too central to drain the obstructed peripheral ducts.

Biliovenous fistulas can cause a transient rise in bilirubin after biliary drain placement, but this usually resolves spontaneously [25].

Biloma Drains

Bile leakage from a bile duct injury can cause bile peritonitis, as well as bilious fluid collections that can become infected. These fluid collections can be drained percutaneously, under CT or ultrasound guidance. When an infected biloma is drained, the fluid can initially appear purulent, then may turn bilious if there is a continued

bile leak after the infection clears. Ideally, the drain should be placed near the bile leak to provide optimal drainage. The drain can also be used as an aid to biliary drainage. Contrast injection may demonstrate the leak and can opacity bile ducts, providing a target for drainage in a decompressed system. This technique tends to work better after the initial drainage, when the collection has decompressed and there is a more mature fistula to the leak.

The amount of drain output allows monitoring of the amount of bile leak over time. If there is less than 200 ml/day of bilious output, which is trending down, then the bile leak might resolve on its own. Persistent drainage greater than 100–200 ml/day should be treated with endoscopic or percutaneous biliary drain placement [14, 26].

Sometimes, the diagnosis of bile leak is unclear, even with a drain in place. For example, a patient with elevated bilirubin will have bile in serous fluid collections, even without a bile leak. In these cases, drain fluid can be tested for bilirubin. A drain fluid to serum bilirubin ratio greater than 5 is highly sensitive and specific for diagnosing bile leaks [27].

The biloma or abscess drain can typically be removed when the output is less than 20 ml/day and the patient has no fever or pericatheter leakage. An abscessogram or a CT scan can be performed prior to removal. An abscessogram shows if the tube is clogged or malpositioned, as well as the size of the residual collection and any connection to bile ducts. A CT scan shows the position of the tube and any undrained collections.

Other Treatments

Several innovative percutaneous techniques have been described for treating refractory bile duct injuries.

Retrievable Covered Stent for Cystic Duct Leak

Permanent metal biliary stents have an average patency of 30 months when used for benign disease [28], and are thus not typically used for benign disease. However, a retrievable covered self-expanding metal stent (Song stent, TaeWoong Medical, Kimpo, Korea) has been used to treat cystic duct leaks [29]. This stent has a drawstring that can be pulled to collapse the stent and pull it into a sheath. It has a reported success rate of 100 % for resolving postoperative bile leaks, in a series of 11 patients, after an average of 31 days of stenting. Viabil covered metal stents, which are more widely available, but do not have a drawstring, can also be retrieved percutaneously, by using forceps to pull the stent into a sheath [30].

Bile Duct Embolization

Leaking bile ducts that are completely isolated or that are refractory to biliary drainage can be embolized with ethanol or glue. Ethanol typically requires multiple treatments, whereas glue can be successful with a single treatment [31]. The leaking bile duct is accessed percutaneously, and then irrigated with normal saline, which provides ions that are necessary for the glue to polymerize. The duct is then embolized using *N*-butyl cyanoacrylate glue mixed with Ethiodol and tantalum powder, delivered through a microcatheter that has been irrigated with dextrose [31].

Rendezvous Procedures

A complete bile duct transection is difficult to cross using either a percutaneous or endoscopic approach. An endoscopic rendezvous procedure combines percutaneous and endoscopic access in order to snare a wire across a complete common bile duct transection. An internal/external biliary drain can then be placed over the wire. This allows the transection to heal after several months of drainage [32].

Alternatively, percutaneous rendezvous can be performed by primarily sticking the common bile duct with a 21-gauge needle in a retrograde direction (Fig. 27.5). Central punctures like these substantially increase the risk of a hepatic artery injury, but using a small caliber needle with a 0.018″ wire will reduce this risk. The retrograde wire may provide access across an obstruction that could not be crossed from above, thus allowing a wire to be pulled down across the lesion [33].

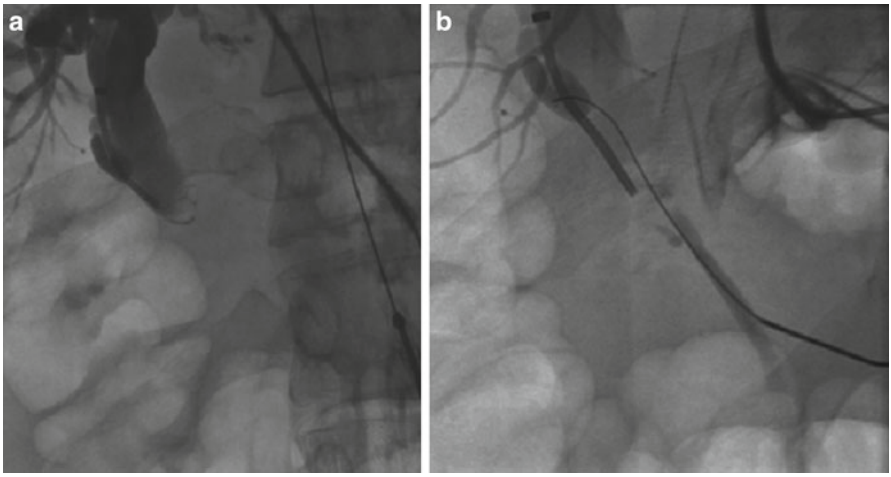

Fig. 27.5 (**a**) Common bile duct occlusion could not be crossed from above. (**b**) Percutaneous puncture of the common bile duct from below enabled crossing of the stricture (percutaneous rendezvous procedure). Direct puncture of the common duct carries a risk of hepatic artery injury. This risk is reduced by using a 21 gauge needle and 0.018″ wire

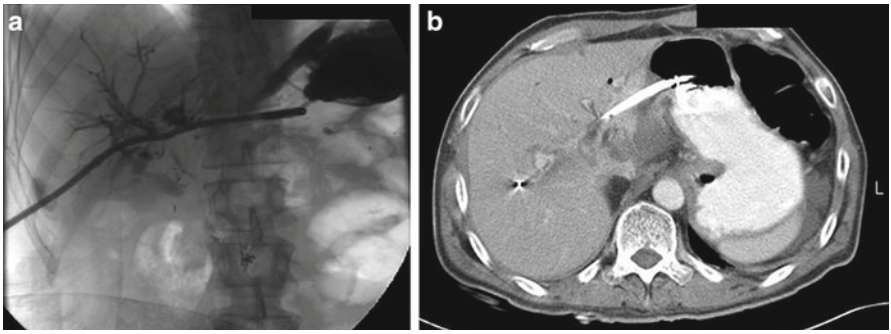

Fig. 27.6 Hepaticogastrostomy tube in a patient where internal drainage through the common bile duct was not possible. (**a**) The common bile duct is obstructed near the surgical clips in the porta hepatis. (**b**) CT shows the hepaticogastrostomy tube entering the stomach

Percutaneous Hepaticojejunostomy and Hepaticogastrostomy

In patients with refractory bile leaks, or biliary obstruction that cannot be crossed, a percutaneous hepaticojejunostomy or hepaticogastrostomy can be created using a metal stent, or catheter, thus creating an alternative drainage pathway (Figs. 27.6 and 27.7).

In one report, the bile ducts were accessed percutaneously, and a snare advanced out of a leaking bile duct into the peritoneum. The target jejunal loop was then punctured through-and-through with a needle. A wire placed through the jejunal needle was snared out through the bile ducts, thus achieving through-and-through access. A covered metal stent was then deployed over the wire to create a hepaticojejunostomy [34].

In another report, after obtaining percutaneous access to the bile ducts, a sheath, 5 F catheter, and 0.038″ needle from the Rösch-Uchida transjugular liver access set was advanced through the bile ducts, and used to puncture the stomach under CT guidance. A wire was advanced through the bile ducts into the stomach, then snared out through the mouth, in order to achieve through-and-through access. A metal stent was then deployed over the wire to create a hepaticogastrostomy [35].

Summary

Biliary drainage can be used to treat postsurgical biliary injuries that are not accessible endoscopically. Small bile leaks can resolve spontaneously. If a biloma drain outputs more than 200 ml/day, biliary drainage can divert the bile away from the leak, allowing it to heal. Postsurgical biliary strictures can be treated with large bore biliary drains and cholangioplasty. Innovative percutaneous techniques for treating refractory bile duct injuries include covered biliary stents, bile duct embolization with glue, rendezvous procedures, and percutaneous hepaticojejunostomy and hepaticogastrostomy.

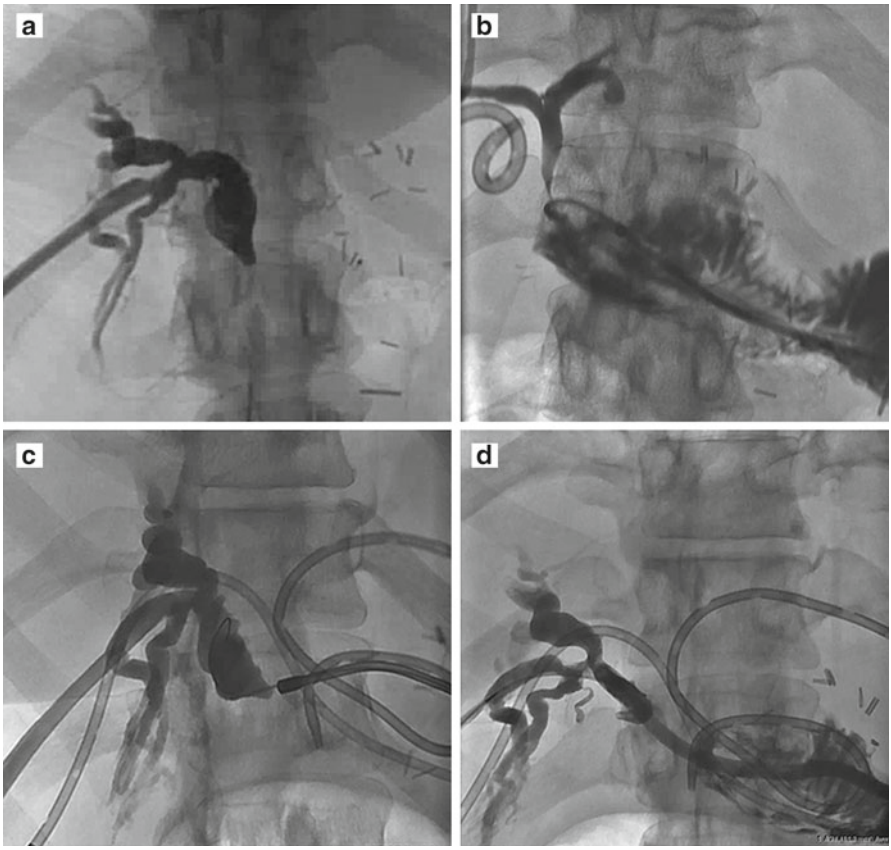

Fig. 27.7 Percutaneously created hepaticojejunostomy. (**a**) Isolated right hepatic duct from an obstructed surgical hepaticojejunostomy. (**b**) Percutaneous jejunostomy to gain access to the pulled up loop of jejunum. (**c**) Isolated right bile ducts were accessed using a 21 G needle placed through a cannula placed through the percutaneous jejunostomy site. (**d**) After obtaining through-and-through access, a hepaticojejunostomy tube was placed

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Chapter 28
Operative Repair of Common Bile Duct Injury

Damian J. Mole and O. James Garden

Abbreviations

CBD	Common bile duct
CHD	Common hepatic duct
LHD	Left hepatic duct
RHD	Right hepatic duct
CHA	Common hepatic artery
PHA	Proper hepatic artery
RHA	Right hepatic artery
LHA	Left hepatic artery
BDI	Bile duct injury
VBI	Vasculobiliary injury
HRQOL	Health-related quality of life

Introduction

This chapter addresses the operative repair of acute bile duct injury (BDI), in particular, that sustained at laparoscopic and open cholecystectomy. More specifically, the chapter focuses on repair of iatrogenic BDI as an unintended consequence of

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cholecystectomy. Deliberately not discussed in this chapter is the management of bile duct injuries due to blunt or penetrating trauma, or injury sustained at elective hepatectomy or gastroduodenal surgery, although the management issues are not dissimilar to those involved in bile duct injury related to cholecystectomy. The most important factor for patients undergoing laparoscopic cholecystectomy is prevention of BDI through safe surgical practice and surgical awareness, and this most important aspect of surgery to the gall bladder is covered elsewhere.

Incidence of Bile Duct Injury

More than 750,000 laparoscopic cholecystectomies are performed annually in the United States [1] and 80,000 annually in the United Kingdom [2, 3]. Prior to the widespread adoption of laparoscopic cholecystectomy, BDI occurred in an estimated 0.2 % of cholecystectomies [4]. With the introduction of laparoscopic cholecystectomy, the incident rate of iatrogenic BDI has increased approximately twofold, to 0.3–0.5 % incidence in most large series although even with large prospective studies, the true incidence varies due to a lack of consensus in agreeing what constitutes bile duct injury and an incidental bile leak.

Mechanisms of Injury

In nearly all cases, BDI results from an error in cognition during the initial phases of anatomical orientation, when the operating surgeon, corroborated or unchallenged by the assistant, misidentifies the key anatomical landmarks to allow safe dissection to achieve the critical view [5]. This fundamental "root cause" of error can progress into any type of BDI, from a lateral injury to the common bile duct (CBD) whilst attempting intraoperative cholangiogram (Strasberg type D) [5], to completed excision of the hepatic duct confluence (Garden's Type E6 addition [6] to Bismuth E1–5 classification [7]). It is important to understand the mechanisms of injury since this will impact on subsequent management. There are numerous variations, combinations, and permutations in the pattern of injury seen, which have been exhaustively covered by a series of classification systems. The main classification system in common use is that of Strasberg [5], which incorporates in its types E1–5 the original classification system of Bismuth [7] (Fig. 28.1).

The classical CBD injury, described by Davidoff [8], occurs where the surgeon initiates anatomical orientation too medially or commences dissection too low below the anatomical landmark provided by Rouviere's sulcus and the inferior border of segment IV [9, 10], misidentifies the CBD for the cystic duct, clips and divides it, proceeds proximally towards the hilum, injuring the RHA in the process as it passes under the CBD, encounters an "accessory cystic duct" (this being the CHD), dividing it and thus excising a segment of CBD with the gall bladder (Figs. 28.2 and 28.3).

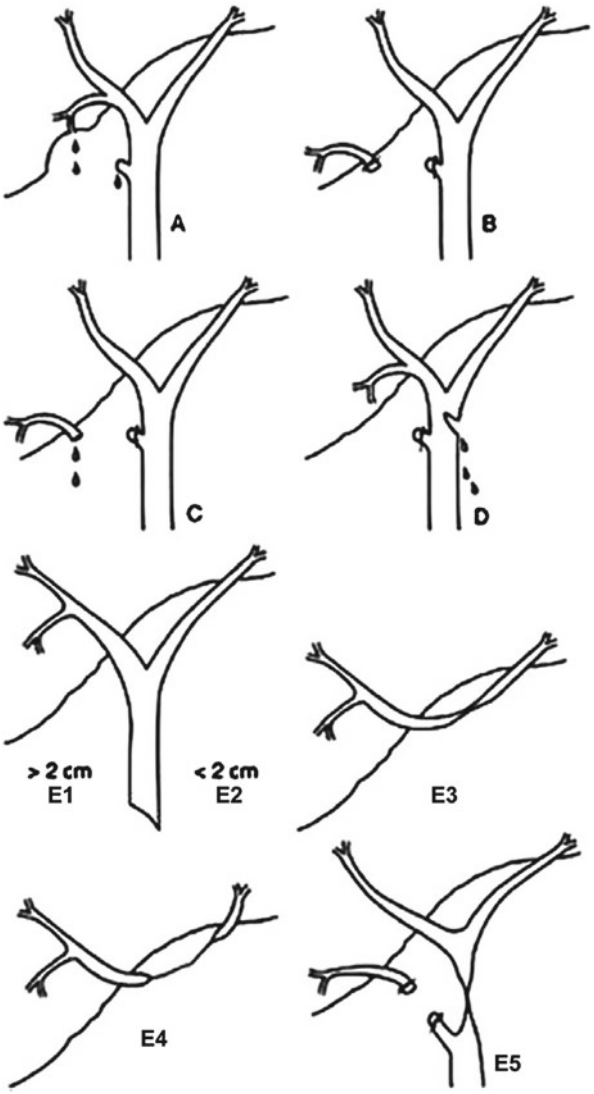

Fig. 28.1 Strasberg classification of iatrogenic bile duct injury. This figure was published in J Am Coll Surg, 180, Strasberg, S.M., Hertl, M. & Soper, N.J., *An analysis of the problem of biliary injury during laparoscopic cholecystectomy*, 101–125, Copyright Elsevier (1995) [5]

Complete excision of a portion of the bile duct has occurred in the pattern of the classical bile duct injury. The biliary confluence has been excised, leaving exposed right hepatic duct (RHD) and left hepatic duct (LHD) orifices. The main portal vein (MPV) is exposed. The right hepatic artery (RHA) has been mistaken for the cystic artery and clipped and divided as it passed behind the common hepatic duct

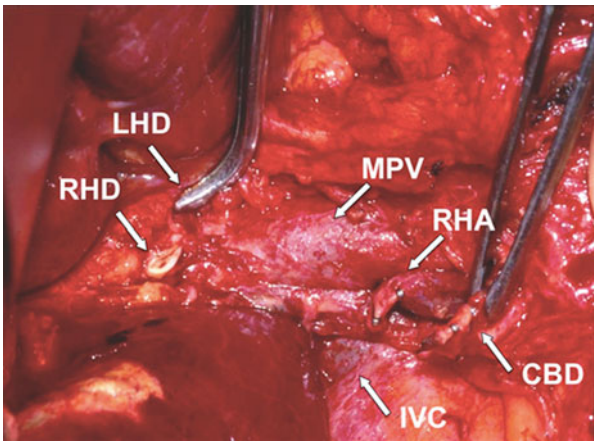

Fig. 28.2 Intraoperative photograph of a major bile duct injury with concomitant vasculobiliary injury (Strasberg E5)

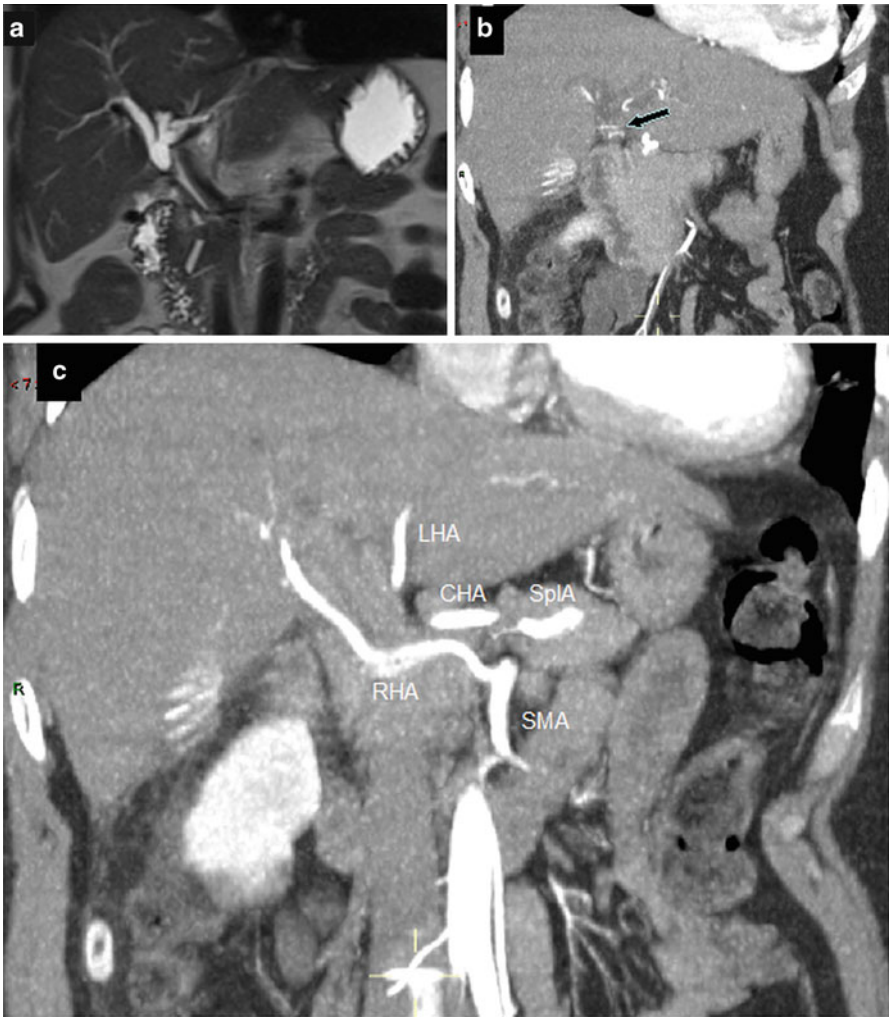

Fig. 28.3 The classical CBD injury as described by Davidoff, Strasberg E2. A segment of the CHD was excised between clips. The injury was not suspected intraoperatively. Bile leakage in the first 2 postoperative days was minimal but right upper quadrant pain and a rising bilirubin prompted an MRI scan.

(no longer present). The distal common bile duct has been mistaken for the cystic duct and has been doubly clipped and divided. The inferior vena cava (IVC) is visible posteriorly to what remains of the hepatic pedicle.

Physical Mode of Injury

The physical mode of injury is also critical to the strategic planning of the surgeon planning bile duct repair, as this will greatly influence the timing and choice of repair technique. A cold, sharp incision, for example, such as that made by scissors, is likely to be associated with far less collateral tissue damage than a high-energy injury inflicted by prolonged dissection, diathermy, ultrasonic shears, or other energy dissector. Similarly, a shredding-type injury caused by repeated forceful passages of a stone retrieval basket or a rupture-type injury caused by overinflation of a balloon during transcystic CBD exploration will result in a less discrete injury that may not lend itself to direct repair at the time of surgery. The degree of generalized tissue disruption will also influence the likelihood of subsequent stricturing of either the residual ductal tissue or the anastomotic repair.

Comprehensive Recording of BDI: The ATOM Classification

There are now multiple classifications for BDI each with their own merits. However, so many systems lead to complexity and an inability to compare injury severity and outcome between series. Therefore, the European Association for Endoscopic Surgery achieved consensus in formulating a multi-parameter template for recording BDI. Using semantics, the anatomy (A), time of injury (To), and mechanism of injury (M) are recorded as the ATOM classification [11]. The anatomical record includes the level of injury, and whether the lesion is partial or complete, with division or occlusion. The presence of VBI is recorded. Whether the injury was detected intraoperatively in the early postoperative period or detected late is recorded. Lastly, whether the injury was energy-driven or mechanical is recorded. The system is comprehensive and ensures that all relevant attributes of a BDI are recorded. It also serves as a reminder to the surgeon to consider each of the various attributes during the strategic planning phase of bile duct repair. Unfortunately, it is probably not sufficiently simple to be employed routinely by most surgeons in day-to-day practice but nonetheless is useful for the specialist surgeon in considering the nature of the injury and the optimal management approach.

Fig. 28.3 (continued) (**a**) Primovist-enhanced MRI scan showing complete occlusion of the CHD within 2 cm of the confluence (E2 injury). (**b**) CT confirms two clips placed across the CHD (*black arrow*). (**c**) Arterial phase contrast CT shows a replaced right hepatic artery arising from the superior mesenteric artery. This anatomical variant may well have saved the patient from a major arterial injury had there been a normally sited right hepatic artery

Assess the Patient and the Injury

In the event of a suspected iatrogenic BDI, particularly at the time or subsequent recognition of the injury, the absolute priority must be patient safety. If the BDI is recognized intraoperatively and there is not ongoing life-threatening hemorrhage, further dissection by the primary operator to establish the extent of the injury is generally ill-advised even if the primary operator is an experienced surgeon. Further dissection at this stage risks an extension of the injury or an additional vascular injury that will considerably worsen the situation. It is recommended that a second senior surgical colleague (who ideally is an expert hepatobiliary surgeon) be called into the operating theater to provide an objective assessment and give advice. The initial temptation is for the primary operator to perform an immediate repair, which is not always the correct course of action. Similarly, many would recommend that the primary operator who caused the BDI is not best placed to carry out the best repair. Apart from the fact that the primary operating surgeon at that moment in time is by definition error-prone (for whatever reason), in the maelstrom of emotions that may be present at the time of iatrogenic BDI, the judgment of the primary operator is unlikely to remain uncompromised.

Concomitant Vascular Injury: The Vasculobiliary Injury (VBI)

It is well recognized that concomitant vascular injury at the time of BDI, termed vasculobiliary injury (VBI), is associated with a significantly worse outcome [12, 13]. The right hepatic artery is most commonly injured (in 12–61 % of BDI [12]) due to its usual anatomical location passing behind the CHD. If injury to the RHA occurs in isolation, in other words without BDI, then there are a few long-term consequences. The reason for this is the potential for the development of collateral arterial circulation through the smaller arteries that run vertically alongside the CBD at the 3 o'clock and 9 o'clock positions, and the important transverse arterial anastomosis across the hilar plate at the main biliary confluence at the hilum [13] (Fig. 28.4).

Angiographic flow studies have demonstrated a return to near normal arterialization of the right liver after interruption of the RHA through these important potential collaterals. However, although an increase in flow across the transverse hilar network is seen after 10 h, flow is not completely compensated for at least 4 days [14]. Therefore, in the presence of acute VBI, immediate repair may in fact result in an inferior long-term outcome due to recurrent stricture because early surgery and immediate anastomosis may further disrupt this collateral arterialization. Many units expert in tertiary management of BDI [12], including the authors' unit, will preferentially delay biliary repair in the context of VBI to allow adequate collateralization across the hilar plate with the aim of achieving a better long-term outcome.

In the immediate intraoperative setting, the continuity and flow in the RHA can be established by the second expert surgeon, with care being taken to avoid exacerbating any injury. In this setting, intraoperative ultrasound, duplexed with

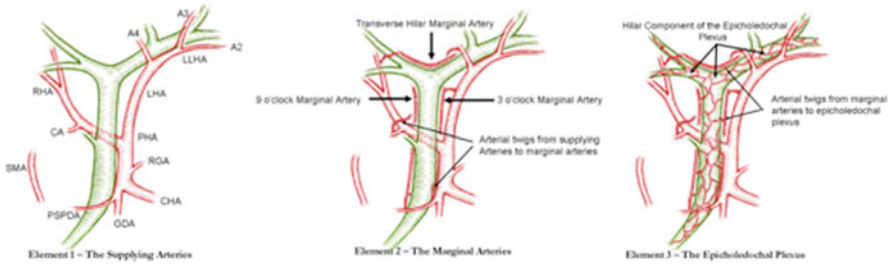

Fig. 28.4 (**a**–**c**) The blood supply of the bile duct. (**a**) Element 1 is comprised of the major named arterial vessels (SMA, superior mesenteric artery; CHA, common hepatic artery; GDA, gastroduodenal artery; PSPDA, posterior superior pancreaticoduodenal artery; RGA, right gastric artery; PHA, proper hepatic artery; RHA, right hepatic artery; LHA, left hepatic artery; LLHA, left lateral hepatic artery; A2, A3, and A4, arteries to liver segments 2, 3, and 4; CA, cystic artery). (**b**) Element 2 is comprised of the marginal arteries running in the 3 and 9 o'clock positions on both sides of the common bile duct and transversely across the hilar aspect of the bifurcation of the common hepatic duct. (**c**) Element 3 is the epicholodochal plexus forming a network in and on the wall of the ductal system. This figure was published in HPB, 13, Strasberg, S.M. & Helton, W.S., *An analytical review of vasculobiliary injury in laparoscopic and open cholecystectomy*, 1–14, Oxford (2011) [13]

color flow Doppler, may be helpful. If a concomitant significant arterial injury is detected which involves the right hepatic artery, the hilar plate, and biliary confluence, primary reconstruction of the biliary tree should be deferred to allow adequate collateralization to occur over a period of time. A delay of approximately 3 months is optimal in the authors' practice. Controversy exists over whether a primary repair of the artery, with an excision of the injured segment and primary anastomosis, or with the use of an interposition vein graft or jump graft, will lead to improved outcomes, and there is insufficient case volume reported in the literature to make a clear assessment [15]. Often there is a loss of vessel extending into the liver substance. Arterial reconstruction in this context is technically demanding, likely to failure, and risks worsening an already suboptimal situation. Therefore, if arterial revascularization is attempted, this should only be undertaken by surgeons highly experienced in the technique. The majority of centers will adopt a deferred approach to bile duct repair in the context of VBI to establish whether the vascular component of the injury will result in ischemic damage to the affected liver and biliary tree. In the context of a delayed early presentation (e.g., postoperative day 1) or late presentation (beyond 7 days), the arterial tree should be imaged, ideally with CT angiography, to confirm the arterial anatomy and define the precise extent of VBI.

Underestimating the Extent of Injury

A significant practical pitfall exists in underestimating the extent of the injury in cases of BDI and VBI. In the majority of injuries, surgery has occurred in the incorrect anatomical framework and the usual caution regarding careful dissection,

gentle tissue handling of critical structures, and judicious use of energy devices, particularly diathermy, has been misapplied. Furthermore, because operations in which a BDI has occurred are frequently reported to have been "more difficult than usual," with "more bleeding than usual," the extent of the injury can go beyond that initially expected from the exact site of the bile leak or transection point. Similarly, due to radial dissipation of energy applied during diathermy injuries of the CHD, what initially appears to be a pinpoint diathermy injury to the CHD may in fact progress into an extensive ischemic and thermal injury to a larger section of duct that may take several days to declare [6].

Immediate Repair

Many would advocate an attempt at primary repair of the BDI in the patient in whom BDI is recognized intraoperatively and a suitable second expert surgeon is available to attend the operating theater for advice and preferably take over as operator, and in whom there is no likelihood of significant vascular injury. If this is to be undertaken, exactly what surgery is required is dependent on the level and extent of injury, and the repairing surgeon should be aware of the high failure rate of immediate repair (63 % in one large series [16]) and the need to perform a Hepp-Couinaud repair, ensuring a wide hepaticojejunostomy extending up the left main hepatic duct. If a significant injury to the RHA is identified, as discussed above, the authors recommend delaying the repair to allow adequate collateralization through the transverse hilar network. However, in certain circumstances, it is acceptable for an experienced hepatobiliary surgeon to undertake a satisfactory repair, if this can be achieved without excessive dissection of the hilar plate, and therefore without further compromising the arterial supply.

Management of Strasberg Type A to C Injuries

Cystic duct stump leaks and accessory duct (of Luschka) leaks (Strasberg Type A) are usually diagnosed in the early postoperative period, often with the patient reattending hospital after discharge. These minor leaks are best managed by ERCP and biliary stenting with good outcomes. It is unusual for an isolated injury to an aberrant posterior sectoral duct (Strasberg Type B (occluded) and C (leaking)) to require reconstruction, and, if suture control of the leaking duct at the lateral edge of the gall bladder fossa is not immediately and easily achievable, the authors' recommendation is to perform laparoscopic washout and ensure the correct placement of an adequately sized tube drain in the subhepatic space to allow the segmental bile leak to dry up over a period of several weeks (Fig. 28.5). Surgical reconstruction is technically demanding and the risk-benefit assessment of Roux-en-Y hepaticojejunostomy to a nondilated isolated posterior sectoral duct orifice does not make

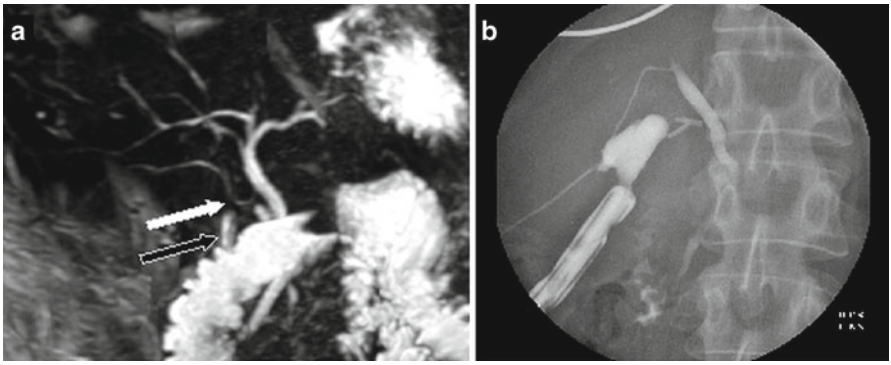

Fig. 28.5 Isolated posterior sectoral duct injury sustained at laparoscopic cholecystectomy. The patient had been discharged home and presented 1 week postoperatively with biliary peritonitis. Laparoscopy and washout was performed with placement of a tube drain in the subhepatic space. A tangential injury at the right-hand (lateral) edge of the gall bladder bed was identified. (**a**) MRCP showing an accessory posterior sectoral duct (*white arrow*) with low insertion into the CBD. The tip of the tube drain is visible (*black arrow*). (**b**) Tubogram at 2 weeks post-washout with contrast introduced retrogradely down the drain demonstrating communication with both portions of the accessory duct via a small volume reservoir. Clips on the cystic duct stump are visible in a satisfactory position. Normal anterograde flow of bile is seen in the main CBD and into duodenum. Sepsis and bile leakage were controlled and the leak was successfully managed conservatively. The leak resolved spontaneously in approximately 6 weeks after which the drain was removed

surgical sense in the context of an uninjured remaining biliary tree. ERCP and stenting are not helpful in isolated posterior sectoral duct injury as there is not usually communication with the main biliary tree. In this situation, the right posterior sector may atrophy over time. There is, however, a risk of developing recurrent sepsis in the undrained sector, and in time this may require resection, as discussed below.

Management of Strasberg Type D Injuries

Lateral injuries to the CHD or CBD without transection, affecting <50 % of the circumference of the duct, are associated with a concomitant vascular injury in 20 % of cases [4]. In a report of 10,123 laparoscopic cholecystectomies performed at a single center, the incidence of BDI was 0.2 %, and 70 % of those were Strasberg Type D [17]. The decision to perform a primary suture repair of the injured duct and arrange biliary drainage (through ERCP or T-tube) in addition to peritoneal drainage will depend largely on whether there was a thermal component to the injury. If the lesion has been made using diathermy or any other energy device, it is unlikely that the repair will be effective either in the short term as the injured tissues fibrose and retract, or in the long term, due to stricturing. In cases of thermal injury, particularly if extensive, it is recommended to completely excise the injured portion of duct

trimming back to healthy tissue and reconstruct the biliary tree by hepaticojejunostomy including the left duct. Technical recommendations for this are given below. In cases of a cold injury, i.e., partial section with scissors for example whilst attempting a cholangiogram, it is reasonable to attempt a primary suture repair, with adequate biliary drainage by ERCP and intra-abdominal covering drains. Placement of a supporting T-tube across the anastomosis is unnecessary and likely to be harmful. If immediate direct repair is undertaken, the surgeon should be aware that the failure rate is reported as 64.3 % in a large retrospective series [16].

Management of Strasberg Type E Injuries

The intraoperative recognition of a major BDI should initiate an immediate call for specialist expert assistance. The critical steps that need to be taken quickly and accurately are to, (1) define the level and type of BDI, (2) recognize the presence of associated VBI, (3) rapid appraisal of the general state of the patient in terms of comorbidity and intraoperative instability from sepsis or significant hemorrhage, and, most importantly, (4) decide whether the most appropriate personnel are present in the operating theater to make this assessment, make the decisions, and effect any repair.

All Type E injuries and thermal injuries to the CHD or CBD will eventually require biliary reconstruction. The decision to reconstruct the bile duct at the same operation as the BDI occurred is dependent on having a physiologically stable patient, free from sepsis, without an associated vascular injury. In the absence of these preferred conditions, immediate repair is not recommended due to a high chance of early failure. The revision rate of immediate Roux-en-Y hepaticojejunostomy reconstruction during the index operation in which BDI occurred is 62.9 % [16].

Hepp-Couinaud Hepaticojejunostomy: Technical Aspects

The technique of biliary reconstruction ensuring a wide and long hepaticojejunostomy using the left hepatic duct was described by Hepp and Couinaud in 1956 [18] but did not enter the published literature in English until 1985 [19]. The Hepp-Couinaud technique remains the gold standard for biliary reconstruction. An inverse J-shape incision or bilateral subcostal incision gives excellent exposure. A fixed retractor (e.g., Omnitract™ or Thomson Retractor™) is invaluable for facilitating this. An operating headlight and surgical loupes will enhance the accuracy of dissection and repair. Careful dissection of the undersurface of the liver is performed, and in particular the base of segment 4b is dissected clear so “lowering the hilar plate.” In the acute setting, clips on the cystic artery may be removed and the artery formally ligated. The distal CBD should be identified, and if it has been transected,

any clips should be removed and the distal duct sutured with an absorbable suture, for example, polydioxanone. In the delayed setting, this area will be significantly adherent and fibrosed, and it is not usually necessary or straightforward to identify the distal CBD remnant.

Careful dissection is continued on the anterior surface of the proximal CHD and the peritoneal reflection at the base of segment 4 identified overlying the hilar plate. With gentle traction on the hepatic pedicle (facilitated by a finger in the foramen of Winslow), the hilar plate is lowered to define the left hepatic duct. This may also require opening up of the gallbladder bed and dividing adhesions or any bridge of liver between segments III and IV. The goal is to achieve wide exposure of the damaged ducts and to perform a long wide choledochotomy, which is achieved by incising the CHD and extending it upwards and to the left side along the left hepatic duct. The incision is continued as far the arterial branch to segment 4b crossing from the LHA, but with great care not to injure this small branch. The small segment 4 arterial branch may be dissected free and retracted to the left to allow a further extension along the LHD to achieve a choledochotomy measuring 1.5–2 cm. Excessive extension to the left should not be undertaken as this risks ending up in multiple small subsegmental ductal orifices in the left portion of the hepaticojejunostomy. The right hepatic duct can be visualized through this orifice, and the choledochotomy may be extended towards the RHD if required, although this is rarely necessary given the long transverse lie of the extrahepatic portion of the proximal LHD. Careful dissection to free any adhesions and scar tissue is facilitated by a Cavitron Ultrasonic Surgical Aspirator (CUSA) which will accurately define ductal structures.

A 70 cm retrocolic Roux limb is fashioned to lie tension-free adjacent to the anastomosis. The key to successful repair is a careful accurate mucosa-to-mucosa anastomosis. The authors use a standard Bismuth-type interrupted biliary anastomosis with 5.0 polydioxanone sutures. Many centers advocate the retention of transanastomotic percutaneously placed biliary drains to stent the newly made anastomosis, but in the authors' practice this is not performed routinely, and certainly no new percutaneous biliary drains are placed if none are present at the time of reconstruction. The placement of an intra-abdominal tube drain in the subhepatic space behind the Roux limb is usual but is becoming less favored in the authors' current practice if the anastomosis appears sound/secure.

Although some centers advocate the use of the duodenum for reconstruction [20], this technique is not widely adopted, and in the case of an early leak results in more immediate problems. The authors have observed patients who have experienced significant symptoms from enteric reflux through this anastomosis in patients whose injury was repaired before referral. Secondary cholangitis and biliary cirrhosis have been observed in referred patients. The available literature on outcomes using this technique does not separate BDI from other elective liver operations requiring biliary reconstruction, and until long-term outcome data are available, it is not possible to recommend using the duodenum as a suitable alternative.

Delayed Early Repair

Even with routine use of the Hepp-Couinaud anastomosis, outcomes of immediate (intraoperative or within 7 days), especially with an associated VBI, may leave the patient exposed to recurrent biliary symptoms. It is highly advisable to delay any attempts at repair in the acutely unwell patient with sepsis or other significant organ dysfunction, and particularly in the event of VBI. Surgery in the acute stage will add further to an already stressed physiology and likely lead to a poor outcome, and an anastomosis that will ultimately require revision. Therefore it is advisable to gain control of bile leakage with external intra-abdominal drains, percutaneous transhepatic biliary drains, and adequately treat sepsis. A short general anesthetic for peritoneal washout, completion of the cholecystectomy, and placement of good drains should be considered as part of the surgical resuscitation and stabilization, but the surgeon should avoid the temptation to perform the definitive biliary reconstruction in the acute setting in the unwell patient. This approach is often useful in the patient in whom the BDI has not been recognized intraoperatively, and who may even have got home for a short period before being readmitted acutely unwell with biliary peritonitis and sepsis. A critical care environment is most appropriate for this patient group.

Late Presentation

The long-term consequences of BDI can present over the course of many years [21]. Recurrent episodes of sepsis due to inadequately drained segments may be the presenting features, and in more severe cases, secondary biliary cirrhosis may occur. Recurrent cholangitis can result in intrahepatic lithiasis. The undrained segments will atrophy over time, and this is exacerbated by a VBI [13]. A revision procedure for biliary reconstruction is commonly required and, in particular, for those BDI reconstructed in the early phase [16]. This is technically demanding surgery and not to be undertaken lightly.

Preoperatively, sepsis should be controlled as much as possible, which will often require antibiotic therapy and percutaneous biliary drainage of the affected segments, and attention paid to the nutritional state of the patient and requirement for parenteral vitamin K supplementation. In cases of suspected secondary biliary cirrhosis, Childs-Pugh scoring of liver function to assess risk should be performed, and the presence of esophageal varices excluded by endoscopy. Cross-sectional imaging to define ascites and examine the portal system to document cavernous transformation and the extent of intra-abdominal varices should be performed. Because some revisional surgery will require liver resection, it is critical to define the extent of cirrhosis preoperatively.

Liver Resection Following BDI

Certain situations arise following BDI for which the best treatment option is liver resection. The initial BDI is usually a Strasberg Type E4 or E5 injury [22], or E6, and most often a VBI with injury to the RHA. The indication for liver resection may be largely anatomical, for example if the confluence is so disrupted that a long distance intervenes between the left and right biliary systems (Fig. 28.6), or stricturing extends into the secondary biliary divisions on the right side, or may be because a portion of the liver is either nonfunctioning, ischemic, or becoming a risk to health from recurrent sepsis (Fig. 28.7). The latter situation arises from atrophy due to a combination of chronic biliary obstruction coupled with arterial ischemia, from recurrent sepsis due to undrained segments, abscess formation from arterial injury, or later on, consequences of recurrent cholangitis, for example intrahepatic lithiasis with chronic sepsis. Where the liver damage affects the entire organ and has caused significant secondary biliary cirrhosis with portal hypertension, liver transplantation may be the best option. However, where liver resection is possible, this should be considered, particularly in the non-cirrhotic liver.

The decision to proceed to right hepatectomy may be made easy by the findings of compromised vascular supply, inaccessible right sectional or segmental ducts, and right liver atrophy when the left liver is hypertrophied and/or the left duct is easily accessible allowing a wide bilioenteric anastomosis. Conversely, the finding of a small left liver may require a left duct approach with either drainage of the left ducts or a compromised anastomosis to the right ductal system which if it fails in the longer term would still allow an option of a delayed right hepatectomy.

The frequency of liver resection after BDI ranges from 1 % to 16 % [22–24]. Right hepatectomy is by far the most commonly performed resection, accounting for 80 % of hepatectomies [22]. Mortality is higher than in most series of liver resection, at 11.1 % overall in published cases, with some series reporting mortality as high as 27 % [25], and the biliary fistula rate in published studies ranges from 25 % to 39 %. Long-term outcome is good; for example in the patient series of Laurent et al. 13 of 18 patients were symptom free after a median of 8 years after hepatectomy [23].

Outcomes

Operative morbidity and mortality after BDI depends on age, comorbidity, untreated sepsis, and underlying liver disease. In particular, liver cirrhosis is associated with a high operative (within 30 days) mortality, ranging between 5 and 23 % [26]. The rate of recurrent biliary stricture is approximately 11–19 % in most series [27], and risk factors include biliary cirrhosis at the time of hepaticojejunostomy and sepsis

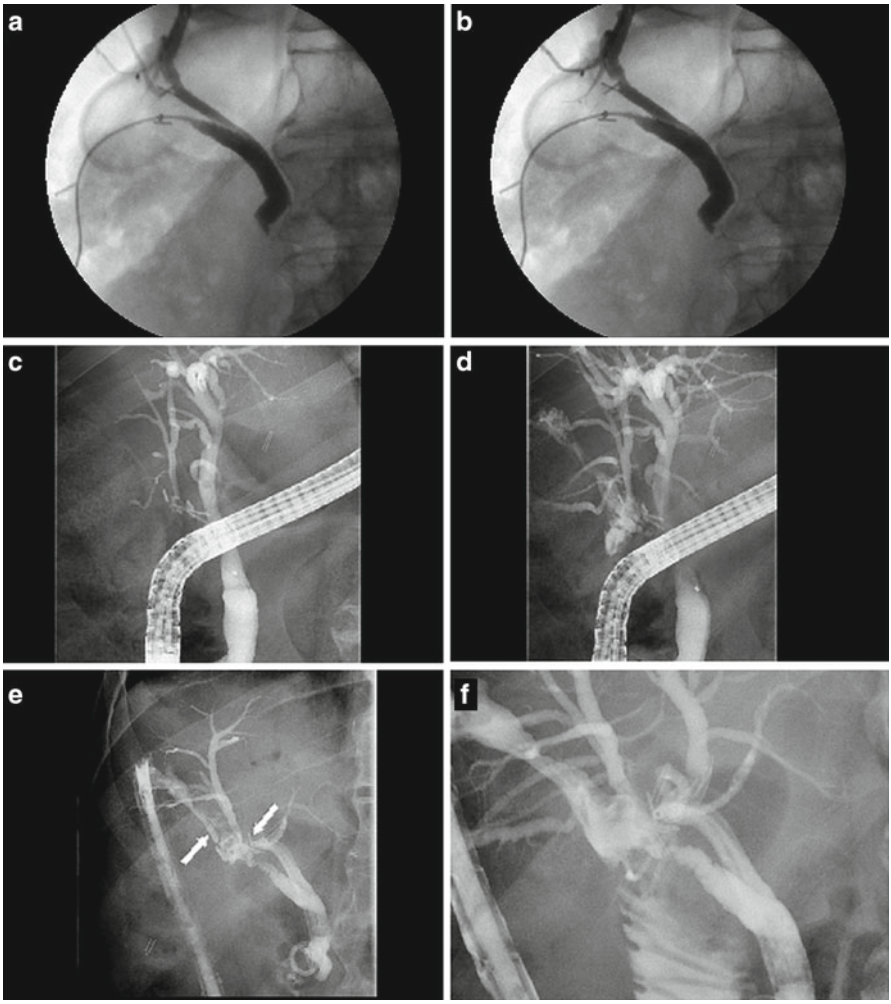

Fig. 28.6 A significant right main hepatic duct injury (Strasberg E5) likely to require right hepatectomy. This injury was recognized intraoperatively at laparoscopic cholecystectomy and the operation converted to open but the extent of the injury was underestimated at that time. (**a**) Initial image from the intraoperative cholangiogram performed via the cystic duct. Two clips ("X marks the spot") overlay the right main hepatic duct near its origin. The right anterior sectoral duct partially fills but is suggestive of injury or partial occlusion. (**b**) The next IOC image taken shows retrograde filling of some right posterior sectoral ducts which drain into the left main duct but no further filling of the anterior sector. Drains were placed. (**c** and **d**) ERCP on day 4 showing the left ductal system in continuity and clips at the origin of the right main duct with partial retrograde filling of the right anterior sectoral ducts. Further contrast injection shows leakage out of the duct with secondary filling of right-sided ducts no longer in continuity. (**e**). Tubogram filling the right ductal system demonstrating clips in an abnormal position (*white arrows*). (**f**) Close-up tubogram image showing an absent portion of the right hepatic duct between the incorrectly sited clips. This patient is being managed by drainage and sepsis control with a plan for interval right hepatectomy in 3 months

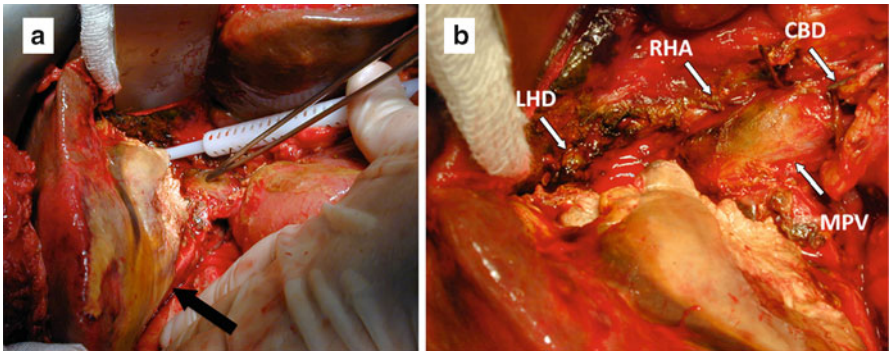

Fig. 28.7 A major vasculobiliary injury with complete excision of the extrahepatic bile duct (Garden E6). (**a**) Initial operative view shows obvious devascularization of the right hepatic lobe with necrosis (*black arrow*). (**b**) Careful exposure and identification of the extent injury shows a complete excision of the extrahepatic biliary tree. Indicated by *white arrows* are the left hepatic duct orifice (LHD), the right hepatic artery which has been clipped and divided (RHA), the distal remnant of the common bile duct which has been clipped and divided (CBD), and the entire length of the main portal vein that has been denuded (MPV). This patient proceeded to right hepatectomy and Roux-en-Y biliary reconstruction

at the time of primary repair are associated with increased long-term stricture rates [28]. These data include Hepp-Couinaud reconstructions done by experts at high volume centers. Although many reconstruction failures requiring revision occur within 2 years, 20–40 % present beyond 5 years after the initial surgery [26]. Long-term follow-up is therefore an important part of management, as the development of secondary biliary cirrhosis missed due to lack of follow-up may preclude revisional surgery and mandate liver transplantation. The rate of liver transplantation after BDI is low (5.7 % of patients in one series [29]), but not negligible, and always in the setting of secondary biliary cirrhosis.

It should be borne in mind that late development of cholangitic symptoms may result from reflux from a Roux limb that is compromised by adhesions favoring reflux of intestinal content into the biliary tree, or from a short Roux limb. The authors have also observed some patients whose recurrent cholangitis pursues a nocturnal pattern and has been found to be due to stasis in a redundant end of a previously constructed Roux limb. Investigation of these patients with CT or barium studies may be helpful in establishing whether revisional surgery short of resection or transplantation can be considered.

Medicolegal Considerations

In a large series of patients who had undergone BDI and surgical repair at Johns Hopkins Hospital, 62 of 167 patients responded to a quality of life questionnaire, 70.5 % sought litigation for their injury, and a similar proportion felt that they had

"won" their case [30]. In the United Kingdom, the majority of BDI for which the patients seeks redress through litigation are settled prior to court. It would be good practice in most healthcare organizations for a surgeon who injures the bile duct during elective laparoscopic cholecystectomy to inform his or her clinical director. Good practice and an institutional culture of safe patient care should include some form of audit of BDI and a reappraisal of the laparoscopic surgical technique employed to ensure that any one process, team, or individual is not an outlier with regard to BDI. Because in most occurrences of BDI the injury arises as a misperception of anatomy and errant anatomical orientation, the surgeon will find it difficult to avoid being deemed culpable for the injury. It is important to be clear that a mistake does not necessarily imply negligence on the part of the operator, although there are now accepted anatomical orientation strategies to minimize the risk of BDI and undertake safe laparoscopic cholecystectomy.

Quality of Life

All patients who sustain unexpected complications as a result of surgery are at risk of a decrease in health-related quality of life (HRQOL). Patients who sustain a BDI during the course of elective laparoscopic cholecystectomy are particularly at risk, although there are conflicting reports and opinions in the literature and among surgical profession and the medicolegal community. In a large series, patients reported negative effects of biliary drains on intimacy, appearance, practical activities of daily living, and embarrassment. Half of patients reported low mood and lassitude. Chronic pain is an issue, and more so in the longer-standing injuries [30]. Interestingly, mental QOL scores were worse overall in comparison to physical components of the scores [31]. Certainly, an effective biliary reconstruction appears to improve HRQOL compared to the preoperative state in one study examining exclusively Type E injuries, but whether scores ever return to those present prior to BDI is not known [32]. In a meta-analysis of six HRQOL studies after BDI, Landman et al. confirmed a long-term detriment on mental HRQOL after BDI [31].

Practical Considerations: SCARF

In summary, the key practical considerations when faced with a BDI are to do no further harm, evaluate the injury, and ensure that the most appropriate repair strategy is followed that is likely to result in the best long-term outcome for that patient. Specific considerations are summarized in Table 28.1 and follow the mnemonic, SCARF.

Table 28.1 SCARF: a practical approach to management of bile duct injury

S is for	Safety	Is the patient safe from further immediate harm?	Ensure adequate control of life-threatening hemorrhage
	Sepsis	Are adequate measures in place to treat sepsis?	Administer appropriate antibiotic therapy. Resuscitate appropriately
	Surgeon	Is the surgeon in charge of care the most suitable individual?	Consult an expert hepatobiliary specialist who was not involved in the primary injury
C is for	Containment	Have steps been taken to limit further extension of the injury?	Avoid further unnecessary or uncontrolled dissection which may cause or exacerbate vasculobiliary injury
	Control	Is there adequate and effective control of bile leak?	Place suitable external drains in the peritoneal cavity. Consider the requirement for percutaneous or endoscopically placed biliary drains
A is for	Artery	Is there an associated vascular injury?	Obtain CT angiogram to define the hepatic arterial system
	Anatomy	What is the precise anatomical extent of the biliary injury?	Obtain cholangiogram, either intraoperatively if safe to do so, or postoperatively by MRCP, by ERCP, or via percutaneous transhepatic biliary drain
R is for	Repair	Is the repairing surgeon experienced in the Hepp-Couinaud technique?	Perform a Hepp-Couinaud biliary reconstruction, extending along the left hepatic duct
	Revision	Is the previous biliary repair satisfactory?	With careful consideration to optimum timing, perform an expert revision by the Hepp-Couinaud technique
F is for	Follow-up	Are adequate follow-up arrangements scheduled?	Serial clinical assessment and imaging by MRCP and serum liver function tests should be in place
	Further surgery	Is there recurrent sepsis? Risk of secondary biliary cirrhosis? Other complications, e.g., intrahepatic lithiasis	Consider liver resection of the affected segments. Be aware that liver transplant is a recognized consequence of BDI

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Chapter 29
Commentary: Operative Repair of Common Bile Duct Injury

Javier Lendoire

Iatrogenic bile duct injury (BDI) can occur in any surgical procedure performed in the upper abdomen, but cholecystectomy remains the leading cause of these injuries. Still an unsolved problem of laparoscopic cholecystectomy, BDI occurs with an unacceptable frequency even in the hands of experienced surgeons and remains a matter of concern despite substantial experience accumulated with the operative repair. The chapter by Mole D and Garden J provides a broad overview of the mechanisms, diagnosis, management, and outcome of the different types of BDI. The authors also propose a practical approach for the management of BDI.

Pathogenesis of BDI presents different aspects to be analyzed. Misidentification of the cystic duct is the most common error in 97 % of the BDI. Constructing a mental image that convinces the surgeon that the common bile duct or the right hepatic duct is the cystic duct amounts for the central error in most of the injuries. Risk factors like severe inflammation of the gallbladder or troublesome hemorrhage can be associated with the different types of injuries. Faults in technical skill are present in only 3 % of the procedures. In reference to the mechanism of injury, the thermal lesion, more commonly associated to the laparoscopic approach can result in large bile duct defects and vascular damage due to the thermal spread of the diathermy. As the authors highlight, at the time of the suspected iatrogenic injury it is critical to consider as a priority the patient safety. It is estimated that the majority of BDI are still managed at the facility where the injury occurred and that the definitive biliary repair is frequently performed by the surgeon responsible for the injury [1]. Primary and secondary repairs by the primary surgeon are associated with reduced success rates and increased risk of death. If a BDI is recognized intraoperatively a primary repair can be attempt, usually not by the primary surgeon, whose judgement is compromised but by a second experienced HPB surgeon. In this way the

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morbidity, the hospital stay and the hospital costs will be reduced. An inadequate primary repair will increase the incidence of biliary stenosis and introduce complications that will need new therapeutic procedures. Especially in cases of complex injuries, every attempt to repair the injury goes up in the biliary tree and can severely damage the duct confluence with the possibility of isolating the right or left hepatic ducts. The common guidelines to be followed for an operative BDI repair are the following: expose the damaged area avoiding too much dissection, observe that the end of the injured bile duct is free from burns and attritions, perform intraoperative cholangiography in every bile leak, confirm vascular integrity, perform an hepaticojejunostomy with an isolated Roux-en-Y with opposition of both mucosas and reabsobable sutures, preferable with the use of magnification. Laparoscopic repair of a BDI can also be performed following these guidelines in up to 1/3 of the patients diagnosed intraoperatively most commonly in Strassberg types A–D. The selection of the appropriate patient according the experience of the surgeon in HPB and laparoscopic complex techniques are highly relevant for the outcome.

The era of laparoscopic cholecystectomy brought a higher incidence of complex biliary injuries, in general more difficult to diagnose and treat. A practical definition for a complex BDI comprise (1) injuries that involve the confluence, (2) injuries in which a repair attempt have failed, (3) any type of BDI associated with a vascular injury, or (4) any type of BDI associated with portal hypertension or secondary biliary cirrhosis. As the authors showed, concomitant vascular injuries are present in a wide range (12–61 %) and it occur more frequently than believed in the past. Although the routine use of arteriography in patients with BDI from referral centers have demonstrated 41–61 % of right hepatic injury, it seems that the real frequency of this type of injury is around 25 %. A vasculobiliary injury may be classified into two types of which the right hepatic artery injury accounts for about 90 %. The uncommon type of vasculobiliary injury involves the proper hepatic artery, the common hepatic artery, the main portal vein or a combination of those. Clinical presentation can range from non-specific symptoms, most of them in patients with a right hepatic arterial injury, to the development of a pseudoaneurysm with intraperitoneal or intrabiliary haemorrhage (hematobilia) or a rapid progression to a hepatic infarction. Up to 67 % of the vasculobiliary injuries will present liver ischemia that can progress to sepsis, liver abscess, or atrophy. Strassberg et al demonstrated an association between extreme vasculobiliary injuries and a fundus-down cholecystectomy technique attempted in the presence of severe inflammation in and around the gallbladder [2]. According to the authors prevention of such injuries requires the surgeon to recognize the features of severe contractive inflammation and avoid the fundus down technique when these conditions are present. Immediate repair of vasculobiliary injuries in general should be avoided. Arterial anastomosis is an exception, should be attempted by surgeons with experience, most of them in liver transplantation but the benefit has not been clearly demonstrated. Right hepatic artery ligation in a noncholestatic liver is usually well tolerated without important clinical consequences owing to blood from collateral vessels. Understanding the blood supply to the liver is critical for the timing of the bile duct repair in cases of complex injuries. Longitudinal and hilar shunts thru the marginal and hilar arteries, well depicted by

the authors, are critical in the outcome of the biliary repair in patients with associated vascular injury. Radiological intervention plays a critical role in this type of injuries that usually require a delayed surgical repair. In selected cases of early repair a Hepp-Couinaud reconstruction represents the most successful approach to avoid postoperative anastomotic stricture. In rare situations, management of complex BDIs requires liver resection or transplantation. As the authors states, up to 16 % of liver resection for BDI has been reported. Patients with combined arterial and Strasberg E4 or E5 injury presents 43.3 times more risk of requiring hepatectomy for definitive treatment. Concerning the timing of the liver resection, two groups of patients became evident in a recent study by Li et al. First, those with an injury-induced liver necrosis that required an early resection within a few weeks after BDI. Second, a group were liver resection was indicated several months or years after cholecystectomy for the treatment of liver atrophy following long-term cholangitis due to biliary strictures [3]. In a recent review, only 9 % of the resected patients required an urgent procedure but with a high mortality rate. In patients with extensive ischemia and fibrotic biliary lesions performing an hepatectomy could provide better results and long term outcomes in comparison with a repeat hepaticojejunostomy. Comparative studies are needed to precisely determine the circumstances in which hepatectomy might be justified. Successive failures of therapeutic procedures or the use of inappropriate treatments may be the cause of late complications such as portal hypertension and secondary biliary cirrhosis. As a result of the development of such complications, a small proportion of patients with complex lesions may require a liver transplantation as the only possible treatment. In total 63 patients with liver transplantation in an acute and chronic settings were reported in the English literature. In the first National survey by Ardiles et al., a significantly decrease in the use of liver transplantation for BDI was demonstrated [4]. The explanation can be related to an improvement of the understanding of the pathology, better prevention of the injuries, more appropriate initial management, and a multidisciplinary and specialized approach of the complications. Ten years survival of these series was 45 %. There are three scenarios of the indication of liver transplantation for BDI that require consideration: the first is acute liver failure (within 24–48 h) due to massive ischemic liver necrosis as a result of an associated vascular injury of the hepatic artery and portal vein. Although death is common before liver becomes available, liver transplantation offers the only chance of survival. The second scenario is when acute liver failure develops later (after weeks, months) owing to sepsis of hepatic origin. It is related to stenosis of hepaticojejunostomy and can be associated with a vascular injury and liver necrosis. The indication of liver transplantation should be assessed carefully in each of these patients. Third scenario is secondary biliary cirrhosis caused usually by a long standing anastomotic stricture or multiple biliary strictures. Patients must be included in the waiting list and timing of transplantation is critical to achieve comparable results with other transplant indications [5].

Surgical community needs to work towards creating a safety culture where even a rare event like BDI are accounted for by better training and standard use of safety measures. Regularly reporting of injuries is critical to better understand its consequences and provide more effective actions into their prevention.

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Chapter 30
Management of Isolated Sectoral Duct Injury

Michael G. House

Chapter Text

The most common cause of benign strictures involving the intrahepatic bile ducts is injury occurring either as a single event or with recurring inflammatory insults. Depending on the degree and chronicity of inflammation, ductal and periductal fibrosis of the intrahepatic bile ducts may lead to stricture formation with a solitary focal pattern or extensive multifocal segmental stricturing throughout the liver. The latter pattern is classically associated with primary sclerosing cholangitis, biliary cirrhosis, or biliary sclerosis, conditions which are covered in other chapters included in this textbook.

This chapter focuses predominantly on ischemic-type strictures involving intrahepatic segmental and sectoral bile ducts. Such strictures reflect a direct injury to the bile duct epithelium or the pericholangiolar arterial plexus. Intrahepatic bile duct strictures lead to dilatation of the upstream branches of the intrahepatic biliary tree corresponding to the segments drained by the affected bile duct. Depending on the location of the bile duct stricture (e.g. hepatic duct, sectoral duct, segmental duct), intrahepatic ductal dilatation may emerge with a hemiliver, sectoral, or segmental pattern which may be detected incidentally on transabdominal ultrasound or cross-sectional imaging.

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Clinical Presentation and Radiographic Appearance

Clinical jaundice is typically not a component of the clinical presentation for patients with a sectoral or segmental bile duct stricture, and alterations of serologic liver function tests are usually subtle. Patients are commonly asymptomatic, but depending on the etiology of the bile duct stricture and precedent medical history, they may present with cholestatic symptoms (e.g., pruritus) or cholangitis (e.g., fever, malaise). Chronic strictures of the intrahepatic bile ducts may be associated with segmental or sectoral patterns of liver parenchymal atrophy which are apparent on imaging but usually not associated with metabolic or synthetic hepatic insufficiency.

The most important, and occasionally most difficult, aspect of evaluating a patient with an intrahepatic bile duct stricture is differentiating between a benign and malignant etiology of the stricture. Table 30.1 lists the most common diagnoses responsible for strictures of the intrahepatic bile ducts. While this list is extensive, diagnostic evaluation should begin with testing directed at determining the nature and pattern of biliary stricture formation. After careful clinical history taking, diagnostic imaging plays a vital role in determining the nature of the biliary stricture. Ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) provide useful information, and are usually included with the initial evaluation of an intrahepatic biliary stricture prior to surgical referral. MRI with intravenous contrast enhancement and cholangiopancreatography (MRCP) modality offers detailed imaging to determine best the nature, extent, and pattern (segmental, sectoral, hemiliver) of biliary strictures, Fig. 30.1.

Risk for Isolated Sectoral Bile Duct Injury

Bile duct injuries encountered during cholecystectomy account for the majority of postoperative strictures involving only a sectoral bile duct. The misidentification of an aberrant right posterior sectoral hepatic duct as the cystic duct may lead to errant ligation or division of this sectoral duct during laparoscopic or open cholecystectomy. The wide range of anatomic variations of the anterior and posterior sectoral ducts of the right system place them at greatest risk during cholecystectomy. Low-entry insertion of the right posterior sectoral duct into the common bile duct is a particular high-risk situation for a Bismuth V bile duct injury during cholecystectomy. Preoperative imaging, especially MRCP, or intraoperative cholangiography may assist recognition of aberrant right hepatic duct anatomy and guide operative strategies and techniques to avoid inadvertent injuries [1]. Postoperative sectoral bile duct strictures may also result from partial hepatectomy, liver transplantation, common bile exploration, biliary dissection during pancreatoduodenectomy, or hepaticojejunostomy [2]. The latter two procedures result in isolated

Table 30.1 Diseases associated with intrahepatic bile duct strictures

Benign diseases	Malignant diseases
Iatrogenic bile duct injury	Cholangiocarcinoma
Traumatic liver injury	Gallbladder carcinoma
Primary sclerosing cholangitis	Hepatocellular carcinoma
Recurrent pyogenic cholangitis	Mixed cholangiohepatocellular cancer
Autoimmune sclerosing cholangitis	Biliary cystadenocarcinoma
HIV-associated cholangiopathy	Metastases to bile ducts
Radiation-induced cholangiopathy	
Ischemic biliary sclerosis (vasculitis, drug induced)	
Biliary cystadenoma	
Bile duct hamartoma	
Biliary-type IPMN	

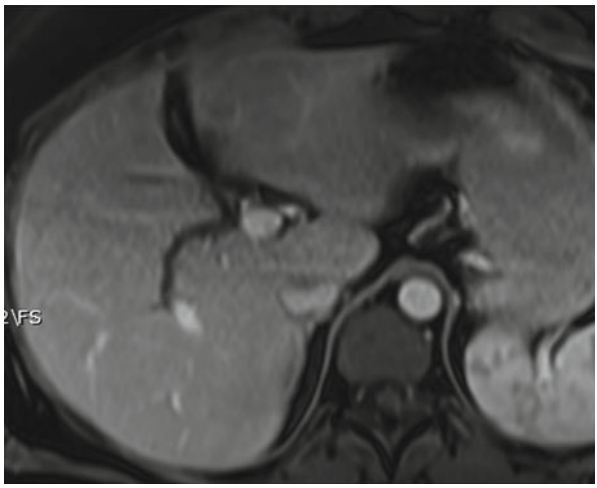

Fig. 30.1 Isolated dilation of the right posterior sectoral duct 1 month after laparoscopic cholecystectomy. The MRI and MRCP images show no evidence of *right* hepatic artery injury

sectoral bile duct strictures or leaks when aberrant ductal anatomy is not recognized intraoperatively. Biliary T-tube insertion has been associated with sectoral bile duct strictures often in conjunction with common hepatic duct strictures. Electrocautery injuries and extensive circumferential dissection of the perihilar bile ducts can lead to ischemic strictures which often present months to years after injury. In approximately 15 % of patients, the right anterior or posterior hepatic duct joins the left duct independently [3]. Such anatomic variations potentiate postoperative isolated sectoral duct leaks or strictures after left hemihepatectomy.

Management

A postoperative sectoral bile injury associated with a bile leak is a particularly challenging problem to manage. Initial management should be focused on controlling the bile leak with percutaneous drainage along with imaging to characterize the level of injury and any associated vascular injuries (e.g., hepatic artery branch). Contrast-enhanced CT and MRCP are useful in this regard, Fig. 30.2. Percutaneous drains within subhepatic bile collections can be used to identify an elusive sectoral origin of a bile duct leak with careful fluoroscopic drain sinography.

Endoscopic retrograde cholangiopancreatography (ERCP) and endobiliary drainage are helpful only in cases when a partial thickness injury of a sectoral bile duct has occurred. In most cases, sectoral duct injuries are isolated from the extrahepatic biliary tree and not identified on ERCP.

Percutaneous transhepatic cholangiography with biliary drainage of a non-dilated sector of the liver can be considerably difficult. However, percutaneous catheter access of a transected sectoral duct facilitates delayed operative identification of the duct injury and successful biliary enteric anastomosis. Some experts advocate prolonged transanastomotic stenting for up to 12 months to avoid biliary restenosis of a small non-dilated sectoral duct incorporated into a cholangiojejunostomy even though this adjunctive measure may not be feasible or necessary in all cases [4].

In the absence of an active bile leak, patients with sectoral bile duct strictures will present many months or even years after injury [5]. As discussed above, sectoral injuries may present with subtle alterations of hepatic function testing, cholestasis, cholangitis or pain. Initial evaluation of an isolated sectoral bile duct injury begins with contrast-enhanced cross-sectional imaging, ideally MRCP, to determine the level of duct injury, perfusion of the hepatic artery branches, and the presence of sectoral or segmental liver atrophy [6, 7].

Remote bile duct injuries resulting in strictures associated with sectoral liver atrophy in asymptomatic patients do not require restorative interventions [8]. Symptomatic patients with sectoral duct strictures and respective liver atrophy resulting from remote bile duct injury are best treated with partial hepatectomy,

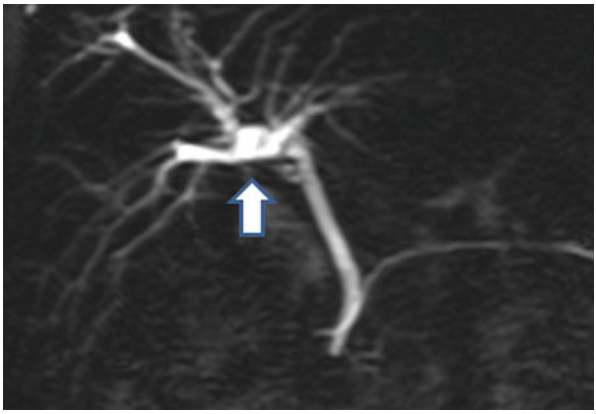

Fig. 30.2 Haste sequences of this MRCP demonstrate dilation of the *right* posterior sectoral duct. The *white arrow* marks the site of stricture of the posterior sectoral duct relative to the confluence with the anterior sectoral duct

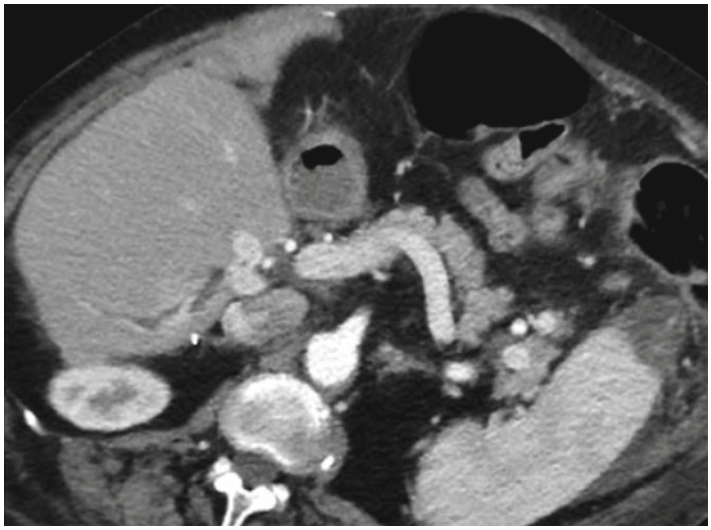

Fig. 30.3 Atrophy of the right posterior liver sector is displayed on this CT scan from a long-standing stricture of the posterior sectoral duct following a ligation injury during open cholecystectomy

e.g., anatomic sectorectomy or bisegmentectomy, Fig. 30.3. Symptomatic strictures that are recognized relatively soon after injury and before liver atrophy is apparent should be managed with restorative intent up front with plans for operative cholangiojejunostomy. Depending on the level of sectoral duct stricture, biliary enteric anastomosis may require hepatic parenchymal dissection in order to prepare the sectoral duct for technical suturing. Occasionally, a lengthy or intrahepatic sectoral duct stricture may not be amenable to biliary reconstruction. These situations require hepatic sectorectomy/sectionectomy. Biliary enteric anastomoses which are performed under potentially ischemic conditions (e.g. hepatic artery injury) may be associated with delayed or long-term biliary stricturing and restenosis. Few outcome data exist, but many surgeons favor hepatic resection over biliary reconstruction under these circumstances.

Summary

Injuries to isolated sectoral bile ducts are diagnosed early when active bile leaks are present. Controlling the bile leak and characterizing the ductal anatomy and any associated injuries are fundamental principles of management prior to definitive operative repair. A sectoral duct stricture with secondary liver atrophy from a remote injury requires hepatic resection instead of biliary drainage in the symptomatic patient. Symptomatic patients with a sectoral duct stricture from a recent injury should undergo restorative internal bilioenteric drainage after careful preoperative imaging and assessment.

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Chapter 31
Commentary: Management of Isolated Sectoral Duct Injury

Invited Commentary

Reid B. Adams and Claude A. Jessup

Intrahepatic Bile Duct Stricture—Etiology, Evaluation, and Treatment

An isolated intrahepatic bile duct stricture or injury is uncommon. When it occurs, it can be a vexing problem. Following hepatic trauma or operation, an intrahepatic duct may be injured directly or from ischemia. Typically this is an asymptomatic finding noted during follow up imaging. The ducts proximal to the site of trauma or surgery are dilated and do not require therapy. It would be rare for a patient to develop either pain or cholangitis in the area of the dilated ducts that required therapy. Pain in this circumstance is treated symptomatically with medication. Cholangitis in the affected bile ducts is treated with antibiotics and drainage by placement of a percutaneous transhepatic catheter (PTC). In either case, persistent or recurrent symptoms may require resection of the affected hepatic segments, although this would be rare.

Equally problematic is the finding of asymptomatic intrahepatic biliary dilation (imaging done for another indication or for vague upper abdominal symptoms) without a history of injury or a known inflammatory process. The concern with this finding is distinguishing a benign versus malignant etiology. The presence of a mass in conjunction with an isolated ductal stricture raises the likelihood of cholangiocar-

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cinoma, which should be treated accordingly. However, in the absence of a mass, the differential diagnosis includes a small (non-mass forming) cholangiocarcinoma, IgG4-related or unilobular primary sclerosing cholangitis, or a nonspecific inflammatory stricture. Practically, these are difficult to separate from each other. An elevated serum IgG4 is consistent with IgG4 sclerosing cholangitis, which is treated with a course of steroids. In the absence of an elevated IgG4 or a response to a course of steriods, however, it is difficult or impossible to rule out a small cholangiocarcinoma. Hence, hepatectomy of the affected bile duct and its surrounding parenchyma becomes the practical treatment option for this presentation.

Finally, another cause of intrahepatic biliary strictures is recurrent pyogenic cholangitis (oriental cholangiohepatitis), which is endemic in Southeast Asia. While uncommon in the USA, the incidence is increasing in the West as a result of immigration. Stone formation in the intrahepatic ducts leads to multiple ductal strictures and cholangitis. While the details are beyond the scope of this chapter, the treatment is multidisciplinary combining radiological, endoscopic, and surgical approaches.

Most commonly, the initial finding of biliary dilation is by ultrasonography or computed tomography. Definitive imaging, however, begins with contrast-enhanced magnetic resonance imaging (MRI) including an MR cholangiogram. This defines the ductal and vascular anatomy and detects any associated masses. Cholangiography, whether percutaneous or endoscopic, may be helpful in some cases to define the anatomy, perform biopsies (although the diagnostic yield is low), or drain the occluded ducts. A non-operative approach is rarely definitive therapy, though. In patients with a chronic stricture, hepatic parenchymal atrophy, in the distribution of the obstructed ducts, is commonly seen on cross-sectional imaging. Jaundice does not occur in patients with hemi-lobar or smaller areas of atrophy unless there is concurrent hepatic parenchymal disease or dysfunction.

Sectoral Bile Duct Injury Management

Strasberg classifies sectoral bile duct injuries following cholecystectomy as Type B, C, E4 and E5. Type B and C injuries are isolated sectoral (typically right posterior) ductal injuries, usually due to aberrant right hepatic ductal anatomy. E_4 injuries involve a stricture at the confluence of the right and left hepatic ducts, effectively isolating the right and left ductal systems. An E5 injury is a combination of an aberrant right sectoral bile duct injury and an E_4 stricture. Each of these injuries requires a different approach for treatment.

The critical first step in treating this group of patients is to control any bile leak and treat their sepsis. Typically one begins by percutaneous drainage of all bilomas. If this is insufficient, a laparoscopic approach with abdominal irrigation and drain placement is helpful, particularly if diffuse bile peritonitis is present. Following treatment of the bile peritonitis or biloma, a contrast enhanced MRI and MRCP is done to elucidate the biliary and vascular anatomy. Establishing the status of the right hepatic artery is important as the incidence of concurrent right hepatic artery

occlusion in patients with a biliary injury is estimated to be>20 %. Furthermore, right hepatic artery occlusion is associated with a higher rate of anastomotic stricture following repair; thus, it impacts the timing and nature of the repair.

The type of bile duct injury dictates the approach to biliary drainage; the goal in all cases is to effectively drain each isolated segment/sector of the biliary tract. This may require placement of one or more PTCs. We usually wait a minimum of 12 weeks following control of sepsis and the biliary tract prior to pursuing definitive surgical therapy. This allows for resolution of the acute inflammation that accompanies biliary sepsis or biloma and the evolution of any additional bile duct stricturing that may occur as a result of a thermal or ischemic injury. In addition, this gives time for the development of collateral circulation to the right ducts and liver from the intact left hepatic arterial branches. Because of the tenuous nature of high hilar injuries or a minimal length of the residual aberrant right sectoral duct, this approach seems prudent to insure an optimal, well vascularized repair. We consider and perform immediate repair (<7 days from injury) for less complex injuries (E_1 and E_2) in patients without sepsis or right hepatic artery occlusion.

Strictures that appear late (>3 months) usually have an insidious onset of symptoms (jaundice or pain) and don't have bilomas or an acute inflammatory component. Once the biliary anatomy is fully understood and appropriate preoperative management is completed, the patient can be taken to surgery for definitive repair. Regardless of the antecedent presentation, before a patient is taken to the operating room for definitive surgical repair, it is critical that a complete cholangiogram is performed. We find three-dimensional cholangiography or cholangiography combined with computed tomography helpful in complex cases to insure the entire biliary tract has been defined and to understand the anatomy. Prior to repair, each isolated bile duct segment/sector should have a PTC placed within it and the tip advanced to the distal most part of the duct. This significantly facilitates intraoperative identification of the occluded bile duct(s). We work closely with our interventional radiologist to manage these patients, as their expertise is essential to successful therapy.

Type B injuries limited to a sectoral duct, in the absence of cholangitis, tend to be asymptomatic. These do not require therapy. Rarely, a patient may present with persistent right upper quadrant abdominal pain due to the atrophic sector and strictured, dilated duct. Alternatively, and also rare, they may develop cholangitis in the atrophic, obstructed sector. Resection of the affected sector, following PTC drainage and antibiotics if cholangitis is present, is appropriate therapy. If a type B injury of the main right hepatic duct occurs, this may present early with serum liver test abnormalities or cholangitis; asymptomatic lobar atrophy usually presents late as an incidental finding. Again rarely, patients may present late with persistent pain attributable to the stricture and/or lobar atrophy. If a main right hepatic duct occlusion is discovered early, it is treated preoperatively as outlined previously followed by definitive restoration of bilioenteric continuity with a Roux-en-Y hepaticojejunostomy. When a patient has lobar atrophy and cholangitis or pain, or has a concurrent right hepatic artery injury, right hepatectomy is a safe and effective treatment option.

Type C injuries are discovered acutely due to symptoms from the bile leak. Consequently, when they are ready for definitive therapy, treatment is restoration of bilioenteric continuity by hepaticojejunostomy. If the duct is a sectoral duct and very small, ligation is an option, but not preferred due to the risk of cholangitis developing in the ligated ductal system.

Type E_4 and E_5 injuries require complex repairs as outlined in prior publications. A key feature to these repairs, as well as some type C repairs is division of the cystic plate at its junction with the anterior right portal pedicle to allow access to the right bile duct(s). Exposure of the bile ducts at the portal plate require lowering of the portal plate (Hepp-Couinaud approach); using the ultrasonic dissector to excavate or resect liver around the end of the normal or aberrant right hepatic duct facilitates additional exposure, if necessary.

Other technical tips include cutting the end of the PTC tube flush with the ductotomy and placing a retaining suture through the cut end of the tube. The tube is then pulled up into the duct proximal to the ductotomy. In this way, the tube can be pulled down into the area of the anastomosis with the retaining suture, if necessary. If not, the suture is cut and removed prior to completing the anastomosis. By doing this, the tube is not in the anastomosis when it is constructed. We find this much easier than trying to construct the anastomosis around a tube within the ductotomy. We do not stent the bilioenteric anastomosis with a PTC or other tube. One only has to look at the inflammatory changes present in the common bile duct after placement of a plastic endoprosthesis to appreciate the extent of the inflammatory reaction from these tubes. Empirically, this cannot be healthy for the bilioenteric anastomosis, particularly since many of these are done to relatively small ducts. The PTC tube is left proximal to the anastomosis and prior to discharge a cholangiogram is performed. If there is no leak and the anastomosis is widely patent, the tube is removed before the patient goes home. If there is anastomotic edema, leak or other problem, we leave the tube in place for several weeks and repeat the cholangiogram later. If needed, the PTC can be exchanged and advanced through the anastomosis.

Another important issue is fastidious construction of a mucosal to mucosal anastomosis between healthy biliary and jejunal epithelium. To insure the jejunal mucosa is present at the anastomosis, the mucosa is always tacked to the serosa at the jejunotomy site using interrupted 6–0 absorbable monofilament sutures. This looks similar to a colostomy when finished and insures that the jejunal mucosa opposes the biliary epithelium in the anastomosis. This is particularly useful when doing an anastomosis to a small duct with limited visibility. Finally, the anastomosis is constructed in a fashion described by Blumgart many years ago. We use interrupted 6–0 or 5–0 monofilament absorbable sutures to construct the anastomosis. The anterior row is placed first as this tents open the duct orifice and facilitates placement of the posterior row of sutures. The posterior row sutures are placed so that the knot will be tied within the anastomosis. After placing the posterior row sutures, the bowel is "parachuted down" to the bile duct and the posterior sutures tied. Prior to placing the anterior row of sutures, place the tip of a right angle clamp through the open

anterior portion of the anastomosis and into the bowel, opening the clamp to insure that none of the anterior mucosa is trapped in the anastomosis. This prevents partial anastomotic obstruction from mucosal bands. Since the jejunal mucosa was already tacked to the serosa, it is relatively easy to place the anterior sutures through the jejunotomy, confident that the mucosa is present at the site of apposition with the bile duct. The anterior sutures are tied externally. A closed suction drain is placed in the sub-hepatic space.

Sectoral bile duct injuries are challenging clinical situations. As a result, following the fundamental principles outlined in this chapter and the associated references are essential to obtaining an optimal therapeutic outcome.

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Chapter 32
Liver Resection for Bile Duct Injury

Michael D. McCall, Alexander K. Bressan, and Elijah Dixon

Introduction

Cholecystectomy is one of the most common procedures performed by the general surgeon, it is estimated that over 600,000 cholecystectomies are performed in the USA every year [1]. With the advent of the laparoscopic version of this procedure, the indications are broadening and the number of cases is ever increasing [2]. Unfortunately, the number of complications is also increasing. These complications may include: wound infection, abscess formation, bile leak, hemorrhage, and bile duct injury (BDI). Injury to the common bile duct is a rare event, occurring in anywhere from 0.3 to 0.6 % of cases [3–5]. This rate is nearly double that of the pre-1990s era, before the introduction of laparoscopic cholecystectomy, and has remained constant despite advances in technique and technology [6–8]. This consistent rate of injuries could be related to the number of new surgeons performing laparoscopic cholecystectomies or to the increased complexity of cases being attempted via a laparoscopic approach [9]. At the extreme, this would equate to over 3000 ductal injuries each year in the USA alone.

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It should be noted that while iatrogenic causes lead to the vast majority of bile duct injuries and strictures, this is not the only source. Congenital strictures can form in cases of biliary atresia or with congenital cysts. Trauma, endoscopy, and percutaneous biliary procedures can all lead to bile duct injury and strictures. Finally, inflammatory strictures can form in a multitude of situations. These could include chronic pancreatitis, Mirizzi's syndrome, choledocholithiasis, and primary sclerosing cholangitis [10]. The majority of this chapter focuses on bile duct injuries caused during operative cholecystectomy.

The presentation and consequences of a bile duct injury can present either in the early postoperative period (hours to days) or in a delayed fashion (months to years). Early findings could include pain, fever, and sepsis from bile leakage, jaundice secondary to biliary obstruction, and hepatic ischemia from an unrecognized vascular injury. A more insidious onset may develop in the case of a late-developing biliary stricture. Here the patient may present with recurrent cholangitis, biliary fibrosis or even hepatic fibrosis and atrophy [11]. In fact, these late findings could also be the consequence of an early, and possibly inadequate, repair attempt. The exact nature of the presentation, the location of the injury, the presence of an associated vascular injury and prior attempts at repair are all important considerations when deciding on the best management for a bile duct injury.

The true incidence of vascular injury during laparoscopic cholecystectomy is unclear. The reason for this is twofold: one, most reports of vascular injuries are presented in the context of a concurrent biliary injury and two, an isolated vascular injury is unlikely to cause any clinically significant symptoms. The most common vascular injury during laparoscopic cholecystectomy is to the right hepatic artery (RHA) [12]. An autopsy study by Halasz et al. showed that injury to the RHA was present in 7 % of cadavers that had undergone laparoscopic cholecystectomy in life [13]. Interestingly enough, there were no abnormalities to the liver or bile ducts in these cases. In a multi-institutional study incorporating over 77,000 laparoscopic cholecystectomies, the incidence of RHA injury was 12 % in those patients with a bile duct injury [14]. However, if angiography is performed in all cases of bile duct injury, the rate is nearly 50 % [15]. It is likely that the RHA is either mistaken for the cystic artery or is injured through the use of "blind clipping" during dissection, especially if there is bleeding.

The diagnosis of a vascular injury was historically made through the use of conventional angiography. More recently, computed tomography (CT) with a dedicated arterial angiography reconstruction is utilized. In most cases, an isolated arterial injury goes unnoticed. However, rare complications are possible including right lobe atrophy, necrosis, and abscess formation [16–19]. The combination of a vascular injury with a biliary injury however may prove more problematic. Early, limited case series showed increased morbidity, more difficult reconstruction and a higher incidence of anastomotic stricture in this situation [16, 17, 20]. More recent and larger series, centered in locations with hepatobiliary expertise, show that there is no difference in mortality or stricture rate [15, 21], while there may be an increase in morbidity [21, 22]. Unfortunately, the majority of these series were analyzed in a retrospective manner.

There have been numerous classification schemes for bile duct injuries. The most useful in the era of laparoscopic cholecystectomies is the Strasberg system which was originally described in 1995 [23]. One of the benefits of this system is that it includes leaks, partial transections and complete occlusions in addition to describing strictures. An advantage of newer systems, such as the Stewart-Way system [21, 24], is that they incorporate vascular injuries into the classification scheme. This is an important distinction as the association of a concomitant vascular injury may lead to an alternate clinical decision pathway. However, this newer system is hindered in that it does not include injuries around the bifurcation or late complications including strictures. In these instances, the Strasburg system has the advantage. Another advantage of the Strasberg system is that the classification scheme itself pairs nicely with current treatment modalities. Most Strasberg A injuries can be managed by endoscopic means. As the severity of injury progresses and moves closer to the bifurcation, operative methods are more likely employed. For example, most Strasberg E4 and E5 injuries can be effectively repaired using a Roux-en-Y bilioenteric anastomosis [11]. However, there are instances where more radical surgery is necessary, whether because of compromised hepatic vascularization or lobar necrosis/atrophy. In these instances, hepatectomy has been employed in conjunction with reestablishment of biliary continuity. This chapter details the history of hepatectomy for bile duct injury including the indications, predictive factors, and results.

Indications for Hepatectomy in Bile Duct Injury

Most cases of bile duct injury can be managed using endoscopy. In those requiring surgery, usually injuries closer to the bifurcation, hepaticojejunostomy reconstruction is usually sufficient. However, with higher injuries involving the biliary confluence, a bilioenteric anastomosis can be more challenging especially if there is wide disruption of the right and left bile ducts. There may even be an associated vascular injury, recurrent cholangitis, or prior attempts at repair—all making a successful repair less likely.

Historically, alternatives to treatment of these complex bile duct injuries have included metallic stenting and liver transplantation. Stenting can offer short-term relief for biliary strictures with a mean patency rate of 30 months [25]. Transplantation is a somewhat contested option in patients with benign disease, mainly reserved for those with chronic liver failure from secondary biliary cirrhosis [26, 27]. A third option is to perform a formal hepatectomy. This removes the bile duct confluence along with the diseased liver parenchyma, allowing improved access to the remaining bile duct of the remnant liver [28]. This is turn should provide the basis for a safer and more successful bilioenteric anastomosis.

In 2010, Truant et al. reviewed the literature for hepatic resection as treatment of bile duct injury occurring after cholecystectomy [29]. Thirty-one studies were included (years 1993–2009), totaling nearly 1756 patients referred for bile duct injury. Of these, 99 (5.6 %) patients underwent hepatectomy. The majority of these

were right hepatectomies (80 %); this is reconciled by the fact that the right hepatic artery was the most common vascular injury (53 out of 80 patients with a documented vascular injury).

Hepatectomy in the included series occurred during two time points: early hepatectomy, occurring within 2 weeks of cholecystectomy, and delayed hepatectomy [29]. Nine early hepatectomies were performed, mainly due to parenchymal necrosis caused by combined biliary and vascular injury. There were multiple indications for hepatectomy occurring in a delayed fashion; these included recurrent biliary sepsis, biliary strictures after continuous cholangitis, intrahepatic abscess, unsuitability of the proximal stump for anastomosis, intrahepatic lithiasis, right hepatic lobe atrophy, and secondary biliary cirrhosis.

Multivariate analysis was carried out on studies that included bimodal treatment. Hepatic artery injury and Strasberg E4/E5 injuries were independent predictors of the need for hepatectomy [29]. In fact, 92.6 % of patients requiring hepatectomy were considered to have "complex" bile duct injuries–bile duct injuries with disruption of the confluence or a combined biliary and arterial injury [29]. The odds ratio of requiring a hepatectomy was 43 for this latter group. A more recently published series echoed these findings with an odds ratios of 45 if there was injury to the right hepatic artery [11]. In this series, 50 % of the hepatectomies occurred within 5 weeks of laparoscopic cholecystectomy, mainly to control sepsis from liver or bile duct necrosis. Stewart et al. showed that RHA injury was more commonly associated with subsequent need for hepatectomy in a series of 261 laparoscopic bile duct injuries [21]. Of note, complications occurred more often with RHA injury among cases repaired by the primary surgeon than by a specialized biliary surgeon.

A further association with the need for hepatectomy is the presence of prior attempts at reconstruction [29]. Truant et al., in their review of 99 hepatectomies, found a trend towards significance ($p=0.06$) for prior biliary reconstruction when comparing those who underwent hepatectomy versus biliary repair. It makes sense that each prior attempt at repair compromises future repair attempts through loss of duct length and the need for more substantial dissection.

It would seem that there are two distinct time points for hepatectomy after bile duct injury with two distinct lists of indications (Table 32.1). In the early postoperative period (within 5 weeks of cholecystectomy), hepatectomy is performed to control sepsis, liver necrosis or bile leakage. In the remaining patients, hepatectomy is performed later and

Table 32.1 Indications for hepatectomy after bile duct injury

Early indications (within 5 weeks)	Delayed indications
• Control sepsis • Control bile leakage • Liver necrosis • Bile duct necrosis	• Recurrent cholangitis/sepsis • Proximal bile duct stump unsuitable for anastomosis • Intrahepatic lithiasis • Intrahepatic abscess • Lobar atrophy • Secondary biliary cirrhosis

usually after prior attempts at repair. Removal of atrophic liver, treatment of recurrent sepsis, and facilitation of a healthy anastomosis are all indications in this group.

Results of Hepatectomy for Bile Duct Injury

Morbidity

Unfortunately, morbidity is not an insignificant occurrence in BDI patients treated with hepatectomy. In recent series, morbidity rates are as high as 60 %, with infectious complications predominating [11, 27, 28, 30]. Biliary fistula rates occur in as many as 39 %, with most of these requiring a return to the operating room [11]. Other infectious complications include biliary collection, subphrenic abscess, and wound infection (with or without underlying abdominal abscess). Other notable complications include postoperative hemorrhage, ascites, and pleural effusions [10, 11, 28]. In one series, 67 % of patients were transfused with an average of 6.0 ± 3.6 blood cell units, with one patient requiring a repeat laparotomy for hemorrhage control [28].

Overall, these rates are much higher than those observed after hepatectomy performed for other indications [31]. It is likely that the reasons for this rise in morbidity are multiple. Prior attempts at repair, biliary peritonitis, and chronic infection all play a role and are found in at least two-thirds of the patients requiring hepatectomy [11, 27, 28].

Mortality

Li et al. presented a series of ten patients requiring hepatectomy for bile duct injury [11]. One of these patients (10 %) died in the postoperative period due to multiorgan failure and sepsis. This result mirrors the large series published in 2010 reviewing 99 hepatectomies for bile duct injury [29]. A postoperative mortality rate of 11.1 % was found. Notably, the mortality rate was significantly higher in those undergoing urgent (within 2 weeks) hepatectomy as compared to non-urgent hepatectomy. However, other smaller series have shown 0 % mortality in this patient population [27, 28, 32].

Large series of patients undergoing surgical repair for BDI have been reported.

Sicklick et al. reported on 200 patients with major bile duct injuries, with a postoperative mortality rate of 1.7 % in those undergoing definitive biliary reconstruction [33]. Similarly, Lillemoe et al. reported on 156 patients showing a mortality rate of 0.6 %; a single patient died of a pulmonary embolus [6]. It makes sense that patients undergoing hepatectomy for BDI would have a higher mortality rate than those undergoing primary reconstruction. As noted above, these patients typically have more complex injuries leading to higher rates of peritonitis and sepsis [11].

Long-Term Outcomes

Despite the high morbidity and mortality in the short term, the long term outcomes are very encouraging. In the largest series to date, Laurent et al. followed patients for a mean of 8 years [28]. Nearly 75 % had no symptoms and only one patient developed recurrent bouts of cholangitis requiring antibiotic therapy. None of these patients required a liver transplant. Li et al. found similar results over nearly 3 years of follow-up; 80 % of patients had mild or no symptoms [11]. Unfortunately, one patient went on to develop secondary biliary cirrhosis and required transplantation. Multiple smaller series echo these results, with the vast majority of patients requiring a hepatectomy remaining "good" or symptom-free over time. These results are well captured in a recent review [29].

Conclusions

Unfortunately, bile duct injuries remain a devastating and ever-increasing complication of cholecystectomy. While the vast majority of patients can be managed non-operatively, many will require bilioenteric anastomosis. Those with complex injuries—mainly injuries at the confluence with associated vascular injury—are at risk for requiring formal hepatic resection. These patients can expect a nearly 60 % morbidity and up to a 10 % mortality risk. However, despite this, the long-term results are very encouraging. The majority of patients remain symptom-free over follow-up and very few require repeat surgery. Underlying all this is the need for prompt referral to centers with specialization and expertise in hepatobiliary surgery. Multiple attempts at repair not only make subsequent surgery difficult, but they put patients at increased risk of hepatectomy and subsequent morbidity.

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Chapter 33
Commentary: Liver Resection for Bile Duct Injury

Timothy M. Pawlik

Bile duct injury can be a devastating complication of laparoscopic cholecystectomy. While the overall incidence is low, injury of the bile duct remains the most feared complication of what otherwise is a routine general surgery procedure. Traditionally, the occurrence of a bile duct injury was associated with a very high incidence of morbidity and even mortality. Many of these patients were subjected to multiple procedures, operations, and long-term morbidity. A subset of patients required transplantation, while some patients even died from sequela of the bile duct injury. With advanced imaging, more sophisticated surgical techniques, as well as a better general understanding how to manage this condition, most patients with bile duct injuries can now expect good long-term results with most patients returning to a normal quality of life [1]. In particular, patients who have an injury to the extrahepatic bile duct below or at the level of the bifurcation can typically be managed with a Roux-en-Y bilioenteric anastomosis, which is associated with good, durable long-term outcomes. However, as noted by McCall and colleagues, a subset of patients will suffer a more complex injury. Specifically, patients with a concomitant vascular injury, those with a complete disruption/injury of the hepatic duct confluence, and those with lobar necrosis/atrophy may require a more radical procedure that may necessitate a hepatic resection.

In general the need for hepatic resection for a bile duct injury is low with most major centers reporting an incidence of less than 5 %. The indication for hepatic

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resection includes the damage to a vascular structure, usually the right hepatic artery. In turn this can induce hepatic atrophy, as well as de-vascularization of the ipsilateral duct, making a bilioenteric anastomosis challenging as well as at risk for leak or future stricturing. The other indication for hepatic resection may be a high injury that disrupts the hepatic duct confluence or a chronic stenosis of the bilateral bile ducts up to the second order radicles. Typically, the indications for hepatic resection for a complex bile duct injury can be characterized into two groups: early indication for vascular-injury associated liver necrosis versus late indication for treatment of liver atrophy, bile duct strictures and cholangitis [2]. In these settings, a subset of patients may be better served with a formal hepatic resection such as a right hemi-hepatectomy or right trisectionetomy. In a very small subset of patients, a central hepatectomy may be employed to facilitate exposure of the bile ducts within the substance of the hepatic parenchyma and allow for the construction of separate enterobiliary anastomoses to the right and left hepatic ducts. This approach, however, may be technically more challenging and a hemi-hepatectomy with a unilateral hepatico-jejunostomy to the preserved liver may be technically easier and preferred.

Laurent and colleagues reported 18 patients who underwent a major hepatectomy, 14 of whom had a right hepatectomy [3]. In this series, the authors noted that at a median follow-up of 8 years, 17 (94 %) patients had excellent or good results, including 13 patients without symptoms. In separate study, Perini et al. reported on nine patients who had a liver resection for the treatment of post-cholecystectomy biliary stricture—all of whom had Strasberg E3/E4 injuries [4]. In this study, eight out of the nine patients underwent a right hepatectomy. At a mean follow-up of 69.1 months, the overwhelming majority of patients were asymptomatic. While the long-term outcomes following hepatic resection for the treatment of complex bile duct injury are generally good, the perioperative morbidity typically is higher compared with a hepatico-jejunostomy alone. Several series have noted morbidity in the range of 30–60 %, including biliary leaks, deep space infections, as well as bleeding and need for transfusion [3, 4].

In sum, while liver resection is part of the surgical armamentarium for the treatment of select cases of complex bile duct injury, it is not commonly required. In fact, even when examining the experience of several large centers that are referred the most complex bile duct injuries, the use of liver resection was applicable to few patients [3–5]. As such, the overwhelming majority of patients can be managed without a major hepatectomy. Liver resection, however, may be appropriate for the small subset of patients who have a major disruption at the hepatic confluence or those patients who develop specific complications of bile duct injury such as lobar atrophy, necrosis, or bile duct strictures. These challenging patients with bile duct injuries should be referred to high-volume hepatobiliary centers for management in order to ensure the best chance at optimal outcomes.

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Chapter 34
Liver Transplantation for Common Bile Duct Injury

Kelly M. Collins and William C. Chapman

Liver Transplant for Bile Duct Injury

Indications for liver transplantation after bile duct injury fall into two major categories: Chronic liver disease due to secondary biliary cirrhosis and acute liver failure due to an associated major vascular injury. The exact incidence of liver transplantation due to biliary injury is difficult to estimate because the etiology of liver failure for these patients is not always adequately captured in current transplant registries. Furthermore, the current literature of iatrogenic injury resulting in liver transplantation is mostly limited to case reports and small case series (Table 34.1) [1–18]. There is a rare but important role and need for liver transplant in highly selected cases of bile duct injury. According to the U.S. United Network for Organ Sharing (UNOS) registry, between the years of 2000 and 2010, among 51,334 liver transplants in the United States, only 111 were performed for secondary biliary cirrhosis, and of these, less than one fourth specified an associated bile duct injury (UNOS data) [19]. Internationally, secondary biliary cirrhosis is the etiology of 1 % of transplants in the European Liver Transplantation Registry (ELTR) and approximately 2 % in the Argentinian population [1, 4, 20]. While the etiology of obstruction leading to secondary biliary cirrhosis is not consistently reported, most case series describe the use of transplantation as a consequence of iatrogenic injury [1, 3–5, 7–16, 18, 20–22].

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Table 34.1 Literature on iatrogenic injury resulting in liver transplantation

Reference	*N*	Injury	Time	Indication for Txp	Outcome
Robertson et al.	1	LC	12 months to transplant	Cirrhosis	Alive 27 mos post
Nordin et al.	4	LC	Median time from injury to referral 4.8 years	Recurrent cholangitis, microabscesses, portal HTN, cirrhosis	3 survived OLT (follow-up 7 mos, 2 years, 46 months); 1 died 7 months post-OLT
Schmidt	2	LC	NA	Anatomic stricture and cirrhosis	
De Santibanes	16	Cholecystectomy (13; open 14, lap 3), hydatid surgery (1), right hepatectomy (1), stenosis secondary to formaldehyde injection (1)	Injury to OLT 60 mos	ESLD; progressive jaundice; intractable ascites; bleeding 2/2 portal HTN; recurrent cholangitis; intractable pruritis; poor QOL	2 early post-op deaths; 3 last post-op deaths; 11 alive at median 62 months; survival: a, 3, 5: 81, 75, 75 %
Loinaz	12	7—hydatid disease (7), biliary surgery (5), cholecystectomy (4), trauma (1)	NA	Cholestasis, liver failure, quality of life	Survival 1, 3, 5 (75 %, 75 %, 75 %, 62.5 % at 10 years)
Parilla	27	Cholecystectomy (open 13, laparoscopic 14)	Injury to OLT median 26 months	Acute liver failure (14 pts); secondary biliary cirrhosis (13 points)	2 patients died on waitlist; 5 pts died within 30 days—4 after txp for acute liver failure and 1 after txp for secondary biliary cirrhosis; overall 5-year survival 68 %
Lubikowski	5	Cholecystectomy	Median time from injury to listing 11 years	Secondary biliary cirrhosis	100 % survival median of 53 months follow-up
Yan	1	Cholecystectomy	NA	Secondary biliary cirrhosis and portal hypertension	Alive (unknown duration of follow-up)

McCormack	1	Cholecystectomy (lap to open)	NA	ALF	Death POD 24, infection
Oncel	1	Open Cholecystectomy	Injury to transplant 15 years	Recurrent cholangitis, abscess, secondary biliary cirrhosis	Alive 4 years after transplant
Fernandez	3	Cholecystectomy	NA	ALF, liver necrosis, recurrent cholangitis	Acute liver failure (1 death prior to OLT, 1 death POD5 PNA); recurrent cholangitis patient, death on POD6
Thomson	5	Cholecystectomy (2 open, 1 lap, 2 lap to open)	Injury to OLT 245 months and 237 months	Secondary biliary cirrhosis; liver failure	One patient died awaiting transplant; one died after retransplant *x*2 for HAT; one patient survived OLT—unknown duration of FU
Bacha	1	LC	Injury to OLT 3 months	Necrosis; sepsis	Alive 9 months after transplant
Strasberg	1	LC	Injury to OLT 39 days	Necrosis, biloma	Death POD 14 due to sepsis

The reasons for transplantation in the setting of bile duct injury can be grouped into the following categories:

- Secondary biliary cirrhosis
- Biliary stricture and portal hypertension
- Hepatic failure and complex injury
- Uncontrolled/recurrent sepsis of biliary tree
- Bile duct injury in patient with underlying liver disease
- Pruritus
- Poor quality of life

This chapter will review the existing literature, pathogenesis, and histology of liver disease associated with bile duct injury, evaluation of the potential transplant recipient, and technical factors in this patient group.

Review of the Existing Literature

There are less than one hundred reported cases of liver transplantation secondary to bile duct injury in the existing literature (Table 34.1). The majority of reported cases are due to biliary injury at the time of cholecystectomy; however, there are several cases of injury for hydatid liver disease and for nonbiliary surgery [1, 3–5, 7–16, 18, 20–22]. While the majority of reported cases are referrals for transplant due to secondary biliary cirrhosis due to biliary injury, there are also reports of acute liver failure, usually secondary to an associated major vascular injury [3, 5, 9, 12, 15, 18]. Patients with secondary biliary cirrhosis were transplanted for the following reasons: cirrhosis, recurrent cholangitis, sequelae of portal hypertension, intractable ascites, pruritus, and/or poor quality of life [1, 3–5, 7–16, 18, 20–22].

This existing literature likely fails to completely capture the small number of patients seen at transplant centers with secondary biliary cirrhosis due to biliary injury. At our center, over the past 20 years, we have performed four liver transplants for iatrogenic injury to the bile duct (unpublished data). As noted previously, based on the UNOS data as currently reported, the number of transplants performed in the United States for this diagnosis is small.

In the largest existing series, Parilla et al. describe 27 patients over a 13-year period, all of whom sustained biliary injury after cholecystectomy (13 open and 14 laparoscopic) and subsequently underwent liver transplantation for either acute liver failure (14 patients) or secondary biliary cirrhosis (13 patients) [12]. They found a higher rate of vascular injuries associated with the laparoscopic procedure, consistent with other authors [14, 15, 21, 23–25]. Overall, the 5-year survival was 68 %, with the majority of deaths occurring in the early postoperative period in patients who were transplanted for acute liver failure [12].

Few conclusions regarding outcomes can be drawn from these small series. Liver transplantation is a treatment option for patients with acute liver failure or

biliary cirrhosis after bile duct injury; however, patients who develop acute liver failure have poor survival and often die of infection-related complications. Patients with secondary biliary cirrhosis have acceptable long-term outcomes, with a 3-year survival of greater than 70 % [4, 7]. The major challenge of OLT, in patients with secondary biliary cirrhosis, is the extensive right upper quadrant surgery that so many have undergone with previous bile duct repairs.

Pathogenesis

Bile duct injuries leading to transplant have been described in open and laparoscopic cholecystectomy as well as nonbiliary surgery [1, 3–5, 7–16, 18, 20–22, 26]. The most common procedure associated with common bile duct injury is cholecystectomy, both open and laparoscopic [1, 3–5, 7–16, 18, 20–22, 26]. The incidence of bile duct injury during laparoscopic cholecystectomy in larger series is approximately 0.3–1 % compared to 0.1–0.2 % for historically reported rates in open cholecystectomy series [23, 27–31].

Case reports of patients requiring urgent liver transplant for acute liver failure are usually in the setting of a major vascular injury to either the common or proper hepatic artery and/or to the portal vein [3, 5, 9, 12, 15, 18, 21]. Fernandez et al. describe two cases, one in which portal vein injury during laparoscopic converted to open cholecystectomy resulted in portal and hepatic arterial injury and acute liver failure, and a second case in which hepatic arterial injury resulted in sufficient necrosis to cause acute liver failure. One of the patients received an urgent transplant, while the second died while on the waiting list [5]. Zaydfudim et al. reported on two cases of major vascular injury requiring emergent liver transplant. In this report, one such vascular injury occurred in a patient undergoing right adrenalectomy. The common bile duct, portal vein, and common hepatic artery were transected resulting in acute liver failure and referral for urgent transplant. Remarkably, the patient was alive at 6 years after transplant [18].

Injuries to the bile duct sustained during laparoscopic cholecystectomy are more often proximal injuries, rather than their open counterparts, and more likely to have an associated vascular injury [21, 23, 25]. Vascular injuries have been reported in up to 12–57 % of patients with bile duct injuries [14, 32, 33]. These patterns of injury are well described [15, 25] and frequently involve injury to the right branch of the proper hepatic artery or an aberrantly located replaced or accessory right hepatic artery. The contribution of vascular injury to formation of stricture might be overestimated. Alves et al., in a retrospective review of 55 patients with bile duct injury who were studied angiographically at the time of their repair, found associated vascular injury in 47 % of patients [32]. Forty three of the patients underwent Hepp-Couinaud repair (side to side anastomosis of the jejunal limb to the main left hepatic duct) and were followed to evaluate the influence of vascular injury on their outcome. With a mean follow-up of 56 and 61 months (without and with arterial injury respectively),

there was no difference in the long-term stricture rate [32]. This can be explained by the blood supply to the left and right ductal systems, which consists in part by the hilar plate arterial plexus that connects the right and left hepatic arterial systems. This allows the confluence of the ducts and higher to maintain vascular supply in the setting of a contralateral arterial injury [34]. It additionally informs why a high bilioenteric repair, with dissection based anterior to the duct, is necessary to avoid ischemia in the repair when the blood supply from the ascending marginal vessels based of the pancreaticoduodenal and gastroduodenal arteries has been disrupted and the bile duct blood supply comes exclusively from the hepatic artery [35].

A high percentage of patients will go on to have biliary stricture, with reported rates as high as 50 % in some series [17, 27, 28, 33, 36–38]. The factors affecting the development of stricture and outcomes after repair including level of injury, timing and type of repair, surgeon experience, and presence of biliary peritonitis continue to be debated [6, 17, 21, 22, 27, 28, 33, 35–40]. The ability to accurately study these factors is limited by the variation in initial treatment and delay in presentation due to failed recognition of the injury or initial management at a low volume center. After repair, patients should be followed with imaging and lab studies for evaluation of liver function for years, as strictures may be a late development. In a series reported by Pitt et al., at 5 years, only 80 % of post repair strictures had been identified, some occurring as late at 19 years after repair [33, 37].

Early referral to a hepatobiliary specialist center is recommended, as a multimodality approach (with gastroenterologists and interventional and diagnostic radiologists) can be beneficial in establishing appropriate diagnosis, ensuring utilization of endoscopic treatment techniques, and involvement of a hepatobiliary surgery specialist. Surgeon experience has been found to correlate with increased patient survival [29].

Any sign of stricture needs to be timely and aggressively managed in order to avoid sequelae of portal hypertension and fibrosis from obstruction. If a stricture develops, a multimodality approach should be employed for management, with good cholangiographic success and symptom relief being reported using endoscopic balloon dilation and stenting [22, 41, 42]. Refractory strictures may require surgical revision.

Pathologic Consequences of Stricture: The Evolution of Portal Hypertension and Secondary Biliary Cirrhosis

Prolonged biliary obstruction can result in two major structural changes that require transplant: (1) portal hypertension and (2) progressive hepatic fibrosis with progression to secondary biliary cirrhosis.

The damage to the biliary system is the result of the chronic insult from high local concentration of hepatotoxic bile acids at the canalicular membrane leading to a process of ductular proliferation and portal inflammation along with fibrogenesis

and matrix deposition, known as ductular reaction [3, 43, 44]. If not arrested, this process results in scarring. As this process progresses, mechanical interference with bile flow develops in the intrahepatic biliary radicles and perpetuates bile and bile salt accumulation in the parenchyma, i.e., cholestasis [45].

In patients with chronic cholestatic disease, histologic and vascular remodeling meeting the requirements for cirrhosis occur in the minority of patients, and the injury patterns are typically inhomogeneous; however, a higher proportion exhibit fibrosis and/or clinical sequelae of portal hypertension in the absence of cirrhosis [3, 43–47].

Portal hypertension, in the setting chronic large bile duct obstruction, is not completely understood. While intuitively portal hypertension would be a result of cirrhosis because of the deterioration of the normal vascular architecture and replacement of parenchyma by fibrous septa that contain only small shunt vessels, histologic studies confirmed that, in patients with primary sclerosing cholangitis and in secondary biliary cirrhosis, clinically evident portal hypertension exists in the absence of cirrhosis [3, 43–47]. In a histologic study of 28 patients with chronic biliary obstruction and portal hypertension and 76 patients with chronic biliary obstruction alone, Weinbren and colleagues found that most of these patients lacked the distorted vascular relations necessary to be considered cirrhotic. The clinical features were attributed to the combination of diffusely thickened hepatocyte plate and increased fibrous tissue in which the normal relation was maintained between the portal tracts and hepatic venous radicles [44]. Similarly, Abraham et al., in a review of 306 explants for cholestatic liver disease, found that the majority of patients with cholestatic liver disease have findings of cirrhosis on explant at the time of transplant, with only 26 of 306 (8.5 %) being precirrhotic [41].

In patients with chronic obstruction, there is no conclusive data regarding the timing of progression from fibrosis to cirrhosis or factors contributing to progression. It is well accepted that the longer the duration of the obstruction, the more likely it is that fibrosis will occur [22, 43, 47, 48]. Negi et al. reported a prospective series of 64 patients with postcholecystectomy bile duct strictures. Biopsies of the liver collected at the time of bile duct repair were reviewed and 35 (54 %) of the patients included had advanced fibrosis at the time of surgery, with a mean duration of biliary obstruction of 16.6 ± 3.4 months. Factors significantly associated with the presence of advanced fibrosis were duration of biliary obstruction, basal ALT level, and time to normalization of ALT after surgical repair. The grade of fibrosis correlated with the demonstrated positive correlation with the grade of portal inflammation, ductular proliferation, and cholestasis. Fibrotic changes occurred as early as 1 month after biliary obstruction with a mean duration of biliary obstruction associated with development of portal or periportal fibrosis at 3.9 months, severe fibrosis and numerous septa at 22.5 months, and development of cirrhosis at 62 months. There was no significant difference in the incidence of cirrhosis in patients with clinical cholangitis or infected bile [47].

In 71 patients, Sikora et al. found that all patients biopsied at the time of bile duct injury repair had some degree of fibrosis (mean time from injury to repair, 270

weeks in patients with cirrhosis and 90 weeks in patients with fibrosis only). Fibrous changes on liver biopsy were identified in patients as early as 11 weeks after bile duct injury at time of cholecystectomy [43]. Johnson et al. similarly studied hepatic injury looking at biopsies in patients after bile duct injury. Six of 16 patients had evidence of moderate to marked fibrosis and four of these had evidence of evolving cirrhosis, with the mean time from injury to repair of 480 days [39].

There is evidence in animal and human models that relief of obstruction can lead to recovery of fibrosis and portal hypertension [43, 44, 48, 49]. Therefore, if evaluation of biopsy shows mild fibrosis without evidence of cirrhosis, multidisciplinary review is mandatory to ensure that all interventional and surgical options are exhausted prior to being considered for transplant.

The exact time to regression of fibrosis is unknown but has been reported as quickly as weeks in a rat model and as early as 1 year in humans following surgical relief of obstruction. Depending on the degree of liver injury at time of relief of obstruction, the liver may or may not recover post-obstruction. Patients should be followed clinically and with repeat biopsy, after obstruction has been alleviated, to assess for regression.

Transplant Evaluation Preoperative Management

All patients being considered for transplant must undergo a thorough medical and psychosocial evaluation. General considerations and contraindications to transplant have been described previously and should be followed [50]. Specific considerations in the two categories of patients undergoing transplantation in the setting of bile duct injury are listed below.

Chronic Liver Disease

The evaluation of the patient with chronic liver disease will focus on the following: establishing the diagnosis, evaluation of alternative treatments, evaluation for complications of liver disease, and determining the appropriate timing for liver transplant.

A thorough history and physical examination should be obtained with attention to any underlying liver disease. Hepatitis serologies should be obtained. Hepatitis treatment should be pursued at the discretion of the treating medical team and requirements for alcohol abstinence are determined by transplant center. Prior surgical records and imaging should be obtained for review.

Liver biopsy can be used to establish the diagnosis and assess any other contributing factors to liver disease. Needle biopsy provides adequate tissue for diagnosis and can be performed percutaneously with ultrasound guidance or using a tran-

sjugular method. Transjugular biopsy may be preferred for patients with thrombocytopenia or ascites.

The presence and degree of portal hypertension is determined largely by clinical signs, including hepatosplenomegaly, ascites, dilated abdominal wall veins or caput medusae, and/or varices. It can also be confirmed by measurement of the hepatic venous pressure gradient if there is uncertainty, but we reserve this procedure only in equivocal cases.

Initial evaluation and management should ensure that the biliary injury has been appropriately treated, i.e., bilomas or abscesses have been drained, biliary drainage is adequate, and cholangiographic evaluation performed to characterize the injury and the current anatomy. ERCP, MRCP, or PTC can be utilized for this purpose and choice of modality may be directed by center preference and available expertise. While MRCP is noninvasive and sensitive for detection of fluid collection, biliary stricture, and biliary leak, its major limitation is its use for diagnostic purposes only. ERC may not evaluate proximal bile ducts in the setting of complete transection. PTC allows for evaluation of the proximal ducts, can be used in the setting of a Roux reconstruction, and can be used for treatment and diagnosis but is the most invasive of the other modalities.

Quality imaging should be obtained to evaluate the vascular anatomy and lesions suspicious for hepatocellular carcinoma. Portal vein patency is best evaluated with contrasted CT or MRI. If there is portal vein thrombosis, the extent of the thrombus needs to be determined as well as if the superior mesenteric vein (SMV) is patent and of adequate caliber for graft inflow. Hepatic artery occlusion, celiac axis occlusion, and portal vein thrombosis are not contraindications to transplant but should be considered in operative planning. Almost all patients can undergo adequate evaluation of their vasculature with contrast enhanced cross-sectional imaging (MR or CT), with the use of angiography reserved for highly selected cases where uncertainty exists.

Hepatocellular lesions should be evaluated and treated per transplant center protocol. In our center, patients undergoing evaluation for liver transplant with hepatocellular carcinoma are treated with chemoembolization to either downstage the tumor to within Milan criteria or treat while they are waitlisted.

Many patients referred will have percutaneous biliary drains (PTBD) in place at time of referral. If imaging suggests that they are not adequately decompressed, cholangiography should then be performed and drainage optimized. If drainage is optimized and recurrent cholangitis persists, antibiotic prophylaxis may be required in the interval to transplant.

The criteria for candidacy for liver transplant in the setting of secondary biliary cirrhosis are not well established but should include at least one of the following: cirrhosis by biopsy, MELD greater than 15, fibrosis and portal hypertension in setting of biliary stricture without percutaneous/endoscopic or surgical potential for revision, and/or poor quality of life: recurrent cholangitis requiring hospitalization with biliary tract stricture not amenable to surgical reconstruction.

Steps in evaluation of liver transplant candidate with secondary biliary cirrhosis:

1. History and Physical
   (a) Evaluate for additional contributors to liver disease (alcohol use, hepatitis, NASH)
2. Establish diagnosis of cirrhosis
   (a) Imaging
   (b) Biopsy
3. Multidisciplinary review (hepatology, pathology, interventional and diagnostic radiology)
   (a) If biopsy does not show cirrhosis or portal hypertension, is there a chance for recovery of the liver with relief of obstruction via endoscopic/interventional or surgical methods
   (b) Review vascular and biliary anatomy
      – Is the biliary system adequately decompressed?
      – Will the patient require a vascular conduit for arterial and/or portal venous inflow at the time of transplant?
4. Evaluate for surgical candidacy
   (a) Cardiopulmonary fitness
   (b) Comorbidities (HCC, HCV, Hepatopulmonary syndrome (HPS), Hepatorenal syndrome (HRS))
5. Multidisciplinary evaluation (hepatology, anesthesia, surgery, social work, and psychology) and listing

Acute Liver Failure

For patients with acute liver failure, evaluation includes the likelihood of the patient to survive the procedure based on their overall clinical stability, the presence of any irreversible complications of liver failure (i.e., irreversible cerebral edema), and the presence of sepsis. Special consideration must be given to sepsis in these cases as there has been contamination at the original procedure, which is potentially ongoing, given the nature of the injury. Ongoing sepsis (except confined to the native liver) is a contraindication to transplant.

Coagulation parameters should be optimized in preparation for the operating room in anticipation of increased level of technical difficulty of the dissection due to prior surgery.

Imaging should be obtained to ensure vascular anatomy suitable for transplant.

Intraoperative Considerations

Donor Selection

Standard donor selection criteria apply, with the optimal donor being a young, otherwise healthy donor that sustained an injury that resulted in brain death. Special consideration should be given to the use of extended criteria donors.

Techniques for organ procurement from brain-dead, heart beating donors have been described previously and do not significantly differ in these circumstances [50–53].

Given the increased likelihood for arterial conduit and the need for available quality arterial vessels, donors at extremes of age, with known atherosclerotic disease, or imaging with atherosclerosis, should be used with caution. Donor iliac vessels should be procured as is standard for all cadaveric liver procedures. If there is a shortage of vessels or unexpected poor iliac quality, the carotid vessels may be procured as well. If a center has stored cadaveric vessels of appropriate blood type or cryopreserved vessels, these may also be utilized. Vein grafts from the iliac and, if needed, saphenous vein should be procured.

Due to the additional dissection time potentially required due to adhesions and disrupted anatomy, careful planning must occur between the procuring and recipient teams to minimize the cold ischemia time of the graft.

In some extreme cases, the anatomy encountered during the hepatectomy is such that the recipient is unsuitable for transplant. In patients where there have been multiple prior interventions or any concerns regarding the suitability of the patient's vascular anatomy, we will backbench the graft in a separate sterile area so that, if needed, it can be used in an alternate recipient.

Given the risks associated with the use of deceased after cardiac death (DCD) grafts, including sensitivity to warm and cold ischemia and increased risk of hepatic arterial thrombosis, they should probably not be used in this group of recipients.

Recipient Operative Techniques

The technique of recipient hepatectomy has been described previously [50–54]. As with any reoperative surgery, increased difficultly in the dissection due to adhesions, altered anatomy due to prior surgical intervention, and/or ongoing inflammation and infection should be anticipated. This can be complicated in these patients by coagulopathy of cirrhosis and portal hypertension. Steib et al. found that prior surgery correlated with increased blood loss during liver transplant [55].

Several authors have attributed increased blood loss and increased perioperative morality to adhesions created from previous surgery in the setting of salvage transplant after resection for hepatocellular carcinoma and in patients with primary biliary cirrhosis [56–58]. Whether or not previous surgery has an adverse effect on

outcomes remains controversial. However, prior right upper quadrant procedures, including prior biliary bypass, can present additional technical difficulties, sometimes making these very difficult liver transplant procedures [57, 58].

The importance of current imaging of the patient's vascular and biliary anatomy to aid in operative planning cannot be overstated.

Regardless of the location of previous incisions, optimal exposure is critical and is achieved using a bilateral subcostal incision usually with the option for midline extension (Mercedes incision). The groin should be prepped in anticipation of the need for possible venovenous bypass. A generous amount of blood products should be readily available (at least 10 units of cross-matched blood, fresh frozen plasma, platelets, and cryoprecipitate). Perioperative antibiotics should be administered to cover suspected pathogens. If the patient has a percutaneous biliary drain in place, it should be prepped into the field as it can facilitate the portal dissection.

The hepatectomy should proceed as much as possible through the typical sequence. Early assessment of the hepatic arterial pulse should be performed to assess its integrity and the potential need for an arterial conduit. If there is obvious contamination from the injury or biloma, cultures should be obtained.

The portal vein is skeletonized to the level of the confluence of the splenic and superior mesenteric vein. In cases where a piggyback reconstruction is planned, the transection of the portal vein will often facilitate the dissection of the retrohepatic caval branches. The degree of adhesions may dictate whether or not the retrohepatic dissection can be achieved safely. Alternatively, a bicaval technique may be necessary. The decision to create a portocaval shunt or venovenous bypass will be dictated by the patient's hemodynamics. If portal vein is thrombosed and cannot be removed with endovenothrombectomy or if the portal vein has been previously damaged and is unable to be used, an alternative inflow must be chosen. The superior mesenteric vein can be used for inflow with the donor iliac vein serving as the conduit between the native SMV and the donor portal vein. An adequate length of donor external iliac vein is prepared by ligating all side branches using fine synthetic monofilament suture, and the vein is marked to identify the inflow end (external iliac) to avoid twisting the graft at implantation. The SMV is exposed in the recipient. The colon is retracted cephalad and the SMV exposed at the root of its mesentery. A length of SMV adequate to allow a side-biting clamp is dissected. Ligation of 1–2 colonic branches may be necessary for mobilization. The external iliac end of the conduit is anastomosed in an end to side fashion to the recipient SMV using permanent fine monofilament suture (6-0 or 7-0 Prolene). The conduit is passed through tunnel over the neck of the pancreas, retrogastric into the former lesser sac, and the common iliac end of the conduit is anastomosed end to end to the donor portal vein [59]. The suture is tied with a growth factor of approximately one half of the diameter of the portal vein to avoid anastomotic stricture.

If the hepatic artery cannot be used for the arterial inflow, due to damage from prior surgery or inadequate flow, an arterial conduit may be used to establish inflow from the supraceliac or infrarenal aorta. Our preference is to use an infrarenal takeoff and donor iliac vessels as a conduit. The conduit is prepared by oversewing the internal iliac several millimeters from the bifurcation with the external. The

infrarenal aorta is exposed. A side-biting vascular clamp is placed and an aortotomy is made and then enlarged using an aortic punch. The common iliac of the donor is anastomosed to the aorta using 5-0 Prolene. The conduit is then flushed with heparinized saline and passed through a window in the transverse mesocolon, behind the pylorus and into the subhepatic region [60]. The external iliac end of the donor artery conduit is then anastomosed to the donor hepatic artery using 6-0 Prolene.

There are several options to address the bile duct in these cases: choledochocholedochostomy (very rarely), revision of the existing biliary roux limb, or creation of a Roux-Y hepaticojejunostomy. While the recipient bile duct may be preserved in some cases, this should be done with special attention to the blood supply to the duct, which can be evaluated by assessing the backbleeding from the duct when the duct is transected. The duct should then be probed with an 8 French feeding tube to ensure that the ampulla is not stenosed.

When using the existing biliary roux limb, it is imperative that sufficient dissection be performed to verify that the limb was constructed correctly. The ligament of Treitz should be identified and followed to the level of the jejunojejunostomy to verify that this limb does not connect to the biliary system creating a backwards loop. Once this has been clarified, the blind end of the roux limb should be identified and disconnected from the native bile duct. This can be dissected several centimeters down the length of the intestine so that the previous enterostomy can be contained in the short segment enterectomy. Care is taken to avoid disrupting the mesentery of the roux. The limb must be adequately dissected to ensure sufficient length for creation of the new biliary anastomosis without tension (we prefer at least 50 cm). If a mesenteric trap/defect/hernia has been created, this is closed. The choledochojejunostomy is created using interrupted or running 6-0 PDS suture.

If a new Roux limb is required, it is created as previously described with an end of donor bile duct to side of jejunum anastomosis, with at least 50 cm of length to prevent reflux of intestinal contents into the biliary tree and avoid tension.

The postoperative care should be similar as in all patients undergoing liver transplant, with careful management of immunosuppression and prophylaxis for infectious complications. Patients should be placed on antiplatelet treatment with aspirin. If a vascular conduit was required, consideration should be given to anticoagulation.

Conclusions

There is a rare but important role and need for liver transplant in highly selected cases of bile duct injury, both in the acute and chronic setting. While its incidence is low, an understanding of special considerations is necessary to achieve a successful outcome in this challenging patient population. This includes multidisciplinary evaluation and delineation of complex anatomy, along with adequate surgical preparation and anticipation of the need for alternative reconstructive strategies.

Pearls and Pitfalls	
Delineate recipient anatomy	• Define arterial and portal venous anatomy during the transplant evaluation
	• Update as the time to transplant approaches
Anticipate need for alternative vascular conduits	• Have suitable vessels for conduit use if needed (either from the donor or in the center vessel bank that are ABO compatible)
Expect increased difficulty and increased blood loss	• Prepared anesthesia team – adequate blood availability – adequate vascular access
	• Prepared surgical team – adequate surgeon experience and availability
	• Appropriate donor selection – anticipate increased operative time for hepatectomy

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Chapter 35
Commentary: Liver Transplantation for Common Bile Duct Injury

Alan W. Hemming

The chapter by Collins and Chapman accurately describes the role of liver transplantation in the management of the consequences of bile duct injury. To be clear liver transplantation is rarely required in the management of biliary injury or its sequela, although some plaintiffs' attorneys are determined to disagree. A rough guide to an estimate of the frequency of the need for liver transplantation following bile duct injury can be determined, though understandably the following methodology is not completely accurate. Approximately 450,000 laparoscopic cholecystectomies are performed each year in the USA [1]. Bile duct injuries occur at a rate of approximately 0.5 % which would yield an estimated 2250 biliary injuries per year [2]. 2250 injuries per year would represent approximately 22,500 biliary injuries in a ten year period. The authors of the chapter note that in the 10-year period from 2000 to 2010 only 111 liver transplants were performed for secondary biliary cirrhosis in the USA and not all of these cases were secondary to biliary injury. While clearly there is delay from the time of biliary injury until the time of transplant that may traverse many years, if we assume that the rates of injury and development of secondary biliary cirrhosis are relatively stable, and assume that every case of secondary biliary cirrhosis was caused by biliary injury we obtain a rough estimate that at worst only 0.5 % of patients that sustain a bile duct injury will go on to require liver transplantation: a rare but possible event.

In the acute setting of biliary injury liver transplantation may play a role if associated vascular injury leads to acute liver failure. The most common vascular injury associated with bile duct injury is a transection of the right hepatic artery which does not in itself lead to liver failure. Complete transection of the proper hepatic artery also rarely leads to liver failure since portal flow is adequate to support hepatocyte function. However, lack of hepatic arterial flow from injury accompanied by

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extensive porta hepatis dissection may interrupt the network of collateral vascular supply to the remnant biliary tree, (which is dependent on arterial flow) to such a degree that it predisposes to late biliary strictures extending high into right and left sides of the liver . This may eventually lead to the need for liver transplantation in the chronic setting due to progressive diffuse stricturing. Complete transection of the porta hepatis is an infrequent but catastrophic event that leads to rapid, fulminant liver failure and death without rapid transplantation. Patients that have complete transection of the porta hepatis require rapid transfer to a liver transplant center with urgent assessment for transplantation and consideration for total hepatectomy and temporary portacaval shunt construction while awaiting the highest priority liver allocation [3]. Mortality from this devastating injury is high even should the patient survive until a liver is available for transplant.

More commonly occurring, though still a very rare event, is the development of secondary biliary cirrhosis after initial repair of a biliary injury with stricturing at the anastomotic repair site leading to chronic obstruction, infection and progressive liver damage. As pointed out in the chapter only 1–2 % of all liver transplants are done with an associated diagnosis of secondary biliary cirrhosis, however not all of those transplants were secondary to iatrogenic injury. What is clear is that even with appropriate meticulous biliary reconstruction by experienced hepatobiliary surgeons chronic stricturing can occur in 5–10 % of cases. The majority of strictures are amenable to either nonoperative dilation or operative revision prior to the development of secondary biliary cirrhosis; however, occasional patients have the development of subclinical disease that presents only with liver decompensation. Others patients develop recurrent infectious complications that cannot be cleared and eventually lead to transplant. Minimizing the chances of the long-term complications of biliary stricture by involvement of an experienced hepatobiliary surgeon at the time of initial repair of the duct injury as well as a multidisciplinary team, and ongoing surveillance would seem important in reducing the chances of subsequent need for liver transplantation.

Liver transplantation in the chronic situation is approached as for any liver transplant patient with preoperative assessment of overall status and in particular cardiac status prior to listing. Patients in general will have portal hypertension and liver dysfunction/decompensation although there is the rare patient that will require liver replacement as the only way to clear widespread biliary infection in a diffusely damaged biliary tree. Previous biliary tract reconstruction is associated with increased technical difficulty and blood loss at the time of total hepatectomy as the porta hepatis and vascular structures are encased in fibrotic vascularized scar with high pressure portal collaterals. It is not uncommon for there to be a need for either alternate arterial inflow construction, the use of portal vein jump grafts, or both. Unfortunately in the last decade liver transplantation has occurred at a rising severity of illness with many regions in the USA currently transplanting at MELD scores of greater than 35. Performing liver transplantation in patients with MELD scores >35, frequently on dialysis and inotropic support makes the addition of the technical issues associated with liver transplantation after biliary reconstruction a major consideration.

In summary, liver transplantation is an unusual sequela of bile duct injury, however there is the rare patient that will progress to transplantation. Liver transplantation currently has a limited but definite role in the management biliary injury in both the acute setting with associated major vascular injury and acute liver failure as well as in the chronic setting of secondary biliary cirrhosis.

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Part IV
Strictures of Operative Sequelae

Chapter 36
Biliary Strictures from Liver Transplantation

Flavio Paterno and Shimul A. Shah

Introduction

Complications of the biliary tract represent a significant cause of morbidity in liver transplant (LT) recipients [1]. They are reported as the most common surgical complications after LT and the most common surgical cause of post-transplant readmissions [2, 3]. The biliary complications observed after LT include a wide spectrum such as biliary strictures, biliary leaks, biliary stones, and papillary dysfunction. The incidence and types of biliary complications have changed since the beginning of LT. Several factors, such as modifications of the operative techniques, organ allocation policies (Model for End-Stage Liver Disease score, MELD), and donor factors (increasing donor age, use of donation after cardiac death (DCD) donors, living donors), might have contributed to these changes [1]. Currently, biliary strictures are reported as the most common type of biliary complications after LT with a rate of 12–23 % [1, 3–5].

Incidence, risk factors, stricture type, and clinical management of biliary strictures are significantly different according to the type of liver allograft donor: brain-dead donor, donor after cardiac death (DCD), living donor. Among these three types of donors, differences in ischemia-reperfusion mechanisms, anatomic issues, and surgical techniques explain the significant differences in rates, types, and management of biliary strictures.

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Biliary Strictures in Brain-Dead Donor Liver Transplants

Biliary strictures are the most common biliary complications after standard brain-dead donor LT. They are classified into anastomotic and nonanastomotic (NAS) depending on their location in the bile duct. These two types of biliary strictures exhibit significant differences in risk factors, pathogenesis, treatment, and outcomes.

Incidence and Risk Factors

Anastomotic Strictures

Anastomotic biliary strictures after LT from brain-dead donors are reported in about 7–15 % of cases [1, 3, 5–7]. The majority of anastomotic strictures present within 1 year from LT, with the highest incidence in the first 6 months [3, 8]. Early anastomotic strictures have been attributed to technical factors, while later appearing strictures have been related to vascular insufficiency and fibrotic healing (Fig. 36.1).

Several retrospective studies identified potential risk factors associated with anastomotic strictures. A variety of factors related to recipient, donor, surgical technique, and postoperative course have been linked to anastomotic strictures.

A large retrospective study from University of Pittsburgh identified the following factors associated with biliary anastomotic strictures: postoperative bile leak (OR: 2.24, CI: 1.32–3.76, $p<0.01$), post-MELD era (OR: 2.30, CI: 1.60–3.32, $p<0.01$), old donor age (OR: 1.01, CI: 1.00–1.02, $p<0.01$), duct-to-duct anastomosis (OR: 2.22, CI: 1.23–4.06, $p<0.01$) [1]. In another study, postoperative bile leak,

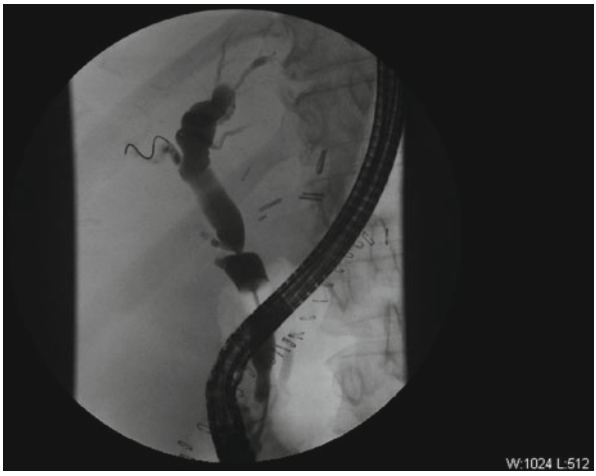

Fig. 36.1 ERCP imaging of anastomotic stricture after liver transplant

era of transplantation, and female donor/male recipient mismatch were associated with increased risk for anastomotic stricture. However, the prevalence of anastomotic strictures was not different between duct-to-duct reconstruction and hepaticojejunostomy [5]. Postoperative leak (OR: 3.63, CI: 1.77–7.46, $p<0.01$) was the only risk factor for anastomotic stricture in another retrospective series that actually showed a protective effect of HTK preservation solution (OR: 0.40, CI: 0.21–0.75, $p<0.01$) [4].

Late anastomotic strictures may have a different etiology and risk factors than immediate postoperative strictures. Fujita et al. looked at anastomotic strictures that occurred 30 days or more after LT. They excluded early anastomotic strictures to reduce the possible effect of technical failure. In multivariate analysis, they found that early recurrence of hepatitis C (OR: 6.44, CI: 2.83–14.7, $p<0.01$), hepatic artery thrombosis (OR: 8.00, CI: 2.17–29.5, $p<0.01$), and cold ischemic time ≥ 12 h (OR: 3.30, CI: 1.10–9.93, $p=0.03$) were associated with late anastomotic strictures [7].

Nonanastomotic Strictures (NAS)

Nonanastomotic stricture (NAS) is usually defined as a biliary stenosis not localized at the anastomosis (Fig. 36.2). The terms "intrahepatic biliary strictures" or "ischemic-type biliary lesion" have been also used to indicate NAS [9]. The reported incidence of NAS varies between 2 and 17 % after brain-dead donor LT [1, 9–11]. There is a significant variation in the rates of NAS reported in different studies. This is related to the era of transplantation (pre-MELD or post-MELD), patient selection, diagnostic criteria, and modalities of care. Higher rates of NAS were noted in centers that place biliary drains at the time of LT and perform routine

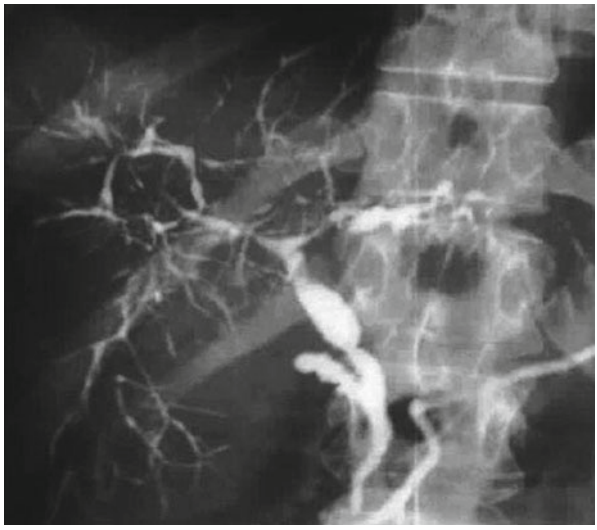

Fig. 36.2 ERCP imaging of ischemic cholangiopathy after DCD liver transplant

protocol cholangiograms [10, 11]. The median time to NAS diagnosis was 11.3 weeks after LT [10]. NAS involve bilateral intrahepatic ducts in the majority of cases (65 %), only one liver lobe in 21 % of cases, only the hilum in 14 % of cases [10]. Retrospective studies showed the following factors associated with NAS: hepatic artery thrombosis, prolonged cold ischemic time, prolonged warm ischemic time, pretransplant diagnoses of primary sclerosing cholangitis, and autoimmune hepatitis [10]. One common mechanism of NAS formation is related to ischemia of the bile ducts that can be secondary to hepatic artery thrombosis or long ischemic times. The impact of preservation solution used during the donor procurement operation is controversial. Some studies showed increased incidence of NAS with high viscosity solution like UW solution [9, 11], while other studies showed no difference in NAS between UWsolution and other low viscosity preservation solutions [10, 12]. Most of these studies are limited because they are retrospective and small size sample.

Another controversial topic is concerning the timing of hepatic artery reperfusion. A recent retrospective study showed a reduced incidence of NAS with simultaneous portal vein and hepatic artery reperfusion [13]. However another study failed to show any difference when compared with the standard sequential reperfusion (portal vein reperfusion followed by hepatic artery reperfusion) [14].

Diagnosis

Biliary strictures may present clinically with jaundice, itching, and fever. Recurrent cholangitis can be a complication of biliary stenoses (reported in almost 20 % of cases). However, almost a third of patients with biliary strictures are clinically asymptomatic [6, 15]. Serum bilirubin elevation has been reported in 58 % of patients with biliary strictures and elevated alkaline phosphatase in 85 % [6].

Abdominal ultrasound is a noninvasive modality used as the first step in the diagnosis. However, ultrasound is not always reliable for early diagnosis of biliary strictures. It detects intrahepatic biliary dilatation only in 56 % of patients with biliary strictures [6]. Magnetic resonance cholangiopancreatography (MRCP) appears to be an effective diagnostic tool for biliary complications in transplant patients. Studies that controlled MRCP findings with cholangiograms reported a sensitivity and specificity respectively of 93–94 % and 89–92 % [16, 17].

Cholangiography, either endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous trans-hepatic cholangiogram (PTC), is considered the gold standard for identifying post-transplant biliary complications. ERCP is an effective diagnostic test in case of suspected biliary obstruction in patients with duct-to-duct anastomosis. The rate of failed cannulation of the common bile duct is very low (5 %) [18]. The main advantage of ERCP is that it is both a diagnostic and therapeutic tool.

PTC represents the first choice in the clinical management of patients with hepaticojejunostomy. Few centers adopt PTC as first-line diagnostic and treatment modality also in recipients with duct-to-duct anastomosis [3]. PTC is also a valid resource in case of failed ERCP. After a PTC is placed, a combined procedure can be performed with ERCP in extending the stent across the biliary anastomosis if the biliary stricture cannot be traversed from the ERCP approach.

Treatment

Anastomotic Strictures

The management of biliary strictures depends on the type of biliary anastomosis, time onset of stricture after transplantation, and institution protocol. ERCP represents the first-line treatment for anastomotic biliary strictures in patients with duct-to-duct biliary reconstruction [3, 6, 8, 19]. The treatment protocol for biliary strictures varies according to the different transplant centers. In most centers biliary strictures presenting 1 month or more after transplantation are usually treated with balloon dilatation and stent placement. Early strictures presenting before 4 weeks are usually treated with only stent: dilatation is not performed due to concerns for anastomosis disruption [19].

The initial success rate of ERCP in relieving the biliary obstruction is 75–92 % [5, 6]. The most common reason of initial technical failure is a severe stenosis that cannot be passed by wire [5]. Most patients require a median number of 3–4 ERCP to treat definitively the stricture with a median total time of biliary stenting of 11 months [5, 18, 19]. In the long term 19–32 % of patients treated with ERCP had a refractory stricture that needed surgical treatment [6, 19].

The overall complication rate per procedure after ERCP in transplant patients is 3.7–6.6 %; however, it is 0.7 % when considering only severe complications. The most common complications include acute pancreatitis, cholangitis, and bleeding [5, 19, 20].

The cases that failed endoscopic treatment are usually treated surgically with conversion to hepaticojejunostomy with a Roux-en-Y anastomosis [8, 21]. The previous failure of nonsurgical treatment (ERCP or PTC) does not affect the outcomes of hepaticojejunostomy [22].

PTC with balloon dilatation is the most common treatment for biliary stricture in patients with hepaticojejunostomy. The long-term success rate of PTC dilatation and drain for biliary strictures is 61 % [23]. PTC is an alternative option when ERCP is not feasible due to difficult papillary cannulation or failure to traverse the stricture with a guidewire. In these setting, PTC is helpful to provide at least external biliary drainage; however a long-term therapeutic success with resolution of the stricture has been noted only in 25 % of patients [24].

Nonanastomotic Strictures (NAS)

NAS represent a major therapeutic problem. Most NAS are treated with balloon dilatation and external drainage. The long-term outcomes of NAS are poor: the complete resolution of NAS is rare and it has been described in only 5 % of patients [10]. Thirty percent of patients with NAS required retransplantation. NAS is also associated with decreased graft survival [10]. In selected cases of dominant hilar stenosis, balloon dilatation can be associated with stent insertion, and even conversion to hepaticojejunostomy can be considered [8].

Controversies

Duct-to-Duct Anastomosis Versus Hepaticojejunostomy

In the majority of standard LT, biliary reconstruction is performed with a duct-to-duct (choledochocholedochostomy) anastomosis [1, 3, 4]. In this type of reconstruction the donor common hepatic duct is anastomosed directly to the recipient common bile duct. Prior to anastomosis, it is imperative to cut back to fresh tissue and ensure adequate blood supply to both ducts arising from the three and nine o'clock arteries. The fibrofatty and lymphatic tissue is kept intact around the ducts to ensure the microvasculature is preserved. An alternative biliary reconstruction is the hepaticojejunostomy with anastomosis of the donor hepatic duct to the recipient jejunal loop arranged with a Roux-en-Y jejuno-jejunostomy.

The benefits of duct-to-duct anastomosis include: shorter operative times, avoidance of one anastomosis (jejuno-jejunostomy), access to the bile duct with ERCP if necessary for diagnosis or treatment, preservation of physiologic biliary drainage, less frequent colonization of the biliary tract. Advantages of hepaticojejunostomy include: avoidance of size mismatch between donor and recipient biliary ducts and avoidance of excessive tension on biliary anastomosis. The percentage of hepaticojejunostomies in LT has been decreasing with the years [1].

The impact of the type of biliary duct reconstruction (duct-to-duct versus hepaticojejunostomy) on complications and anastomotic strictures is controversial and most studies reported are retrospective. While a large study showed increased stricture rate with duct-to-duct anastomosis [1], other reports did not show any difference in stricture rates between the two types of biliary reconstructions [4, 5]. Even in the subgroup of patients with primary sclerosing cholangitis (PSC) treated with LT, there were no differences in stricture rates between duct-to-duct anastomosis and hepaticojejunostomy [25, 26]. In liver retransplantation the most common type of biliary reconstruction is also duct-to-duct (77 %), and no differences in biliary complications were noted between duct-to-duct and hepaticojejunostomy [27].

To Drain or Not to Drain

The use of T-tubes or other types of biliary stent or drains has been a matter of debate for several years. The use of T-tubes in LT has been decreasing due to the reports of increased biliary leaks and cholangitis related to the T-tube [1, 28, 29]. The supporters of T-tubes advocate the use of the T-tube for the following reasons: it provides access to the bile duct for imaging, it helps in monitoring bile output and liver function, it might protect from anastomotic strictures [30, 31]. Many advocate for its use to decrease the bile flow across the anastomosis and allow for healing. Since 2000, four prospective randomized trials on the use of T-tube in LT have been published [29, 31–33]. Two randomized studies reported an increased incidence of biliary complications in the T-tube group (60.4 % vs. 11.1 %, $p<0.01$ [32], 33.3 % vs. 15.5 %, $p<0.01$) [29]. One randomized trial reported an increased overall complication rate in the group without T-tube (52.6 % vs. 27.2 %, $p<0.01$) [31]. The most recent randomized trial did not show any difference in biliary complication rate between the two groups (T-tube: 25.3 %, No T-tube: 19.6 %, $p=$NS) [33]. The discrepancy in the outcomes of these studies likely reflects differences in definition of complications, follow-up time, and varied anastomosis technique (end-to-end vs. side-to-side). A recent meta-analysis showed a lower stricture rate in the T-tube group; however, there were no differences in the rate of overall biliary complications whether or not a T-tube was used [30].

An alternative to the T-tube is the trancystic tube. This tube serves as a combined external and internal stent that traverses the duct-to-duct anastomosis and exits via the cystic duct. It is held in place commonly with a hemorrhoidal band and an absorbable suture. It can usually be discontinued at 6 weeks postoperatively. In a retrospective study, the use of a transcystic biliary drain was associated with a decreased incidence of anastomotic strictures (OR 0.32, CI 0.10–0.98, *P* 0.046) [4]. The drawback of these tubes is the development of bile leaks after removal of the tube from the cystic duct stump. Also, patients can develop dehydration if there is excessive output from the drainage catheter (typically if >1 L per day).

Running Versus Interrupted Anastomotic Technique

Only a few retrospective studies have compared running sutures versus interrupted sutures in biliary anastomoses in standard brain-dead donor LT. In a small retrospective study (100 patients), Castaldo et al. found similar stricture rates (9.8 % vs. 5.1 %, $p=0.37$) and leak rate (7.3 % vs. 8.5 %, $p=0.83$) between continuous and interrupted sutures. They also did not find any difference in anastomosis time between the two techniques [34]. Another retrospective study showed that the suture technique (running versus interrupted) was not associated with anastomotic stricture formation [1]. Furthermore, some centers perform a mixed suture technique

with a running suture on the posterior wall and interrupted suture on the anterior wall achieving similar anastomotic stricture rates [32, 33]. Based on the data, the technique employed for duct-duct anastomosis is at the comfort and experience of the surgeons as there appears to be no difference between running and interrupted suture technique.

Biliary Strictures in Living Donor Liver Transplantation

Biliary reconstruction remains a technical challenge in living donor liver transplantation (LDLT) with an incidence of 15–60 % in selected series that is much higher than deceased donor liver transplant (DDLT) [35, 36]. Despite a lower acuity of liver disease at time of LT, improved donor organ quality with LDLT, and timed nature of the surgery, hospitalization requirements for medical and surgical complications are higher after LDLT than DDLT [37, 38]. In the last 20 years, numerous reports have described the optimal method for biliary reconstruction to reduce the risk of strictures. Since 2008, numerous studies have reported a lower incidence of biliary complications at 5–13 %, due to technical advances and preservation of blood supply. The stricture rate is problematic given that anatomical variations are common, a high incidence of multiple bile ducts, and the blood supply may be poor [39, 40]. Although biliary strictures after LDLT are common, in most recipients they can usually be managed nonoperatively and it does not affect short-term graft survival [35].

Risk Factors

In considering right lobe living donor liver transplantation (RLDLT), the anatomy of the right bile duct remains the biggest risk factor for stricture after LT. A single right duct is found in only 65 % of the cases. In the other 35 % of cases, two or more ducts will be found. Even when there is a single duct, it quickly divides in the anterior and posterior branches. When considering donor safety, one must balance trying to achieve a single duct for transplantation versus being too close to the confluence and risk of stricture in the remaining bile duct. The line and angle of transection in these cases is critical (Fig. 36.3). Careful planning of the biliary anatomy with MRCP, cholangiogram, or other biliary studies can minimize the rate of biliary complications especially stricture [41]. The presence of two or more ducts has proved to be a significant risk factor for biliary complications.

Beyond the biliary anatomy, donor and recipient characteristics have not been found to be determinants for biliary strictures. Several single center series have found associations with strictures, but their effect is largely unknown. This includes donor or recipient age, portal flow, body mass index, and presence of hepatitis C.

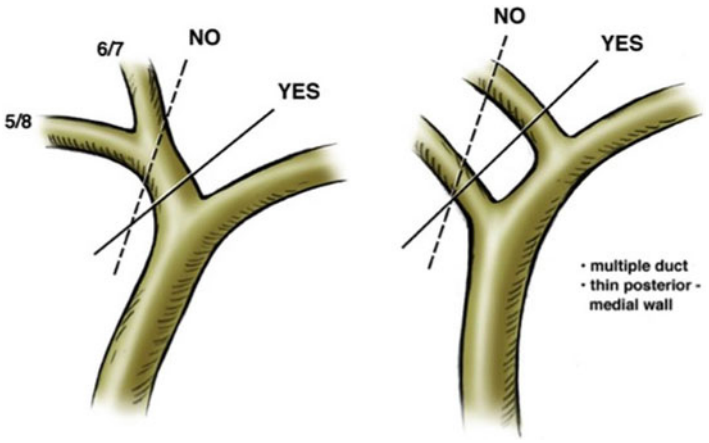

Fig. 36.3 The angle of transection in the donor hepatectomy that is critical for proper blood supply and integrity of bile ducts for anastomosis

Treatment (Nonoperative, Operative)

Approaches to handling biliary strictures after LDLT include ERCP, percutaneous biliary drainage (PTC), and reoperation. Currently, most biliary complications can be managed successfully by nonsurgical approaches. ERCP is the primary modality with PTC reserved for severely strictured or disconnected ducts that cannot be traversed by ERCP or patients who have undergone roux-en-Y reconstruction.

ERCP is the first choice for duct-duct patients with biliary strictures after LDLT. Patients often require multiple sessions of endoscopic therapy with dilation and placement of multiple smaller caliber stents. The successful endoscopic management of biliary anastomotic strictures is achieved in only 58–76 % of LDLT cases which is much lower than in DDLT [35]. This is likely due to multiple, small-caliber anastomoses, peripheral locations, and twisted structures due to anastomotic fibrosis and hypertrophy of the transplanted liver [42]. The median number of interventions per patient with a biliary stricture in a recent high volume RLDLT experience was three ERCPs and four PTCs [35].

For patients with roux-en-Y reconstruction, PTC with balloon dilation is generally recommended as a minimally invasive therapeutic technique. It is associated with an increased risk of complications, though, including bile leakage, hemorrhage, infection, and patient discomfort. As an alternative to surgery, PTC should be the first diagnostic and therapeutic modality to understand the nature of the stricture, length, and assessment of improvement with surgery. Recently, the use of double balloon endoscopy has allowed for endoscopic treatment of strictures in patients with roux-en-Y reconstruction. Magnetic compression has also been used successfully in canalizing severe biliary strictures as well.

Prior to surgical revision of a biliary anastomosis, an extensive workup must be performed for careful delineation of the biliary stricture. This starts with MRCP or

cholangiogram through ERCP or PTC. A CT arteriogram or Doppler study of the hepatic artery should be performed to rule out hepatic artery thrombosis. Surgical revision is associated with best results with isolated, short anastomotic strictures. Long strictures or the presence of multiple intrahepatic strictures are a relative contraindication to surgical revision due to poor results. In these cases, retransplantation should be considered depending on the patient's clinical course [43]. Outcomes following repair of biliary strictures are largely unknown. Successful repair appears to be associated with the absence of biliary leak, which may be associated with ductal ischemia, and lower rates of successful repair [44]. Timing of surgery from diagnosis of strictures with correction within 6 months appears to be an important factor as well; this is due to the cumulative scarring from chronic infection and inflammation in the obstructed duct, which probably occurs over time from prolonged failure of percutaneous and endoscopic interventions [43].

Prevention

There are several principles that can be used to decrease the rate of strictures in LDLT. The most important preventive method is to obtain a healthy well-vascularized duct from the donor operation. Dissection of the hila plate should be minimized to avoid disruption of the microcirculation around the right hepatic duct and artery. The duct is commonly divided after 80–90 % of the parenchymal transection has been performed to improve visualization of the hilar plate and biliary confluence. The duct should be divided sharply and perpendicular to its long axis to minimize the risk of skeletonizing the postero-medial aspect of the right hepatic duct. The third technical point is to preserve the vascular plexus around the common bile duct, which is derived from the gastroduodenal artery and the right hepatic artery [45]. The periductal plexus consists of multiple arteriolar branches, which forms a plexus around the duct. This approach holds true for the recipient hepatectomy as well. Dissection of the hilar duct should be minimized to preserve blood flow to the recipient ducts. A combination of intrahepatic Glissonian transection avoids dissection of the biliary plate and preserves vascularity for multiple anastomoses [46].

The reconstruction of multiple graft bile ducts is challenging since they are typically tiny, thin-walled, and prone to ischemia. When two ducts are close together in a similar plane, ductoplasty may be applicable but it can increase the risk of bile duct stump ischemia. Unification is still preferred to multiple ducts anastomosed separately since multiple biliary anastomoses are associated with increased risk of stricture.

Controversies

In the evolution of LDLT, biliary reconstructions with roux-en-Y enteric anastomoses were felt to be better than duct-duct anastomoses because of a more reliable blood perfusion and ability to obtain a tension-free anastomosis. The roux-en-Y has

been reported to have a lower stricture rate in earlier studies, but recently, this belief has evolved as most surgeons prefer duct-duct due to the ability to manage leaks and strictures postoperatively with nonoperative means. The duct-duct technique is faster, more physiologic, and reduces the risk of cholangitis and infection since the enteric system is not opened. But most importantly, the duct-duct technique allows for investigation and management of postoperative biliary complications through ERCP. Roux-en-Y is more beneficial due to arterial collateral formation of the duct stump but it may also be more challenging than duct-duct due to mucosal edema resulting from portal hypertension and hypervolemia. There is no randomized study comparing the two methods.

The benefit of internal or external transanastomotic biliary drainage remains controversial. Stents provide maintenance of biliary flow in the setting of anastomotic swelling and also access for study with cholangiography. Its drawback is that it is a foreign body and can induce inflammation and future stricture formation. Studies have shown excellent results with and without biliary stents in the duct-duct setting and its role appears more important in the reduction of biliary leaks and maintaining patency when the duct diameter is small (<2 mm). The current recommendation is for the use of biliary drainage in pediatric recipients and roux-en-Y reconstructions; this is due to the likely presence of small bile ducts in these settings.

Donation After Cardiac Death (DCD) Transplantation

Biliary strictures, primarily nonanastomotic strictures (NAS), are common after DCD liver transplants. This is due to the period of warm ischemia time with organ preservation in which stasis and thrombus formation in small vessels is expedited. This likely affects the biliary plexus and develosps an ischemic cholangiopathy of the liver in 20 % of all DCD transplants within 3 months of LT. These strictures are often progressive in nature, are refractory to endoscopic/radiologic interventions, and often progress to cholestatic liver failure. The clinical picture is similar to NAS of other etiologies but more severe and retransplantation is often required in a large percentage of patients [47, 48].

Risk Factors

The time from asystole to cross-clamp has been identified as a major risk factor for the development of ischemic cholangiopathy. Our center uses 30 min as the cutoff for use of these organs due to this risk. Taner calculated that each minute of additional warm ischemia time increases the odds ratio for the development of ischemic cholangiopathy or hepatic necrosis by 16 % [47, 49]. Other risk factors for biliary ischemia include donor age, donor weight, and cold ischemia time.

Prevention

Routine surveillance is very important in the early period after LT to assess for ischemic cholangiopathy after DCD transplants. Many advocate placing a biliary drainage catheter either through the transcystic route or as a T-tube to allow for early intervention and imaging. Other preventive strategies include limiting warm ischemia time to 30–45 min, limiting cold ischemia time to 8–10 h, and avoiding use of older or steatotic allografts. Simultaneous arterial and portal revascularization has been recommended as well [50].

Recently, new approaches to lowering the biliary stricture rate of DCD transplants have been advocated using thrombolytic agents or machine perfusion. Clinical results have been promising using injection of tissue plasminogen activator (TPA) into the donor hepatic artery lowering the rate of ischemic cholangiopathy to 9 % and overall biliary complication rate to 27 % [51]. This approach has led to excessive bleeding and must be managed especially if poor graft quality is present. Recently, a joint experience was reported between University of Toronto and Ochsner Clinic concerning the use of tPA in situ. Between 2009 and 2013, 85 DCD liver transplants were performed with intraoperative tPA injection and compared to 33 DCD liver transplants without tPA. Donor and recipient characteristics were similar between both groups. There was no significant difference in intraoperative packed red blood cell transfusion requirement ($p=0.74$). Overall, biliary strictures occurred less commonly in the tPA treated group (16.5 % vs. 33.3 %, $p=0.07$) with a much lower rate of diffuse intrahepatic strictures (3.5 % vs. 21.2 %, $p=0.005$) (Seal et al. in press).

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Chapter 37
Commentary: Biliary Strictures from Liver Transplantation

Kim M. Olthoff

During my training over 20 years ago, the bile duct anastomosis and postoperative biliary issues were considered the "Achilles heel" of liver transplantation. I still recall my mentor at UCLA playing "Danger Zone" from the movie "Top Gun" on the CD player when it came time to work on the bile duct, mostly in whole deceased donor grafts. We have come a long way since then, but the issue of bile duct complications after transplantation remains a real problem that has yet to be solved. With each technical advance in liver transplantation, we find new bile duct problems that need to be dealt with. Our experience over the years with extended criteria grafts, retransplantation, death after cardiac death (DCD) livers, split livers, and living donor liver transplantation (LDLT) has taught us a great deal, and much of what we have learned can also be applied to non-transplant biliary surgery.

Drs. Paterno and Shah have written an excellent overview of the bile duct issues that liver transplant surgeons encounter. They have reviewed the incidence and treatment of bile leaks, anastomotic and non-anastomotic strictures, risk factors, and potential management. Despite a huge experience, the potential for biliary complications after transplant will always be there, and Drs. Paterno and Shah guide the reader through the essentials.

Our "routine" transplant biliary anastomosis is duct to duct with interrupted suture. In my opinion, the most important factor to prevent leak or stricture is good blood supply. The lessons learned from complex LDLT biliary anastomoses have shown us that duct-to-duct anastomoses without stenting can be done safely with good results in nearly all cases, and even in small pediatric ducts.

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From my perspective, post-transplant biliary issues and strictures can be categorized as follows: those that have essentially disappeared, those that have become much easier to manage, those that have become more complex, and those that will never change and are probably here to stay.

The biliary issue that has essentially disappeared is the use of a T-tube which was meant to prevent leaks and strictures, but also caused many leaks when they were pulled. In our program, the use of T-tubes is now historic. We haven't used a T-tube for many many years, and we have not found any down-sides to this practice—no increased leak, no increase in strictures. If anything, we have fewer. The only thing you sacrifice is the ability to see the quality and quantity of the bile production post-transplant, however one should be able to assess this already in the OR. It is a very rare event when we may use a T-tube for a tenuous duct-to-duct anastomosis when a Roux is not possible.

The postoperative anastomotic stricture in the deceased donor transplant (DDLT) is the type of complication that has become easier to manage for surgeons. Management has transitioned from mostly surgical revision to endotherapy by skilled endoscopists who work closely with the transplant surgeons. Endotherapy with stenting is now successful in about 80 % of cases at 1 year. Since the early 2000s, most endoscopists have subscribed to the theory of using increasing number of plastic stents to gradually dilate strictures with subsequent procedures every 3 months and after 1 year of therapy to remove all stents. There is not wide consensus on the timing of these serial ERCPs and the maximum number of stents to place. Some centers favor more aggressive stenting with many stents placed over shorter treatment durations, as frequently as repeating ERCP every 2 weeks to achieve the maximum number of stents. Our center favors a slightly less aggressive approach.

A more recent development has been the use of larger caliber fully covered metal stents to remediate biliary anastomotic strictures. The most informative recent study was a systematic review comparing plastic stents to metal stents. Stricture resolution rates were highest (94–100 %) when plastic stent duration was 12 months or longer, and stricture resolution rates with metal stents were also high when stent duration was 3 months or longer (80–95 %). However metal stents were associated with a 16 % migration rate [1]. The jury may still be out on the covered metal stents, and we have not employed them yet at our center, but it is gaining popularity. With regard to choledocojejunostomy strictures, balloon enteroscopy has improved management, and direct cholangioscopy really enhances success for very tight strictures.

Our endoscopic experience at Penn demonstrates an approximate incidence of 13 % biliary stricture following DDLT. These are mainly managed with endoscopic stenting and demonstrate a long-term success rate of 75 % achieved after a single round of stent therapy (median 4 ERCPs) with a median duration of 7 months. Of those with recurrent strictures after a round of endoscopic therapy, most had successful remediation after additional rounds of therapy, resulting in a 96 % success rate (V. Chandrasekhara, personal communication). Even though endoscopic therapy has great results, we must not forget that surgical revision with a conversion to Roux-en-Y still remains a definitive treatment for those with a stricture that doesn't resolve with endoscopic stenting.

The scenario where we have encountered more biliary challenges is in the field of LDLT. The increasing practice of LDLT and the experience it has brought us has led to some significant advances in biliary management, but has also produced more headaches. The incidence of biliary complications is definitely higher than in deceased donor transplantation. In the NIH sponsored multicenter A2ALL trial, the overall incidence of all biliary complications was 40 %, compared to 25 % in DD liver transplant recipients. The great majority were bile leaks from the cut surface or anastomosis, but there was also a significant incidence of biliary strictures (14 %), usually presenting 2–4 months after transplant [2]. Most strictures can be handled non-operatively with multiple interventions were needed for resolution, including both ERCP and PTC. These interventions are almost always successful with a median time to become stent, tube, and drain free of 2.3 months, thus avoiding surgical revision, which can be exceedingly complex and dangerous after LDLT. Interestingly (but predictable) that centers who had a large experience in biliary complications also became the most efficient and successful at dealing with them. Three factors have been found to be associated with biliary complications: older recipient age, higher BMI, and the diagnosis of HCV.

In LDLT the ducts are short, flush with the cut parenchyma, and often we are faced with multiple small ducts requiring creative ways of reconstructing. We do mostly duct-to-duct anastomoses, but multiple ducts may require a combination of hepatico-choledochostomy and hepatico-jejunostomy. The key to a successful anastomosis is preservation of the blood supply to the recipient duct, which requires a dissection high into the hilum in order to get enough length.

It is also important to remember that there are also biliary complications associated with the donors who undergo right or left hepatectomy for living liver donation. The A2ALL consortium has the most complete report of donor morbidity and mortality and reports biliary leak rate of 8% and a biliary stricture rate of 0.7%, all occurring early and resolved within the first year (3). Most of the leaks were from the cut surface and closed with simple JP drainage, and the strictures handled non-operatively. Most LDLT donors undergo right hepatectomy that is a very different operation from a right hepatectomy for cancer or other liver disease. Donor hepatectomies require complete transection of the parenchyma without ligating any vascular inflow or outflow, and the bile duct (or ducts) needs to be transected at a level safe for the donor but also considering the recipient side, where fewer issues are encountered if it is a single duct. The donor surgeons utilize different techniques to optimize the area of transection. At Penn, we use fluoroscopy, placing narrow radiopaque markers across the duct and take several images in different planes as a guide prior to actually cutting the duct. The decision on where to divide the duct or ducts sometimes involves some negotiation between the surgeon doing the donor hepatectomy and the recipient surgeon, but donor safety always takes priority.

Biliary complications and strictures following death after cardiac death (DCD) donation is where we have seen little progress, and is the area where it seems some things never change, no matter what innovations we may attempt. DCD livers have expanded the donor pool, but not without significant drawbacks. Patients receiving a liver from a DCD donor a significantly higher risk of developing ischemic

cholangiopathy than brain dead donors, and a lower survival. Reported stricture rates range from 30 to 50 %, and are often refractory to intervention [4]. These patients end up with more readmissions, invasive procedures, multiple tubes, frequent cholangitis and often retransplantation. While these livers may be live saving in some patients, these risks and complications must be taken into consideration when using these grafts. Hopefully some new advances are being investigated with the use of tPA and machine perfusion that may be able to influence these outcomes in the future.

Retransplantation is also an area where biliary complications can plague the transplant surgeon and lead to significant adverse events. We compared patient and graft survival for recipients undergoing retransplantation over a decade at our center, comparing those with biliary complications after retransplantation to those without [5]. We found the complication rate to be 20.9 % in 110 re-transplant cases. The survival rates for those who experienced biliary complications were significantly worse than those who did not, with an increased risk of death (49.7 % at 1 year compared to 91.7 %, $P<0.001$) and more graft loss. These findings show that it is imperative that there is early recognition, expeditious intervention (usually surgical), and preventative measures performed in the clinical management of re-LT recipients.

Biliary complications are not cheap, either. An analysis of the national transplant registry and Medicare claims for over 12,000 recipients revealed that biliary complications were more common in recipients of donation after cardiac death compared to donation after brain death allografts (23 % vs. 19 % $P<0.001$). Among donation after brain death recipients, biliary complications were associated with $54,699 of incremental spending in the first year after transplantation and $7327 in years 2 and 3 (95 % CI, $4419–$10,236). Biliary complications in donation after cardiac death recipients independently increased spending by $94,093 in the first year and $12,012 in years 2 and 3, demonstrating the significant economic impact of this very common perioperative complication and suggests a potential target for quality of care improvements [6]. A follow-up to this paper demonstrated that rates of biliary complications varied widely across the country, and higher rates were associated with increased risk of death, graft failure, and more health-care spending.

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Chapter 38
Recurrent Biliary Strictures After Initial Biliary Reconstruction

Juan Pablo Campana and Eduardo de Santibañes

Overview

Benign biliary strictures (BBS) constitute a serious challenge to the hepatopancreatobiliary (HPB) surgeon. In contrast to malignant obstructions, patients with benign strictures are otherwise in good health and are supposed to live for years, so they require durable treatments. More than 80 % of BBS occur as a complication of cholecystectomy [1], and their incidence has increased since de advent of laparoscopic cholecystectomy. Moreover, the injuries resulting from laparoscopic cholecystectomy are more proximal in the bile duct and more likely associated with a thermal mechanism and vascular injuries than open cholecystectomies. Other surgical procedures such as gastrectomy, hepatic resection, liver transplantation, and operation on trauma may cause biliary strictures. Less common causes of BBS are primary sclerosing cholangitis, chronic pancreatitis and autoimmune diseases such as IgG4-related sclerosing cholangitis [2].

The improper management of BBS can lead to catastrophic consequences such as recurrent cholangitis, portal hypertension or biliary cirrhosis. The first attempt to repair a BBS is the best opportunity to achieve a good long-term outcome, as repair of recurrent strictures is clearly more challenging and is associated with poorer outcome. Additionally, the loss of bile duct length associated with a failed repair is a major factor that limits the success of subsequent interventions.

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The failure of a primary biliary repair can be one of the most challenging scenarios. For the best management of recurrent strictures, the approach should be multidisciplinary, including the joint work of specialized HPB surgeons, interventional radiologists, and endoscopists.

Recurrent Stricture After Bile Duct Injury Repair

Epidemiology

Iatrogenic injury of the bile duct after cholecystectomy is by far the most common and well-studied cause of BBS. In a multicenter trial, Bismuth reported a 0.2 % incidence of bile duct injury following open cholecystectomy. With the introduction of laparoscopic cholecystectomy in the early 1990s, the incidence of bile duct injury rose to 0.3–1.3 % [3, 4]. It was believed that this increase was due to the inexperience of surgeons in this technique, and that it would decrease to figures comparable to open surgery once the *learning curve* was established. However, this trend has not been observed by all the investigators. Currently, the incidence of bile duct injury due to laparoscopic cholecystectomy stands at about 0.6 %. These injuries seem to differ from those associated with the open procedure. Laparoscopic injuries are more proximal in the bile duct and they are more frequently associated with a thermal mechanism and vascular injuries. Besides, a high percentage of these injuries coexist with biliary fistula, a fact that conditions the small caliber of the bile duct. This obscure picture could worsen if the attending surgeon does not make the correct decision once the bile duct injury occurs.

The first attempt to repair a bile duct injury is the most important. It has been proposed that the failure rate following the repair of recurrent strictures ranges between 4.7 and 22 % [5, 6], compared to nearly 90 % success in primary reconstruction in specialized centers [6–9]. Every new attempt of reconstruction necessarily implies tissue resection and a higher dissection in the pedicle with subsequent damage to the vascularization of the biliary tree, making every surgery increasingly challenging.

Predicting Factors of Unsuccessful Reconstruction

Certain factors lead to the failure of the first repair attempt, especially a hepaticojejunostomy. In 1995, Stewart and Way [10], were the first ones to demonstrate the importance of preoperative delineation of the biliary anatomy. They found that surgical repair was successful in 84 % of the patients in whom cholangiographic data was complete. In contrast, only 4 % of the patients without cholangiography and 31 % of the patients with incomplete cholangiographic data had successful outcome.

Inflammation has been well studied as a risk factor for anastomotic failure. In 2003 Huang et al. [11] identified perioperative inflammation as a predictor of poor outcome after primary repair. In the same way, Schmidt et al. found that the presence of active peritonitis was independently associated with long-term complications, such as hepatic abscess, anastomotic stricture, or secondary biliary cirrhosis [12]. Subsequently many authors have confirmed these findings [13, 14]. This may be explained by a double mechanism. Firstly, inflammatory changes in the surgical bed induce tissue friability, which result in increased technical difficulty at the time of repair. Secondly, the inflammatory process may still be active in the postoperative period, predisposing patients to fibrosis, resulting in a late anastomotic stricture. Even if drained effectively, perianastomotic abscesses may predispose to ductal ischemia and fibrotic changes, which cause the delayed stricture. It has been suggested that even in the absence of an intra-abdominal septic environment, bile leak may also increase acute inflammatory changes in the surgical bed [14].

Surgeon's experience and the type of repair are one of the most important factors that determine outcome. It has been found that only 17 % of primary repair attempts and no secondary repair attempt performed by general laparoscopic surgeons are successful [10]. Huang et al. [11] found that biliary repairs performed by nonreferral surgeons were significantly associated with unsuccessful outcomes. In a series published by Goykhman et al. [15], patients who underwent biliary reconstruction by HPB surgeons developed fewer anastomotic leaks and/or strictures than those performed by general surgeons. Additionally, strictures developed after repair by HPB surgeons were significantly more amenable to interventional radiology treatment.

The type of biliary repair is also important. In the series reported by Stewart and Way [10], primary end-to-end repairs over a T-tube for injuries diagnosed during cholecystectomy were always unsuccessful when the duct had been completely transected. The incidence of postoperative stricture can be as high as 60 % [5]. The height of the injury plays an essential role in determining the kind of biliary-enteric repair. For injuries in the immediate supraduodenal portion of the common bile duct (CBD), choledocoduodenostomy is an ideal procedure, with excellent results. However, this kind of injuries is very infrequent. Strictures at or above the hepatic confluence are more challenging than the ones below. Huang et al. [14] have recently shown that hepaticojejunostomy has a fourfold higher risk of long-term complications than choledochojejunostomy. Moreover, the higher the stenosis is, the greater the incidence of vascular associated lesions: 71 % for Bismuth type 4, 63 % for Bismuth type 3 and 33 % for Bismuth type 2 [7]. Many authors have shown that the association of vascular injuries complicates the anastomotic outcome [12, 13]. The median time to treatment failure is significantly shorter in patients with vascular associated injuries [13]. The right hepatic artery lesion is most commonly associated, and this is because this artery has a close anatomic relation with bile duct. As described by Strasberg et al. [16], the blood supply to the ducts depends on three elements: afferent vessels, marginal arteries and epicholedochal plexus. Marginal arteries are disposed at 3, 9, and, rarely, 12 o'clock on the CBD. The hilar marginal

artery, which runs across the top of the hepatic ducts confluence, functions as an arterial shunt between the two sides of the liver. The epicholedochal plexus is supplied by all three or four marginal arteries, and also contributes to this arterial shunt [16]. Thus, it has been suggested that delayed repairs allow collateral circulation within the hilar plate to provide an adequate arterial blood supply to the biliary confluence and the extrahepatic portion of the bile duct before performing surgery [14]. However, injury to the confluence of the right and left hepatic duct may disrupt the hilar shunt, preventing reflow from left to right hepatic artery [16]. A vascular lesion has to be suspected: when a bleeding accident during laparoscopic cholecystectomy occurs, when there is a sudden rise in ALT during early postoperative course, or when there are multiple metallic clips on plain film images of the abdomen. In these cases, an abdominal angiography is always indicated to rule out any arterial or portal venous damage [17]. There still exists some controversy regarding the consequences and implications of the association between a bile duct injury and an arterial injury. Some authors have not found differences in terms of intraoperative management, blood consumption, postoperative complications or long-term outcome between patients with and without vascular injuries [18–20]. These differences in conclusions may be due to a shorter interval time between the biliovascular injury and surgical repair.

The use of transanastomotic stents is controversial. There are no studies that show that their use has an influence in the anastomotic outcome.

In a recent study published by Sulpice et al. [19], it was found that the presence of biliary cirrhosis was determined to be an independent risk factor for anastomotic stricture. They suggested that in these cases, liver transplantation should be discussed at an early stage.

Clinical Presentation

The clinical presentation of biliary restrictures is similar to that of the primary stricture. Most of the patients show abdominal pain coupled with fever or other signs of sepsis. Less commonly, patients have none of these symptoms and complain of weakness, fatigue or asthenia. Some patients may have associated complications to the biliary stricture, such as bile leaks or intra-abdominal collections. Jaundice is not always present in the early course of the illness. In some patients, the stricture may evolve slowly or cause only partial obstruction [21].

Liver function tests (LFT) are of outmost importance and are often altered before clinical manifestations appear. Huang et al. [11] stated that serum alkaline phosphatase levels higher than 400 IU at postoperative month 6 predict long-term nonsuccess. Mild hyperbilirubinemia may also be present at the time of diagnosis, but markedly elevated serum bilirubin levels (>3 mg/dL) are uncommon.

Physical examination might reveal unspecific findings such as epigastric or right upper quadrant abdominal tenderness, abdominal distension, or acute abdominal pain in case of bile peritonitis.

In cases of advanced disease, signs of portal hypertension can be found such as splenomegaly or gastrointestinal bleeding. These findings should alert the surgeon because they predict hepatocellular damage, and possibly a secondary biliary cirrhosis. This should be considered an ominous predictive sign of morbidity and mortality and its diagnosis prior to a therapeutic decision is crucial. It has been shown that portal hypertension increases postoperative mortality ten times [6].

Diagnosis

The diagnosis of a restricture can be easily suspected in a patient with a background of bile duct injury with a subsequent repair. In most of the cases, these patients have a close follow-up, with routine LFT and specific imaging studies for a long period of time after the reconstructive surgery. However, other patients, lost in follow-up, are admitted at an emergency department for symptoms associated with complications of the bile duct obstruction. In these cases, clinical manifestations can be very diverse, going from mild symptoms such as isolated jaundice to a severe medical condition as a septic shock due to a severe cholangitis.

As it was stated above, routine LFT can predict the outcome of a bile duct reconstruction. Alkaline phosphatase levels higher than 400 IU must alert the surgeon and make him suspect a stricture recurrence [11]. Blood tests are important for the diagnosis of a possible cholangitis, which will determine the initial treatment of the patient.

Ultrasound (US) imaging can be a good method as an initial approach. Dilated bile ducts can be found, together with collections that may suggest a possible abscess or biloma. Depending on the clinical manifestations, free abdominal liquid may indicate bile peritonitis or ascitis due to portal hypertension. Doppler US could be useful for the identification of a vascular associated injury, although as we emphasize below, angiography is the gold standard and should always be performed whenever a vascular lesion is suspected. In certain cases, generally depending on the center expertise, ultrasound guided percutaneous drainage can be introduced for abscesses or bilomas.

Nowadays, computed tomography (CT) scan has become an indispensable imaging method. It gives good anatomical information regarding bile ducts dilation, abdominal collections, free liquid, liver atrophy, or associated vascular injuries. Moreover, CT-guided percutaneous drainages are more precise than US guided ones. A contrast-enhanced CT scan should be performed whenever possible because it can be helpful in distinguishing abdominal collections from the intestines in these cases. Modern CT angiographies can be as accurate as conventional angiographies for the diagnosis of associated vascular injuries. They have the advantage of a two-in-one study and that the vascular tree can be reconstructed through software, and a 3D image can be obtained.

Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive, radiation-free imaging method for evaluation of the biliary system. Continued

advancements in MRCP system hardware and sequence design, coupled with novel gadolinium chelate agents, allow for a detailed evaluation of the bile ducts and surrounding soft tissues [22]. MRCP has a higher accuracy in the diagnosis of BDI than endoscopic or percutaneous cholangiography, with the advantage of avoiding the adverse effects inherent with conventional cholangiography [23]. MRCP is particularly useful for patients who have undergone bilioenteric anastomosis as a primary reconstruction, because they are unable to undergo endoscopic retrograde cholangiopancreatography (ERCP) due to altered post-surgical anatomy.

Nuclear imaging procedures, such as hepatobiliary iminodiacetic acid (HIDA) scintigraphy, are valuable methods to evaluate bile excretion through the anastomosis to the intestine. They are of particular value in showing anastomotic patency and function when no tube has been left across the anastomosis at the time of repair [24]. They consist of a radioactive tracer that is intravenously injected and, subsequently excreted in the bile. Not only they are useful in the detection of biliary obstruction, but also they are particularly helpful in the presence of bile leaks, characteristically appearing as focal extrabiliary abnormalities that persist for several hours.

In patients in whom several attempts to repair have failed, the work-up must always include an abdominal angiography because a vascular associated injury can be the reason for failure. Angiography must always include an arteriogram and a portogram. Ninety-two percent of vascular injuries include the right hepatic artery (RHA), while the remainders involve other arteries, the portal vein alone or in combination with arteries that sometimes include the RHA [16]. Angiography may also have a therapeutic role in patients with active bleeding or when a pseudoaneurysm is found, using angioplasties, stents, and the placement of stent grafts. In cases of referred patients, angiography also has a medico-legal character, because, together with cholangiography, it gives a complete preoperative picture of all the possible injuries that took place in previous surgeries. Although catheter angiography remains a critical test, the indications for this procedure are falling nowadays due to technological advances in contrast enhanced magnetic resonance imaging (MRI) and CT scanning.

Currently, the role of ERCP exclusively as a diagnostic tool is limited. In the same way, percutaneous transhepatic biliary drainages (PTBD) employed only to obtain cholangiography are seldom used today. Due to the fact that these are invasive methods and that they also have a therapeutic purpose, they should be reserved for patients with cholangitis or cholestasis.

Management

Preoperative Management

Successful management of these patients requires careful planning. A thorough investigation of the current patient's condition is paramount. As stated before, imaging studies have a principal role in this matter. Before considering any definite

solution, it is important to identify and treat any life-threatening condition. Most of these patients present with infectious complications, such as cholangitis, intra-abdominal collections, liver abscesses, or, occasionally, signs of peritonitis. The initial treatment should focus on the resuscitation of the patient. Broad-spectrum antibiotics should be early initiated if infection is suspected. Abdominal collections as well as liver abscesses may be managed with US- or CT-guided percutaneous catheters. Any unuseful intra-abdominal catheter may be withdrawn in order to reduce unnecessary local inflammation.

Special attention should be paid to the nutritional status of the patient. Most of them have a history of numerous interventions and complications, associated with a chronic and systemic inflammatory condition that leads to malnutrition. This can be even more severe in patients with bile fistulas, because long periods of biliary-enteric discontinuity will impair the function of the intestinal barrier and increase the risk of endotoxemia, together with fat-soluble vitamin deficiency and excessive fluid and electrolyte loss [25]. Enteral feedings through a fine-bore nasal catheter may be necessary in these cases.

Long-lasting biliary strictures may be associated with portal hypertension and secondary biliary cirrhosis. Gastrointestinal bleeding must be addressed before considering any surgical treatment. Endoscopic banding of esophageal varices associated with vasoactive medications has shown good results in the management of variceal bleeding [26]. However, if bleeding is recurrent, transjugular intrahepatic portosystemic shunting (TIPS) should be considered, as it is associated with a high success rate (90–100 % of patients will achieve hemostasis) [27].

Interventional Radiology

Percutaneous procedures have an important role in the initial management of these patients. US- or CT-guided percutaneous drainages are very effective in the treatment of bilomas and intra-abdominal collections. PTBD should be considered in the presence of cholangitis in patients with bilioenteric anastomosis. Whenever possible, internal-external biliary drainages should be used because they have the advantage of preserving the biliary-enteric continuity. Cholangiography obtained through these catheters is especially useful in some cases involving severely distorted anatomy as a result of atrophy, hypertrophy, or dense scarring of the biliary tissue [24].

The high morbidity and mortality rate of redo surgeries reported in the past years have made percutaneous procedures evolve and expand their use. Percutaneous biliary balloon dilation (PBBD) was first reported by Molnar and Stockum in 1978. Recently, major series have been published reporting acceptable long-term results. This technique consists of a transhepatic puncture of the biliary tree with a 22 G needle, guided by US and radiology. Cholangiography is obtained to identify the stricture. A thin wire is introduced through the needle and, once the stricture is passed, a 10-16Fr catheter is placed allowing drainage of the entire biliary tree. During this procedure, or, generally, 2 or 3 days later, the

dilatation is performed. A 10–12 mm diameter angioplasty balloon catheter is inserted across the stenosis and inflated gradually for 1–3 min. Finally, an internal-external biliary drainage is left in place for 6–12 weeks. The longest follow-up was published by Cantwell et al. [28], who achieved 41 % success at 25 years in patients requiring one PBBD, and 20 % in patients requiring two dilatations. Recently, Bonnel and Fingerhut published the largest series with promising results. They have reported a success rate of 85 % with a median follow-up of 59 months [29], in contrast with 56–73 % reported in other series [28, 30–32]. They suggested that this difference might be due to the criterion they chose for removal of the internal-external drainage after the dilatation, which consisted in no residual "balloon waist" observed on at least 2 consecutive sessions 6 weeks apart. This criterion seems to be more predictive of bilioenteric patency stability than free flow of contrast through the anastomosis [28, 30–32]. In the same way, a calibration (i.e., internal-external drainage left in place after the dilatation) of 1 month or less seems to be associated with higher recurrence rates [28]. By contrast, "long-term" calibration duration with large catheters has not shown clinical significant advantages or effectiveness [28].

Most of these procedures require more than one session to achieve good long-term results. In most of the series the mean number of dilatation sessions needed range from 2 to 7.8 [28–32]. However, it has been shown that repeated PBBD procedures are not required when the first PBBD is successful [33].

Percutaneous procedures also have the advantage to diagnose and, effectively treat associated biliary lithiasis. The incidence of lithiasis can be as high as 41 % [29]. Intracorporeal electrohydraulic lithotripsy under cholangioscopic guidance has shown to be safe and effective to treat associated stones. After lithotripsy, fragments can be pushed or flashed through the anastomosis [29].

PBBD has a low incidence of serious complications. Morbidity rates range from 0 to 23.5 % [28–32, 34]. Many patients routinely have uncomplicated minor transient hematobilia that comprises no further treatments. Other more severe, yet less common, vascular injuries have been reported, such as subcapsular liver hematoma or hepatic artery pseudoaneurism, which may require transarterial coil embolization. Infectious complications such as subfrenic or liver abscesses, cholangitis and bilomas have also been well described. Rarely, some patients may suffer symptomatic pleural effusion. Mortality rate is near 0 in all series, and most of the deaths reported are not directly related to the procedure.

Few articles have been recently published suggesting the use of transhepatic metallic stents for hepaticojejunostomy stricture [35]. Long-term placement of metallic stents should not be considered as the preferred treatment. However, as good results have been obtained, they should be evaluated in large series and randomized trials.

There are no randomized trials comparing the results of surgical treatment and PBBD. Although surgical treatment seems to be more successful, it is important to note that many patients are selected for PBBD because they are not good surgical candidates or because they refuse further surgery.

Endoscopic Treatment

Due to its high incidence of failure, primary end-to-end repairs are very uncommon, and strictures of this type of reconstruction are extremely rare nowadays. In these cases, endoscopic therapy may have a role only in the initial management of very high-risk patients, especially if they are under a septic state. Otherwise, most of them are better candidates for another reconstructive surgery.

Most of the recurrent strictures after biliary reconstruction of a bile duct injury are found in hepaticojejunostomies. Performing endoscopic retrograde cholangiography (ERC) in these patients is technically very challenging or impossible due to the evident surgically altered anatomy. However, in recent years new endoscopic technologies have been introduced. ERC with double-balloon enteroscope has been performed by Mönkemüller and Fry [36]. In their small series, they achieved an overall diagnostic success of 90 % and a therapeutic success of 60 %. Subsequently, other groups have published their experience showing acceptable results [37–39]. Further refinement of the endoscope and the biliary accessories may improve the therapeutic success in the future.

Some authors have proposed a hepaticojejunostomy built with a permanent access loop secured subcutaneously or subperitoneally, for patients at a high risk of anastomotic stenosis. This loop allows easy subsequent access for cholangiography, cholangioscopy, dilatation, or stone removal. Only a few reports can be found about this method although it was first described approximately two decades ago [40].

Surgical Treatment

Revision surgery has been for long time the only treatment for recurrent biliary strictures after reconstructive surgery. However, as it was noted by Pellegrini et al. [5] and Chapman et al. [6], the success rate of revision surgery is below the one obtained after a successful initial repair. Morbidity and mortality rates are also higher, and technical difficulty is increasingly more challenging in every repair attempt. Despite these facts, surgical treatment of recurrent biliary strictures continues to be the most successful option in selected patients.

All patients have to be thoroughly studied before deciding any surgical attempt. The work-up must always include an angiography, because, as it was expressed above, vascular injuries can be the reason for failure. Generally, a staged approach combining interventional radiology at the beginning is recommended. In the presence of intra-abdominal collections, portal hypertension or poor general condition of the patient, revision surgery should be postponed. The timing between the first repair attempt and revision surgery is important. Most of bile duct injuries in laparoscopic era are associated with thermal lesions. Thus, it is suggested to defer definitive treatment for 6–8 weeks when local inflammatory phenomena has decreased [17]. However, it should be noted that waiting for bile duct dilatation might be an inadequate strategy. Benkabbou et al. [41], delayed revision surgery in

5 of their patients specifically waiting for bile duct dilatation. They observed that all five patients failed revision surgery associated with severe morbidity during the waiting period.

For most of the cases, biliary-enteric anastomosis is the most adequate. Every revision surgery must include the verification of an erroneous construction of the Roux-en-Y limb and the collection of a sample of bile for culture whenever possible [41]. The damaged area must be exposed avoiding dissecting the biliary structures too much due to devascularization risk. Visual magnifying aids are recommended for this purpose [41]. The end has to be exposed free from burns and attritions. The healthy soft opening of the bile duct is crucial to the success of the anastomosis; however, the number and diameter of the bile duct openings are comparatively of less importance [42]. Intraoperative cholangiography has to be taken to identify other sites of stenosis, calculi and bile leakages. Vascular integrity has to be confirmed. Biliary-enteric continuity has to be performed at least 1 cm above the stenosis with a Roux-en-Y 70 cm jejunal loop and a mucosa-to-mucosa anastomosis. Most of the authors use non-absorbable interrupted stitches [6, 41]; however, running suture with 7/0 reabsorbable material has also been shown to be effective [17, 42]. It has been suggested that the distribution of tension in a continuous suture would be more equal than an interrupted suture and that, without the disturbance of multiple interrupted stitches, a continuous suture would help the surgeons focus their attention more easily in the anastomosis [42]. Some authors have suggested that in patients in whom future interventions were anticipated, an access loop might be designed, by fixing the proximal end of the Roux loop to the anterior abdominal wall [43].

For stenosis at or just below the biliary confluence, the Hepp-Couinaud approach would be the most adequate. This technique allows a simple approach to the extrahepatic main left duct. The dissection of the hilar plate is fundamental to approach the left duct. Needle aspiration is valuable in some circumstances to identify the duct. Finally, a small incision is made into the positive aspiration site. This maneuver creates a wide (2.5–3 cm) opening in the left duct, the confluence, and the beginning of the right duct if necessary [44]. Pottakkat et al. [43] evaluated the outcome of revision surgery in referred patients with recurrent strictures and compared it with patients who had undergone primary repair at their institution and had developed restricture. All of these patients had a Hepp-Couinaud approach. Success rate was 97 % and 94 % for the referred group and the institution group, respectively. No significant difference in terms of outcome was found between the groups. These results not only show the effectiveness of the Hepp-Couinaud approach for revision surgery, but also that recurrent strictures can be successfully managed in tertiary specialized centers.

When the stenosis goes deep into the liver and isolates the right and left ducts (E4–E5 lesions), isolated areas will not be drained by a single anastomosis to the left hepatic duct, as in the Hepp-Couinaud approach. Strasberg et al. [45] suggested a new approach through the gallbladder plate in these cases. This strategy consists of the dissection of the hilar plate just as the Hepp-Couinaud approach, and subsequently bringing the dissection to the right until the gallbladder plate is encoun-

tered. After it is divided, the liver lifts off the right portal pedicle. Finally, the liver (segment 5) may be dissected off the portal pedicle by lifting and coring the base of segment 5. This exposes the anterior surface of the right portal pedicle to prepare it for the anastomosis. Only enough dissection is performed to place sutures into firm, well-vascularized tissue. Minimizing dissection reduces the chance of devascularizing the duct. When the right and left ductal orifices are in close proximity, both ducts and the fibrous tissue between them are anastomosed to a single opening in the bowel. When the right and left ducts are separated by more than 1 cm, a double-barreled anastomosis with two intestinal openings should be made [45].

Sometimes it is necessary to perform a liver resection. If the stenosis has an associated lobar atrophy, or if it is too far inside the liver and is associated with cholangitis, it is recommended to carry out an ipsilateral liver hepatectomy and perform a hepaticojejunostomy with the opposite duct [17, 46]. Sometimes a portal vein embolization (PVE) should be considered before performing the hepatectomy [46], although this is not always necessary [17, 41, 42].

Revision surgery has been for long time associated with high rates of morbidity and mortality, approximately 25 % and 2–13 % [5, 6, 47], respectively. Recent studies have shown similar figures [7, 41, 43]. Overall complication rate varies between 11 and 33 %. Minor anastomotic leak, which resolve spontaneously, is the most common complication. Other complications include wound infection, intra-abdominal collection, cholangitis and intra-abdominal bleeding. Morbidity increases significantly if revision surgery is associated with hepatectomy. Biliary leak can be as high as 80 % [41], although it should be noticed that most of these leaks can be successfully managed with medical treatment.

The existence of portal hypertension is a crucial factor for treatment selection. In Chapman et al. [6] series, mortality rate for patients with portal hypertension who underwent any operative procedure was 23 % compared with only 2 % in patients without portal hypertension. The presence of cirrhosis is also considered an ominous sign. Pellegrini et al. [5], reported only 25 % of good results in these patients. Most of these patients can be good candidates for liver transplantation. Nevertheless, if they have any contraindication for transplantation, portal hypertension should be treated with a transjugular intrahepatic porto-systemic shunt (TIPS) or a mesocaval shunt before any bile duct repair attempt. Good outcome has been reported in three patients who underwent this therapeutic sequence [17].

Liver Transplantation

In spite of all the therapeutic options stated above, a significant percentage of patients develop end-stage liver disease. Recent series have suggested that 3–20 % of the patients with complex lesions should be included on the waiting list for a liver transplantation (LT) as the only possible treatment [7, 12]. It has been reported that the development of liver fibrosis is associated with a delay in the implementation of adequate therapeutic procedures for the treatment of biliary stenosis. Negi et al. [48] found that the mean duration of biliary obstruction before the onset of portal and

periportal fibrosis was 3.8 months, for the development of severe fibrosis 22.4 months, and for cirrhosis 62 months. LT may constitute the only solution available in these cases. Indication for LT include intractable ascitis, progressive jaundice, repeated episodes of gastrointestinal bleeding due to portal hypertension, recurrent episodes of cholangitis, intractable pruritus, and/or poor quality of life. Ardiles et al. [49] published the largest series of LT due to bile duct injuries. In this series, 17 of a total of 19 transplanted patients had undergone previous surgical procedures at the primary center before referral. Major postoperative complication rate was 52 %, and mortality rate was 21 %. Five- and 10-year survival rate was 68 % and 45 %, respectively, with good quality of life and LFT within the normal range. Although LT in these patients can be technically more demanding due to the presence of local inflammation and fibrosis, postoperative results are equivalent to those observed for transplants undertaken for other diseases [50].

Follow-Up

Anastomotic strictures may occur several years after primary surgical repair. Most of the patients with failure of biliary repair develop symptoms within 5–7 years [5], a maximum of 17 years has been published [41]. This emphasizes the need for prolonged follow-up in these patients, even after a successful revision surgery.

It is recommended that these patients should be followed up 2–4 times during the first year after repeat treatment [46]. Evaluation must include a clinical examination, LFT, and abdominal US alternated with dynamic CT scan [43, 46]. In the presence of abnormal results, nuclear scintography may be done to demonstrate the patency of the bilioenteric anastomosis. In patients in whom percutaneous procedures were performed and who still have a biliary drainage left in place, a percutaneous cholangiography is recommended. After the first year, follow-up can be done once or twice per year for a minimum of 5 years [24]. It should be noted that simple LFT could be enough after this period.

Recurrent Strictures After Biliary Reconstructive Operations

Biliary reconstructive surgery can be performed in other surgeries apart from bile duct injuries repair. These surgeries include: Whipple procedure, surgery for choledochal cyst, hepatolithiasis surgery, and liver transplantation. The number of patients who suffer an anastomotic stricture after these surgeries is significantly lower than after bile duct injuries repair surgeries. It is estimated that these procedures account for less than 20 % of the total of benign strictures of the biliary tree [9].

Strictures After Bile Duct Surgery and Whipple Procedure

Anastomotic strictures treatment after a Whipple procedure, hepatolithiasis surgery or choledochal cyst resection should be no different from that in bile duct injury repair surgery. Diagnostic imaging is of paramount importance in these strictures due to the need to discard malignant causes. Tumor markers might be helpful, although false-positive results are frequent in the presence of biliary hypertension. The decision on whether performing a revision surgery in these cases should be taken considering the general condition of the patients and the prognosis of their underlying disease.

Strictures After Liver Transplantation

Bile duct strictures related to liver transplantation can be classified into anastomotic and non-anastomotic strictures. Most anastomotic strictures occur within the first year after the LT. Technical issues appear to be the most important cause of early anastomotic strictures. These may include improper surgical technique, suture materials, tension at the stoma, and heat injury [51]. Bile leakage has been reported to be an independent risk factor for the development of anastomotic stricture [52]. Anastomotic strictures of later onset are mostly related to fibrotic scarring arising from ischemia at the end of the donor or recipient bile duct nearest to the anastomosis [2].

Non-anastomotic strictures show multiple intrahepatic lesions and occur earlier than anastomotic strictures. Most of them are related with ischemic injury from hepatic artery thrombosis, donor hypotension during cardiac death, long warm and cold ischemic times, reperfusion injury, immunologically induced injuries, cytotoxic injuries induced by bile salts, and cytomegalovirus infection [2].

Over the last years, endoscopic management of anastomotic strictures has emerged as an effective option. Endoscopic treatment is less invasive and better tolerated in these patients, whose general condition is not always optimal. It has been suggested that in early-onset anastomotic strictures, i.e., during the first 2 months, endoscopic balloon dilatation (EBD) alone may be effective. For strictures that occur more than 5 months after LT, EBD should be associated with an endoprothesis [53]. Complication rate is 0–24 %, with a long-term success rate of more than 60 %. Complications are generally minor and easily manageable: biliary leakage, cholangitis, pancreatitis, and self-limited bleeding related to sphincteroplasty.

The treatment of non-anastomotic strictures is more challenging. It has been reported that only 10–70 % of patients have a long-term response to endoscopic therapy, compared with 60–100 % of patients with anastomotic strictures [2]. In patients with strictures located in the duct bifurcation, surgical reconstruction with resection of the stenotic area and Roux-en-Y hepaticojejunostomy can be successful. However, intrahepatic lesions tend to be more diffuse and difficult to manage, requiring retransplantation or permanent percutaneous drainage in most of the patients.

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Index

E. Dixon et al. (eds.), *Management of Benign Biliary Stenosis and Injury*, DOI 10.1007/978-3-319-22273-8