From Department of Clinical Science, Intervention and Technology, CLINTEC, Division of Surgery
Karolinska Institutet, Stockholm, Sweden

ASPECTS ON THE ROLE OF PROPHYLACTIC PROCEDURES TO INFLUENCE POST-ERCP COMPLICATION RATES

Greger Olsson

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Aspects on the role of prophylactic procedures to influence post-ERCP complication rates

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Greger Olsson

Huvudhandledare:

Docent Lars Enochsson
Karolinska Institutet
Institutionen för klinisk vetenskap, intervention och teknik, Enheten för kirurgi

Bihandledare:

Med Dr Urban Arnelo
Karolinska Institutet
Institutionen för klinisk vetenskap, intervention och teknik, Enheten för kirurgi

Med Dr Gunnar Persson
Linköpings Universitet
Medicinska fakulteten
Institutionen för klinisk och experimentell medicin

Docent Karsten Offenbartl
Lunds Universitet
Medicinska fakulteten
Institutionen för kliniska vetenskaper

Opponent:

Docent Rihad Sadik
Göteborgs Universitet
Sahlgrenska Akademien,
Institutionen för medicin

Betygsnämnd:

Docent Ib Rasmussen
Uppsala Universitet
Medicinska fakulteten
Institutionen för kirurgiska vetenskaper

Docent Christian Sturesson
Lunds Universitet
Medicinska fakulteten
Institutionen för kliniska vetenskaper

Docent Per Stål
Karolinska Institutet
Institutionen för medicin

To Ann, Christoffer and Johanna

Non haberi sed esse

Tycho Brahe

ABSTRACT

Background: When the technique to use ERCP was introduced almost fifty years ago, the morbidity in treatment of hepato-biliary diseases decreased due to the introduction of this mini-invasive modality, reducing the need for open surgical procedures. However, ERCP procedures are still marred with complications such as pancreatitis, cholangitis, hemorrhage and perforation and every measure must be undertaken to reduce these adverse events.
Objectives: The hypotheses of this thesis were: 1) Prophylactic antibiotics in ERCP do not reduce the complication rates enough to recommend it generally. 2) Prophylactic pancreatic stents reduce the PEP risk more the larger they are. 3) A grading scale for the complexity of the ERCP procedure (HOUSE) was validated in relation to success-rates, complications and duration of the procedure. 4) Preoperative SEMS in periampullary tumors show less bacterial contamination in intraoperatively collected bile than plastic stents, thereby reducing perioperative complications.
Methods: In the first study all ERCPs, included in GallRiks between May 2005 and June 2013, were studied regarding complication rates in relation to prophylactic antibiotics. Further, in the second paper, all ERCPs between 2006 and 2014 where an accidental pancreatic cannulation occurred and a prophylactic pancreatic stent was used were investigated, determinating how the diameter and length of the stent affected the adverse events. In the third study, an ERCP complexity classification, (HOUSE), was validated in relation to success-rates, complications and duration of the procedure. The final study, an RCT compared preoperative SEMS to plastic stents in resectable periampullary tumors regarding intraoperative bacterial, histopathological and surgical technical findings as well as perioperative complications.
Results: In the first study complications were studied in relation to prophylactic antibiotics. We found a reduction of 26 % of OR in overall complications if prophylactic antibiotics were given, but in absolute figures reduction of the risk was a modest 2.6% and the NNT 38 patients to avoid one complication. In our second study an almost fourfold OR elevation (OR 3.58) in complication rates was seen if prophylactic pancreatic stents with a diameter ≤5 Fr were used compared to stents >5 Fr, the complication rates were further lowered (1.4 %) if the stents were >5 cm. The third paper validated a new three-graded ERCP complexity grading scale (HOUSE) in relation to success and complication rates, demonstrating a doubled PEP rate in HOUSE 2 and 3 (7.0 % and 6.8 %) compared to class 1 (3.4%) and longer procedure times, the higher the HOUSE class (HOUSE 1, 40 min; 2, 65 min; and 3, 106 min). In the final study, comparing preoperative SEMS to plastic stents in resectable periampullary tumors, higher preoperative stent dysfunction rates were found among the plastic stents (19 % vs 0 %, p=0.03). Intraoperatively, no differences were seen in bacterial occurrence in collected bile or in operative technical difficulties, but a higher histopathological foreign body reaction (sinus histiocytos) in lymph nodes in the hepato-duodenal ligament in the plastic stent group. Also, the overall postoperative complication rates were increased in the group where plastic stents were used (72 % vs 52 %), as were the frequency of anastomotic leakages (12 % vs 3.7 %), but none of these postoperative complications reached statistical significance.
Conclusion: Prophylactic antibiotics in ERCP lower the overall complication rates but not sufficiently to recommend this as prophylaxis in every ERCP procedure. On the contrary, prophylactic pancreatic stents could be used more frequently in ERCP and larger diameters and longer stents demonstrated lower complications rates. We also launched an ERCP complexity grading scale (HOUSE) and validated it in relation to complication rates and procedure duration. Finally, we demonstrated that SEMS could be used in resectable periampullary tumors and found no differences in bacterial growth in intraoperatively collected bile but a lower preoperative stent dysfunction rate if SEMS were used. Neither did we find any intraoperative technical downsides when using SEMS, or any disadvantages in postoperative complication rates.
Keywords: ERCP, postoperative complications, post-ERCP pancreatitis, antibiotic prophylaxis, pancreatic stent, ERCP complexity grading, preoperative stents, pancreatic cancer, periampullary tumors

LIST OF SCIENTIFIC PAPERS

I. ***The role of prophylactic antibiotics in routine endoscopic retrograde cholangiopancreatography as assessed prospectively in a nationwide study cohort.*** **Olsson, G.,** Arnelo, U., Lundell, L., Persson, G., Törnqvist, B., and Enochsson, L. *Scandinavian Journal of Gastroenterology. 2015; 50:7, 924-32.*

II. ***The impact of prophylactic pancreatic stenting on post-ERCP pancreatitis: A nationwide, register-based study.*** **Olsson, G.,** Lübbe, J., Arnelo, U., Jonas, E., Törnqvist, B., Lundell, L., and Enochsson, L. *United European Gastroenterology Journal 2017; Vol. 5(1): 111–118.*

III. ***The HOUSE-classification: a novel endoscopic retrograde cholangio pancreatography (ERCP) complexity grading scale.*** **Olsson, G.,** Arnelo, U., Swahn, F., Törnqvist, B., Lundell, L., and Enochsson, L. *BMC Gastroenterology (2017) 17:38.*

IV. ***Preoperative biliary drainage by plastic or self-expandable metal stents in patients with periampullary tumors: results of a randomized clinical study.*** **Olsson, G.,** Frozanpor, F., Lundell, L., Enochsson, L., Ansorge, C., Del Chiaro, M., Reuterwall-Hansson, M., Shetye, A., and Arnelo, U.
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List of abbreviations

ALAT	**Alanine Amino Transferase**
ALP	**Alkaline Phosphatase**
ASA	**American Society of Anesthesiology**
ASAT	**Aspartate Amino Transferase**
ASGE	**American Society of Gastroenterology**
B2	**Billroth 2 gastric resection**
CBD	**Common Bile Duct**
CBDS	**Common Bile Duct Stone**
CFU/ml	**Colony Forming Unit per milliliter**
CI	**Confidence Interval**
CRP	**C-Reactive Protein**
CT	**Computerized Tomography**
DGW	**Double Guidewire**
EHL	**Electrohydraulic lithotripsy**
ERCP	**Endoscopic Retrograde Cholangio-Pancreatography**
ESGE	**European Society of Gastroenterology**
EST	**Endoscopic Sphincterotomy**
ESWL	**Extra-corporal Shock-Wave Lithotripsy**
EUS	**Endoscopic UltraSound**
GBY	**Gastric Bypass**
HOUSE	**Huddinge Olsson Urban Swahn Enochsson**
ICU	**Intensive Care Unit**
IQR	**Inter Quartile Range**
ITT	**Intention To Treat**
MRI	**Magnetic Resonance Imaging**
MRCP	**Magnetic Resonance Cholangio-Pancreatography**
NNT	**Numbers Needed to Treat**
NSAID	**Non-steroidal Anti Inflammatory Drugs**
OR	**Odds Ratio**
PEP	**Post-ERCP Pancreatitis**
PGW	**Pancreatic Guidewire**
PS	**Pancreatic Stent**
PSC	**Primary Sclerosing Cholangitis**
PTC	**Percutaneous Transhepatic Cholangiography**
RCT	**Randomized Controlled Trial**
RR	**Relative Risk**
SEMS	**Self Expandable Metal Stents**
SOD	**Sphincter Oddi Dysfunction**
TX	**Liver Transplant**

1. ERCP, endoscopic stents and ERCP complications and prevention

1.1 History of biliary and pancreatic surgery and the development of ERCP and endoscopic biliary stents

1.1.1 Surgery for gallstone disease

When anesthesiology was developed in the mid-19th century—for instance, with the introduction of ether anesthesia by Thomas Green Morton in 1846—the necessary prerequisites for biliary surgery were fulfilled. Another important finding in the mid-19th century was the increasing knowledge of the aseptics gained by Semmelweiss in Vienna in 1847, which was another basis for starting to perform biliary operations.

The first operations for gallstones were performed as two-step procedures where a cholecystostomy/fistulae was created through which the stones could then be removed *(Thudicum J. L. W., et al., 1859).* It then took several years until the first one-step gallstone operation was performed *(Bobbs, J. S., 1868)* remarkably during an attempt to operate on an ovarian cyst. In this case, the gallbladder was opened and only the stones were removed, leaving the gallbladder in situ.

The first cholecystectomy was performed in Berlin in 1882 *(Langenbuch, C. J. A., 1882),* and a few years after that, the first cholecystectomy was performed in Sweden by von Unge *(Bolling G., et al., 1891).* At the time, the operations for gallstone disease were experimental, and several years passed before they became part of routine surgery. Initially, only patients with severe complications with respect to gallstone disease underwent surgery, but gradually cholecystectomy developed into a common surgical procedure. Finally, almost one hundred years later, the development of the laparoscopic technique made it possible to perform minimally invasive cholecystectomies *(Mühe, E., et al., 1986)*; this method rapidly became (and remains) the gold standard for treatment

of gallstone disease. The first laparoscopic cholecystectomy in Sweden was performed by Arvidsson in 1992 *(Arvidsson, D. et al., 1992).* The year before that, in 1991, Petelin described the first transcystic and common bile duct exploration, which was performed laparoscopically *(Petelin*, *J. B., 1991) .*

1.1.2 Pancreatic surgery

Similar to surgery for gallstone disease, pancreatic surgery was dependent on the development of anesthesiology and the invention of aseptics. In 1882, Trendelenburg, performed the first distal pancreatectomy and was followed by Codivilla, who described the first pancreatico-duodenectomy in 1898; but, unfortunately, none of these patients survived their postoperative courses.

Another pioneer in the field of pancreatic surgery was Mayo, who was more successful by choosing smaller and less aggressive endocrine pancreatic tumors on which to operate. Pancreatic surgery was still risky and hazardous but was slowly gaining its place in surgery, but it was not until the 1930s when Whipple performed his first procedures that the field opened for further development *(Whipple, A. O., et al., 1935).* At first, the Whipple procedure was described as a two-step operation, starting with a gastro-enterostomy and a cholecysto-gastrostomy and followed by a duodenectomy and pancreatic head resection three to four weeks later. Since the K-vitamin was not discovered until 1939, the bleeding tendency was still a problem, and it was not until 1940 that Whipple´s team managed to perform the first one-step procedure including resection of the bile duct, gallbladder, duodenum, pancreatic head and part of the stomach, which was the foundation of the pancreatico-duodenectomy still used today. The development of better perioperative supportive care, better radiological imaging and better surgical techniques through the referral of pancreatic surgery to tertiary

referral centers have lowered the perioperative morbidity and mortality from the 1980s until today, but the long-term survival of pancreatic cancer remains disappointingly low with an overall five-year survival remaining under five percent.

As many of the pancreatic tumors are already irresectable at clinical presentation, these were historically treated with bilio-digestive shunts, which are now mostly performed as Roux-en-Y-reconstructions, anastomosing the jejunum to the hepatic duct. This anastomosis was named after the surgeon Cesar Roux, who in 1892 performed the first anastomosis from the jejunum to another organ—but, in his case, not to the bile duct but to the stomach. The number of surgical bilio-digestive shunts has gradually decreased since the introduction of endoscopic techniques (ERCP) in the 1970s, making it possible to insert endoscopic stents in the bile duct without performing a conventional surgical bypass.

1.2 Endoscopic retrograde cholangio-pancreaticography (ERCP)

1.2.1 The Development of Endoscopic Retrograde Cholangio-Pancreaticography

The development of flexible endoscopes in the 1960s made it possible with a side-viewing fiber instrument to insert a catheter through the papilla and inject contrast to image the bile ducts. This was first performed by McCune in 1968 *(McCune, W. S., et al, 1968)* in the USA, but it took several years until the technique was introduced by Lennart Wehlin in Sweden in 1972 *(Cronstedt, J., et al., 1985)*.

Still, ERCP was only a diagnostic tool until 1974 when Classen and Demling in Germany *(Classen, M. et al., 1974)* and Kawai in Japan *(Kawai, K., et al., 1974)* – independently of each other – performed the first sphincterotomies that enabled endoscopic common bile

duct stone (CBDS) extraction. In Sweden, it took another five years until Nordgren *(Nordgren, C., 1979)* and Liedberg *(Liedberg, G., 1979)* performed the first Swedish endoscopic sphincterotomies. ERCP rapidly developed into the first hand treatment of CBDS due to its advantages in reducing postoperative morbidity through its minimally invasiveness, especially in combination with the later development of the laparoscopic cholecystectomy. Simultaneously, the need for diagnostic ERCP vanished as MRCP was introduced in the 1990s, and today almost all ERCPs are therapeutic.

On the other hand, the diagnostic ERCPs were refined when the single-operator peroral cholangioscopy was introduced in 2006 *(The SpyGlass Direct Visualization System™, Boston Scientific, Marlborough, Massachusetts, USA),* making it possible to visualize both the bile and pancreatic ducts *(Arnelo U., et al., 2007)*–this technique had been described already in 1972 but required two endoscopists and a mother-baby- endoscope with poor visual quality *(Classen, M., et al., 1972).*

1.2.2 The cannulation procedure of ERCP

The cannulation is the start of an ERCP when the endoscopist gains access to the desired duct, which is most often the bile duct and more occasionally the pancreatic duct. This can be an easy procedure, but it can, on the other hand, be both challenging and time-consuming. Traditionally, an ERCP catheter was used for the cannulation, and contrast was injected when the endoscopist thought he had entered the bile duct. However, the technique to obtain access has changed over the years, and nowadays the most preferred method is to use a sphincterotome preloaded with a guidewire. The benefit of the guidewire would be to avoid contrast injections to the pancreatic duct, thereby reducing the risk of PEP *(Freeman, M. L., et al., 2005, Lella F., et al., 2004, Zorron Pu, L., et*

al., 2015). Additionally, there are reports that indicate that the guidewire technique might even increase the cannulation success rates *(Cennamo, V., et al., 2009).*

In The Swedish National Registry for Gallstone Surgery and ERCP (GallRiks), an overall cannulation success-rate of 92 % was seen *(Enochsson, L. et al., 2010)*, which reflects the results of success in everyday ERCP in Sweden. The cannulation success rate is also dependent on the number of ERCPs performed by each individual endoscopist, as shown by Freeman *(Freeman, M. L., et al., 2001)* where those endoscopists performing more than two ERCPs per week reached a cannulation success rate of 96.5 % compared to those performing fewer (91.5 %).

1.2.3 The guidewire technique

A guidewire is used inside the ERCP catheter or spincterotome to gain access to the biliary tract – this technique has been shown to minimize the risk of developing PEP compared to the traditional contrast-assisted cannulation technique *(Cennamo, V., et al., 2009, Cheung, J., et al. 2009, Lella, F., et al., 2004).*

1.2.4 Difficult cannulation

When a cannulation should be considered difficult has gained much interest since it is correlated to the post-operative complication rates after ERCP *(Freeman, M. L., et al., 1996).* Different attempts have been made to define a difficult cannulation—for instance, by measuring how many cannulation attempts that have been made before a successful cannulation is reached *(Lee, T. H., et al., 2009)*, how long it took before a successful cannulation was achieved *(Kaffes, A. J., et al., 2005, Katsinelos P. et al., 2008, Laasch, H. U., et al., 2003, Lee, T. H., et al., 2009, Li, J. et al., 2016, Maeda, S., et al., 2003, Zhou, P. H. et al., 2006)* or how many guidewire passes and contrast injections to the pancreatic duct that

had occurred before cannulation was attained *(Kaffes, A. J., et al., 2005, Zhou, P. H. et al., 2006).*

Halttunen and co-workers, *(Halttunen, J. et al., 2014)* recently presented a proposal for defining a difficult cannulation, where one of the following criteria should be met for it to be considered difficult: five attempts of cannulation, five minutes of cannulation or two passages of the guidewire into the pancreatic duct. This definition was based on a significantly increased PEP rate if either of these criteria were fulfilled before cannulation was achieved. If the cannulation took more than five minutes, the PEP rate rose from 2.6 % to 11.8 %, and if the guidewire was inserted to the pancreatic duct once, the PEP rate was 3.7 %, whereas the PEP rate rose to 13.1 % when the guidewire was inserted twice. This definition was adapted by the ESGE in 2016 *(Testoni, P. A., et al., 2016)* to define a difficult cannulation.

1.2.5 Pancreatic guidewire-assisted technique

For a difficult cannulation of the bile duct where the guidewire enters the pancreatic duct, it has been advocated to use the pancreatic guidewire-assisted cannulation, where the pancreatic guidewire is kept in place in the pancreatic duct and a second guidewire is inserted through the papilla, thereby hopefully achieving access to the bile duct through this second guidewire. However, the evidence for such a method is rather conflicting with different cannulation success and PEP rates in different studies *(Angsuwatcharakon, P., et al., 2012, Belverde, B., et al., 2012, Draganov, P. et al., 2005, Gronroos, J. M. et al., 2011, Herreros de Tejada, A., et al., 2009, Ito, K. et al., 2008, Tanaka, R., et al., 2013, Xinopoulus, D., et al., 2011, Yoo, Y. W., et al., 2013).* In a recent Cochrane analysis, Tse concluded that there was an increased risk of PEP following pancreatic guidewire-assisted cannulation, which could be reduced with the use of pancreatic

stents, but that pancreatic guidewire-assisted cannulation did not elevate the cannulation rates compared to repeat conventional cannulation or precut sphincterotomy *(Tse, F., et al., 2016)*. Still, the pancreatic guidewire technique is recommended by the ESGE *(Testoni, P. A, et al., 2016)* in combination with a PEP-protective prophylactic pancreatic stent (see Table 1).

Table 1.

Pancreatic guidewire-assisted cannulation*: Tse, F., et al. meta-analysis, Cochrane Database Syst Rev 2016; (5): CD010571.* PGW=pancreatic guidewire. The table demonstrates the studies included in the Cochrane analysis, when primary cannulation failed (and how this was defined) and then the success rates of the PGW cannulation and the success rates of this secondary cannulation method.

Studies	Year	n	Primary cannulation	When failure?	When failure?(PGW)	PGW failure
Angsuwatcharakon	2012	44	92 %	10 min	10 min	13 %
Coté	2012	87	81 %	6 min	6 min	19 %
Herreros de Tejada	2009	188	73 %	5 tries	10 tries	25 %
Ito	2010	70	93 %	5 tries	No limit	8 %
Maeda	2003	53	50 %	10 min	No limit	7 %
Yoo	2013	71	93 %	10min/tries	10 tries	31 %
Zheng	2010	64	NA	5 tries	No limit	8 %

1.2.6 Endoscopic sphincterotomy (EST)

The EST, where the papilla and the sphincter of Oddi are divided, is performed in the vast majority of ERCP procedures and represents a way of obtaining access to the bile duct and to receive a working channel through which it is possible to intervene through the orifice—for instance, making it possible to insert a stent or to extract bile duct stones. ERCP with EST also represents a good alternative to surgery in the elderly with concomitant diseases, and it has a lower risk of morbidity compared to traditional open surgery.

For a long time, there was hesitation to perform ESTs in younger patients, because of the assumed elevated risk of long-lasting adverse events *(Bergman, J. J., et al., 1996, Costamagna, G. et al., 2002)* caused by the enteric biliary reflux of bacteria from the gut into the bile ducts, increasing the risk of developing cholangiocarcinoma. Those risks have, in later studies, not been verified *(Stromberg, C. et al., 2008)*, and EST is nowadays used in most ERCPs independently of the patient's age as a natural complement to the ERCP facilitating interventions and for gaining access to the bile duct.

Although ERCP is a minimally invasive procedure, there are still complications that occur after sphincterotomy in 4-15 % *(Cheng, C. L., et al., 2006, Christensen, M., et al., 2004, Cotton, P. B., et al., 2009, Cotton, P. B., et al., 1991, Freeman, M. L., et al., 1996)*, depending on the indications, patients and operators, where pancreatitis, cholangitis, duodenal perforation and post-sphincterotomy bleeding represent the most common complications.

1.2.7 Precut sphincterotomy with needle-knife

Basically, there are two different ways to approach a difficult cannulation when a needle-knife spincterotome is used: either through a conventional needle-knife

papillotomy starting at the natural orifice or performed as a separate incision above the natural orifice (i.e., a so-called suprapapillary fistulotomy), for instance, in cases where there is a protruding papilla with an impacted stone. Both methods report similar cannulation success and complication rates *(Abu-Hamda, E. M., et al., 2005, Gullichsen, R., et al., 2005)*, but ESGE recommends a suprapapillary fistulotomy *(Testoni, P. A., et al, 2016).*

There are studies that show that precut sphincterotomy is associated with an increased risk of PEP *(Ding, X. et al., 2015)*, but the elevated risk is most probably related to the timing when the precut sphincterotomy is undertaken. If the precut sphincterotomy is performed as an emergency action after attempting conventional cannulation for a long period of time, then the risk will increase for adverse events, perhaps not as an effect of the precut sphincterotomy itself but rather as a confounding effect of the long duration of repeat cannulation attempts. If the precut sphincterotomy instead is performed early during the ERCP, no increase in PEP rates have been detected compared to conventional sphincterotomy *(Sundaralingam, P., et al., 2015).*

However, one must remember that a precut spincterotomy is a high-risk procedure *(Testoni, P. A., et al., 2010)* that requires an experienced endoscopist to be performed safely and should only be performed in cases where the indication for the biliary access is strong.

Whether early precut sphincterotomy should be preferred to continued conventional cannulation attempts is highlighted in two meta-analyses from 2010 *(Cennamo, V., et al., 2010, Gong, B., et al., 2010)*, which concluded that there might be a lower PEP risk if an early precut sphincterotomy was chosen (2.5 % vs 5.3 %), but the overall complication- and cannulation success rates did not differ.

The ESGE recommendation *(Testoni, P. A., et al., 2016)* is therefore an early precut needle knife fistulotomy because of the lower risk for PEP, performed by an experienced endoscopists (cannulation rate over 80 %). Additionally, they also recommend a pancreatic stent to be used if the pancreatic duct is easily accessed.

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1.2.8 Pancreatic sphincterotomy

In a situation where the guidewire only achieves access to the pancreatic duct, there is the opportunity for bile duct access via performing a pancreatic sphincterotomy, which was first described by Goff in 1995 *(Goff, J. S., et al., 1995).* The pancreatic sphincterotomy could be completed with an additional needle-knife sphincterotomy on the bile duct, giving a bile duct access in 95 % of the cases *(Halttunen, J. et al., 2009).* The complication rates were reported to be similar to a precut sphincterotomy *(Halttunen, J. et al., 2009)* or even lower *(Miao, L., et al. 2015).*

As an alternative to the pancreatic guidewire, a pancreatic stent could be used as an aid for the pancreatic sphincterotomy when trying to gain biliary access *(Goldberg, E., et al., 2005)*, demonstrating good cannulation rates (97 %) with acceptable complications.

1.2.9 Rendezvous-assisted cannulation and sphincterotomy

An elegant way to improve cannulation success rates and to reduce complication rates is to use the so-called “rendezvous approach” in ERCP during laparoscopic cholecystectomy where common bile duct stones (CBDS) are found at the intraoperative cholangiography. The method was initially described by Deslandres as a case report and in 1993 as a case series *(Deslandres, E., et al. 1993).* A guidewire is inserted through the cholangiography catheter into the duodenum, where it is picked up by a snare through

the working channel of the duodenoscope and a sphincterotome is then inserted over the guidewire to secure biliary access and thus reduce the risk for PEP *(Swahn, F., et al., 2013*, *Noel R., et al., 2013)*

1.2.10 PTC-assisted cannulation in ERCP

Percutaneous transhepatic cholangiography (PTC) was previously a method for treatment and performing diagnostics of diseases in the biliary tree, but it has been abandoned as a first-hand method since the introduction of ERCP, since PTC has higher complication rates and is more inconvenient for patients. PTC is still used if cannulation fails during ERCP and could later be used as an aid to cannulation to achieve biliary access.

1.2.11 EUS-assisted cannulation in ERCP

With the introduction of linear echo-endoscopes, new possibilities have developed to achieve biliary access when conventional cannulation fails. Methods have been described where the biliary tree is punctured, either through the stomach to the left hepatic duct or through duodenum to the common bile duct, introducing a guidewire into the bile-duct and out through the papilla for a rendezvous cannulation or deploying a stent directly through the puncture site.

1.3 Endoscopic biliary stents

1.3.1 The Development of Endoscopic biliary-pancreatic stents

The word “stent” originates from the English dentist Charles Stent (1807-1885), who improved the dental impression procedure by adding gutta perche to the material to

increase the plasticity of the substance, creating a material suitable to use for producing stents for biliary deviation. The first plastic stent was used in ERCP in 1979 and has been in use in endoscopy procedures since then as a rather cheap and easy-to-use device.

The fact that the plastic stents clog after three to four months increases morbidity through the need of repeat ERCPs, which makes the plastic stent inferior for long-term use in biliary and pancreatic diseases compared to the later developed self-expandable metal stents (SEMS), which were introduced as the "Wallstent" in the 1990s by Boston Scientific (*Wallstent ™, Boston Scientific, Marlborough, Massachusetts, USA*). The Wallstent was followed by the nitinol based Ultraflex *(Ultraflex™, Boston Scientific, Marlborough, Massachusetts, USA)* stent, which has dominated the market. However, now other SEMS-types are available from other companies; this has provided competition and has led to technical improvements and a balanced price development. Another important feature in the development of the SEMS was the invention of the covered SEMS, where a synthetic covering was applied around the stent consisting of polyurethane, silicone or ePTFE (polytetrafluoro-ethylene); this was initially launched as a method to prevent tumor growth into the stent, thereby improving the patency of the stent but also to make it more smooth to deploy and exchange. The question remains whether the covering really affects the tumor ingrowth and patency *(Isayama, H., et al., 2004, Yoon, W. J., et al., 2006)* or if the covering just makes the SEMS more prone to dislodge from the bile duct *(Kullman, E., et al., 2010, Park, D. H., et al., 2006).*

1.3.2 Bile duct stenting in periampullary tumors with SEMS

1.3.2.1 SEMS in periampullary tumors under palliative conditions

Jaundice is a common initial symptom in periampullary tumors, and the majority of the tumors are irresectable at the time of diagnosis. Nonetheless, is it important to treat the jaundice to minimize its consequences (e.g., the risk of immunosuppression or impaired coagulation). Traditionally, those patients were treated with a surgical bypass (hepatico-jejunostomy) or an endoscopic plastic stent, but with the development of the SEMS, the latter has exhibited a better patency, avoiding operative morbidity, repeat ERCP procedures and giving a lower total cost, despite the higher price of each individual SEMS device.

A recent meta-analysis *(Zorron Pu, L. et al., 2015)* based on 13 RCTs with 1,133 patients demonstrated a lower stent-dysfunction rate in the SEMS group (21.6 % vs 46.8 %, $p<0.00001$) and also a lower re-intervention frequency in the SEMS group (21.6 % vs 56.6 %, $p<0.00001$) but with equal complication rates. The analysis also showed an increased mean survival rate if a SEMS was used (182 days vs 150 days, $p<0.0001$) and a higher patency time for the SEMS (250 days vs 124 days, $p<0.0001$). The total cost when using a SEMS was also lower due to fewer ERCP procedures, but this difference was not significant. A subgroup where plastic stents could be used is the group of patients presenting with distant metastases or in patients with a dysfunctional, previously inserted SEMS; both clinical settings exhibit a short expected survival in these groups, justifying the cheaper plastic stent to be used in these specific situations *(Soderlund, C. et al., 2006)*.

In conclusion, SEMS should almost always be preferred in irresectable periampullary tumors, since it reduces the risk of stent dysfunction and thereby the risk of a repeat ERCP procedure. This evidence has been known since the first RCT published on the

subject in 1992 by Davids in Lancet *(Davids, P. H., et al., 1992)*, and by following this policy one will offer the patients with irresectable periampullary tumors the best palliative care with the least added operative morbidity.

Table 2. Meta-analysis of patency of plastic stent vs SEMS in palliation: *Zorron Pu L., et al., 2015. World J Gastroenterol 2015; 41 (27): 13374-85.*

Studies Author & Year	Plastic Stent Patency (days)	SEMS Patency (days)
Walter 2014	172	293
Moses 2013	153	385
Mukai 2013	112	359
Sangchan 2012	35	103
Isayama 2011	202	285
Söderlund 2006	54	108
Katsinelos 2006	124	255
Prat 1998	96	184
Davids 1992	126	273
Mean p<0.0001	**124**	**250**

1.3.2.2 SEMS in neo-adjuvantly treated periampullary tumors

An increasing proportion of patients diagnosed with pancreatic cancer are considered for neo-adjuvant oncological treatment; this proportion typically includes patients with

locally advanced tumors incorporating the mesenteric or portal vein. During the down-staging treatment, traditionally the bile duct was stented with a plastic stent, and this tradition has been maintained, since there has been a hesitation among pancreatic surgeons to use modern SEMS, as these have been suspected to induce a more intense inflammatory response in the hepatico-duodenal ligament, thereby jeopardizing the later pancreatic resection technically. On the other hand, it is often that the neo-adjuvant treatment period time exceeds a plastic stent´s patency time, thereby risking a repeat ERCP procedure, which costs the patient valuable time of preoperative oncological treatment and carries the risk of delaying the oncoming operation.

This issue was highlighted by Boulay and co-workers *(Boulay, B. R., et al., 2010)*, who studied 49 patients with pancreatic cancer who received plastic stents in a neo-adjuvant situation and demonstrated that more than half of these patients (55 %) required a repeat ERCP procedure due to stent dysfunction, leading to a hospitalization for three days for stent exchange and cholangitis treatment, postponing the ongoing neo-adjuvant treatment and delaying the operation. Their conclusion was that SEMS should be considered in the neo-adjuvant situation to avoid unnecessary stent exchange procedures that delay the operation.

SEMS were also investigated in the neo-adjuvant situation in periampullary tumors by Aadam *(Aadam, A. A., et al., 2012)*, who studied 55 patients with pancreatic cancer of which 32 were borderline resectable. The median time until surgery was 104 days (range 70-260 days), and 88 % of the SEMS remained patent until the operation. Of those patients finally undergoing surgery, only 11% of the SEMS malfunctioned before the operation took place. The study was not randomized but clearly showed better results compared to when plastic stents were used, and no technical problems were

seen during the pancreatic surgery caused by the SEMS; this issue is further discussed later in this thesis and in Paper 4.

Finally, Adams *(Adams, M. A., et al., 2012)* demonstrated several advantages for SEMS in the neo-adjuvant situation in their retrospective study from 2012 that included 52 patients. The complication rates were seven times higher in the plastic stent group with a threefold-increased complication rate requiring hospitalization. The time to a stent related complication was almost five times longer in the SEMS group (44 days vs 200 days, $p<0.0001$); together, this advocated for SEMS in patients undergoing neo-adjuvant oncological treatment for periampullary tumors.

1.3.2.3 Covered versus uncovered SEMS

Initially, when the SEMS were introduced, they had no covering, which would make them more readily invaded by an ingrowing tumor; therefore, a covering was added to the SEMS to avoid this ingrowth. On the other hand, there was a concern that the covered SEMS were more likely to dislodge from the bile duct or that they would block either the orifices of the cystic or pancreatic ducts. The latter could not be confirmed in Kullman´s study from 2010 *(Kullman, E., et al., 2010)*, where the only difference he found between covered and uncovered stents was that the covered ones dislodged more easily (3 % vs 0 %, $p=0.03$), but there was no difference in patency between the stent types. Several studies and one meta-analysis *(Almadi, M. A., et al., 2013)* have shown similar results. The most recent meta-analysis by Moole *(Moole, H., et al., 2016)* included 2,239 patients and demonstrated an increased risk of stent dislodgement if covered stents were used and an increased risk for tumor ingrowth in the uncovered SEMS; this resulted in no differences in survival, patency or adverse events between the stent types. Another meta-analysis by Chen, also from 2016 *(Chen, M. Y., et al., 2016)*, showed

that covered SEMS had a lower rate of adverse events, but again no differences in survival or stent patency were seen. A third meta-analysis from 2016 by Li et al. *(Li, J., et al., 2016)* could neither show any differences in patency or survival, but they preferred covered SEMS since they were easier to remove when an exchange was needed. In conclusion, there seems to be no difference between covered and uncovered SEMS regarding their functions; this is probably because the negative effect of the covered SEMS' higher dislodgement rates are balanced by the non-covered SEMS' increased risk of tumor ingrowth, which leads to no differences between the stent types regarding function and patency.

1.3.3 Up-front surgery for periampullary tumors vs preoperative stenting before pancreatic surgery

Traditionally, in Sweden, all jaundiced patients with periampullary tumors undergo a preoperative biliary drainage procedure, which are most often through an ERCP with an internal stent. This is performed due to logistical reasons while waiting for their operations, most often performed at a referral university hospital several weeks after the onset of their symptoms. The theoretical background for such a policy is to try to reduce the negative effects of the jaundice (e.g., impaired coagulation, increased risk for immunosupression or cholangitis). However, the evidence for such a policy is not strong, as several previous meta-*analyses (Chen, M .Y., et al., 2016, Fang, Y., et al, 2013, Sewnath, M. E., et al., 2002)* have shown negative effects from preoperative biliary drainage. This policy adds morbidity from the ERCPs (like PEP) but also from an increased rate of postoperative infectious complications after the pancreatico-duodenectomy, since the bile becomes infected with gut bacteria from the preoperative biliary drainage, inducing more postoperative adverse events.

The shortcomings of these previous studies are that many of them are outdated and that the preoperative biliary drainage procedures included in these studies were internal endoscopic plastic stents and external PTC drainages with higher morbidity rates than modern SEMS. Actually, the last meta-analysis *(Moole, H., et al., 2016)* showed benefits from a preoperative biliary drainage on postoperative results. However, this meta-analysis contained many retrospective studies, which must be considered when interpreting the results.

The most cited article on the subject is written by van der Gaag *(van der Gaag, N., et al., 2010)* and was published in New England Journal of Medicine in 2010. Here, 202 patients were randomized to either achieve a preoperative biliary drainage through ERCP and a plastic stent or immediate surgery for pancreatic cancer. Complications related to the biliary drainage occurred in 46 % of the patients, and significantly more patients had a serious operative complication in the biliary drainage group (74 % vs 39 %, $p<0.01$, RR 0.54, 95 % CI 0.41-0.71).

In a meta-analysis from 2002 *(Sewnath, M. E., et al., 2002)* based on 5 RCTs (302 patients) and 18 cohort studies (2,853 patients), there were more complications if a preoperative biliary drainage was used compared to up-front surgery, but there was no difference in mortality. However, if the biliary drainage was successful without complications, there were fewer complications in this group compared to the direct surgery group.

Another meta-analysis from 2013 *(Fang, Y., et al, 2013)* including 6 RCTs with more than 500 patients reached the same conclusion with an overall serious complication rate of 60 % in the preoperative biliary drainage group compared to 36 % in the up-front surgery group (RR 1.66, 95 % CI 1.28-2.16, $p<0.001$), but there was no difference in mortality. The main problem with this meta-analysis is that four of the six included RCTs

were based on results from studies including patients with PTC-drainages, which is a method that is no longer routinely used in modern healthcare, since it has been replaced by endoscopic internal drainage.

The opposite findings were achieved by Moole et al. in the latest meta-analysis, which was published in 2016 *(Moole, H., et al., 2016).* They included 26 studies with 3,552 patients; however, not only RCTs but also retrospective studies were included. Their results were opposite to Fangs with a lower odds ratio for major adverse events in the biliary drainage group compared to the direct-surgery group (OR 0.48, 95 % CI 0.32-0.74).

An interesting future research project would be to compare up-front surgery to more modern preoperative biliary drainage with SEMS in a prospective, randomized fashion, which is discussed further in the next chapter.

1.3.4 Preoperative plastic stenting vs SEMS in resectable periampullary tumors

The evidence is overwhelming for the superiority of SEMS compared to plastic stents in irresectable tumors in the palliative setting *(Davids, P. H., et al., 1992, Soderlund, C., et al., 2006, Zorron Pu, L., et al., 2015)*. In contrast, much less is known about the role of SEMS in the preoperative situation of resectable tumors, and prospective RCTs remain lacking. There has been a debate among pancreatic surgeons that SEMS would jeopardize the surgical resection, whether or not a preoperative biliary drainage is used, by inducing more inflammatory reaction in the hepato-duodenal ligament, making the resection more hazardous, the SEMS more demanding to remove and the pancreatico-biliary anastomoses to the jejunum more difficult to create during the Whipple procedure. Another concern has been the higher costs of the SEMS. On the other hand, the increasing number of patients with long neo-adjuvant oncological treatment has led to a

greater number of patients that require stents with longer patency. However, often the tumor status at the time of the ERCP and the stent deployment is unknown, thereby leading the endoscopist to use a SEMS to avoid a repeat ERCP for the patient in case the tumor eventually is found to be irresectable.

Despite that prospective RCTs are lacking, a meta-analysis was performed in 2016 *(Crippa, S., et al., 2016),* containing four retrospective studies and one cohort study (n=704); its conclusions must be interpreted with caution, but the analysis showed clear benefits for the SEMS group. The need for a re-intervention ERCP was seen in 14.8 % in the plastic stent group compared to 3.4 % in the SEMS group ($p<0.0001$), and the postoperative pancreatic fistula rate was also lower in the SEMS group (5.1 % vs 11.8 %, $p=0.04$). No other differences between the groups were seen regarding postoperative complications or mortality, but the main conclusion of the study was that more prospective RCTs are needed to finally solve the issue of preoperative stenting in resectable periampullary tumors.

The only study that is not solely retrospective is the one by Tol et al. from 2016 *(Tol, J. A., et al., 2016)*, where the patients from van der Gaags study from 2010 *(van der Gaag, N., et al., 2010)* were used as a historical control group and compared to 49 prospectively collected patients receiving a SEMS prior to operation for pancreatic cancer (53 randomized, four excluded). Those "new" 49 patients with SEMS then were compared to the 102 patients receiving plastic stents preoperatively and the 94 patients with direct surgery, and both these latter groups were enrolled from the van der Gaags study *(van der Gaag, N., et al., 2010)*.

The biliary drainage complications were almost doubled in the plastic stent group compared to the SEMS (46 % vs 24 %, RR 1.9, 95 % CI 1.1-3.2, $p=0.011$), and the specific stent related complications (stent dysfunction and stent exchange) were much higher in

the plastic stent group (30 % vs 6 %, p=0.03); however, the surgical complications did not differ. The overall complications rates were 51 % in the SEMS group, 74 % in the plastic stent group and 39 % in the early surgery group. But again, the stent groups were not randomized and were performed during different time periods with the plastic stent group used as historical controls, which must be considered when interpreting the results. This also highlights the need for prospective RCTs.

In Decker's retrospective study from 2011 *(Decker, C., et al., 2011),* 29 patients undergoing pancreatico-duodenectomy, were preoperatively biliary drained with 18 plastic stents and 11 SEMS; they showed no stent dysfunctions in the SEMS group compared to stent dysfunction in 39 % in the plastic stent group (p=0.02). Also, no technical problems were seen during the operations. The same conclusion was reached by Cavell et al. in 2013 *(Cavell, L. K., et al., 2013)*, who retrospectively investigated 71 patients who received SEMS and thereafter underwent panceatico-duodenectomy, and they found no differences in serious postoperative complications or mortality but showed more wound infections and longer operational time in the SEMS group, indicating a more challenging operation in the SEMS group. But, this did not affect the resectability grade of the tumor. They concluded that SEMS were not contraindicated in resectable tumors.

The only study, also retrospectively performed, that advocated for plastic stents preoperatively was by Haapamäki and co-workers, *(Haapamaki, C., et al., 2015).* As they found no differences in stent patency, preoperative bilirubin level decrease, amount of bacteria in the bile or in the postoperative complication rates, they therefore argue that one can use cheaper plastic stents if they have the same function as the more expensive SEMS.

Altogether, the overall conclusion seems to be that SEMS are better in the preoperative situation in resectable periampullary tumors, but prospective RCTs are still lacking and are warranted in the future. However, this issue will be further discussed in conjunction with Paper 4 later in this thesis.

1.4 ERCP complexity grading scales

ERCP is the most difficult endoscopic procedure, but the complexity between individual procedures varies considerably.

It is therefore important to develop a grading scale for the complexity of different ERCPs that could be used as a tool to predict, for instance, the postoperative risk of adverse events and thereby be able to intensify prophylactic measures in these particular procedures. One important character of such a grading scale would be to find a system that, as far as possible, could predict all possible obstacles associated with an ERCP procedure. However, some of the technical difficulties in ERCP (e.g., a giant duodenal diverticula, a difficult cannulation due to a small papilla) cannot always be foreseen, but a superior grading scale can anticipate risks and function as important clinical guidance. While complications are important to predict in ERCP, the time and competence required to perform a certain ERCP procedure are also important, as this information could work as an aid in planning activities at different endoscopy centers to better use their resources. A well-balanced ERCP complexity grading scale might also act as a good complement in training programs for endoscopists under training with different skills to find the right level in an endoscopic educational program. Finally, a well-validated grading system may be helpful in comparisons between different endoscopic centers and may also help with billing processes between different health care systems and to

decide when to refer more complex ERCP procedures to tertiary referral centers with the right competence for a specific advanced ERCP procedure.

There have been previous attempts to establish ERCP complexity grading scales, but the few that have been launched have either now become outdated or have not been validated in relation to resource requirements like procedure time but instead only to success and complication rates. ERCP complexity grading systems are further discussed later in this thesis in conjunction to Paper 3 (The HOUSE classification).

1.4.1 The Cotton and ASGE Classification

A recent attempt to establish a complexity grading scale was performed by Cotton and co-workers in 2011 *(Cotton, P. B., et al., 2011).* Actually, this was presented for all types of endoscopic procedures and not only for ERCPs. The aim of the study was to arm the endoscopist with a method to predict problems before the start of the procedure to be able to improve the chance of a technical success of the endoscopic procedure. The method used was to send a comprehensive list of specific endoscopic procedures to 17 members of the ASGE (American Society for Gastro Enterology) Adverse Events Working Party with 26 different ERCP items and ask them to rank the procedure using a four-point scale, from which a median value was calculated to represent the complexity grading of that specific procedure. To make the categories more adequate, certain circumstances for the procedure could be added, for example, if the procedure was performed outside ordinary working hours, if there had been a failed attempt before, if the procedure was performed on a child under three years or if the patient had an altered anatomy of the upper GI-tract (like a Billroth 2-operation). If one of the circumstances mentioned above was present, then one point was added to the grading number judged by the experts.

The advantage of this scale is that it is easy to use and implement in clinical praxis, and the shortcomings of the system are that it is solely “eminence based” and not validated in relation to resource consumption, complications or success rates. Additionally, it does not completely cover all obstacles that could turn up during an ERCP (e.g., a giant duodenal diverticula or if a precut sphincterotomy is required for a difficult cannulation).

Table 3. The Cotton classification: *Cotton P. B., et al., Grading the complexity of endoscopic procedures: results of an ASGE working party. Gastrointest Endosc 2011;73(5): 868-874)*

Cotton	**Type of ERCP**
Grade 1	Diagnostic ERCP, brush cytology
Grade 1.5	Stent exchange, stent extraction
Grade 2	Biliary leak, CBDS <10mm, extrahepatic stent, prophylactic pancreatic stent
Grade 3	Pancreatic stone <5mm, CBDS>10mm, migrated stents, pancreatitis, SOD, papilla minor, pancr.strictures, hilar strictures, intrahepatic stones, intraductal imaging (SPY)
Grade 3.5	migrated pancreatic stents
Grade 4	pancreatic stones >5mm or fix, intraductal therapy (EHL), ampullectomy, Roux-en-Y, pseudocysts, necrosectomy
+1 point for	Billroth 2-op. anatomy, child <3years, previously failed procedure or procedure performed outside working hours

1.4.2 The classification according to Schutz and Abbott

This grading scale was presented in 2000 *(Schutz, S. M., et al., 2000)*, and the aim was to produce more meaningful outcome data to make it possible for different endoscopic centers to compare their success and complication rates. The study was performed first

retrospectively from a database containing all ERCP procedures performed during 1997. Then, all of the ERCPs performed during 1998 were added to the study in a prospective manner for a combined total of more than 400 patients. Those procedures were divided into a five-point scale according to their technical difficulty. To those five levels, a "B-grade" was added if the patient had had a previously failed endoscopic procedure attempt. They also suggested an "S" suffix for patients that have had a previous sphincterotomy. Ultimately, they found more complications and lower success rates in the grade-5 procedures and that the repeat ERCPs have a very low success rate.
They also conclude that their study was a pilot study, which was underpowered and was a preliminary attempt to establish a complexity grading scale. Another shortcoming of the study, now 15 years later, is that the classification contains special complexity grades for diagnostic ERCP procedures; something that was abandoned after the introduction of the MRI-technique (MRCP).

Table 4. Grading ERCP complexity: *Schutz, S. M. and R. M. Abbott. Grading ERCPs by degree of difficulty: a new concept to produce more meaningful outcome data. Gastrointest Endosc 2000; 51(5): 535-539.*

Schutz & Abbott	Success	Complications
1 Diagnostic ERCP	92-96 %	1.5-3 %
2 Therapeutic ERCP EST, small CBDS, nasobiliary drainage	100 %	10 %
3 Complex diagnostic B2, brush cytology	80-100 %	17-20 %
4 Complex therapeutic Large CBDS, dilatation, stents	95-97 %	3 %
5 Very advanced ERCP Precut sphincterotomy, lithotripsi, intrahepatic stones/strictures, B2-op, cholangioscopy, all pancreatic interventions	79-84 %	6-9 %

1.4.3 Morriston Hospital Grading Scale (Ragunath)

This classification was introduced in 2003 *(Ragunath, K., et al., 2003)* to establish a method to achieve a more objective outcome measurement system, and during that year, all ERCPs performed by both experienced endoscopists and trainees were

registered and divided into a four-point complexity scale, where success and complication rates were investigated in each class. They found a linear relationship in success rates for the trainees in relation to the classification, but no relation was seen for the experienced endoscopists, and the latter was explained by the low power of the study (n=305). They also did not reach any significant differences in complication rates, but numerically higher complication rates were found in the more complex procedures (grade 4, 9 % compared to 4 % in the grade 1-3), which was again explained by the authors due to underpowering of the study. Other limitations of the study were that certain problems that evolved during the ERCP could not be anticipated like a duodenal diverticula or a need for a precut sphincterotomy due to a difficult cannulation. A final shortcoming of the scale was these specific levels of the classification contain diagnostic ERCPs, yet these investigations have been abandoned after the introduction of the MRCP; therefore, the classification is hard to implement in modern endoscopic therapy.

Table 5. Morriston Hospital ERCP-Grading Scale: *Ragunath K., et al. Objective evaluation of ERCP procedures: a simple grading scale for evaluating technical difficulty. Postgrad Med J 2003; 79(934): 467-470.*

Morriston Hospital Grading Scale	Successrate %	Complications %
Grade 1 Diagnostic ERCP	87	4
Grade 2 EST, balloon, CBDS<10mm	76	5
Grade 3 Precut sphincterotomy, cytology, CBDS>10mm, lithotripsy, stents, nasobiliary drains	80	5
Grade 4 SOD, papilla minor, B2-op, ampullectomy, pancreatic interventions, cholangioscopy, EHL, PTC-rendezvous	63	9

1.4.4 The classification according to Madhotra

Another ERCP complexity classification was the one by Madhotra *(Madhotra, R., et al., 2000)*, which was presented as an abstract only, and one of the co-authors was the above mentioned Cotton *(Cotton, P. B., et al., 2011).* A database was investigated including

8,094 patients and divided into a three-point scale according to the complexity of the procedure. The conclusion of the study was simply that the success rate was proportional to the grade of the scale without any further explanation expressed in the abstract. Also, this classification included diagnostic ERCPs that are no longer used since the introduction of MRCP, making also this classification difficult to implement in modern endoscopic therapy.

Table 6. Classification according to Madhotra: *Madhotra, R., et al. Analyzing ERCP practice by a modified degree of difficulty scale: a multicenter database analysis. Am J Gastroenterol 2000; 95:2480–1.*

Classification according to Madhotra
Grade 1: Diagnostic ERCP, CBDS <10mm, extrahepatic stent, nasobiliary drainage
Grade 2: Diagnostic ERCP in B2-op, CBDS >10mm, papilla minor, intrahepatic stricture
Grade 3: Roux-en-Y/Whipple, Spyglass, SOD, intrahepatic stones, therapeutic ERCP in B2-op, all pancreatic ERCPs

1.4.5 The classification according to Torun

Recently, in 2016, a new complexity grading scale was introduced by Torun *(Torun, S., et al., 2016).* Completely independently of the introduction of the HOUSE classification, this scale was launched with similar parameters to our HOUSE classification regarding complication rates; however, this had a four-point scale and demonstrated a relationship between the complications of the groups from 1.3 % in the group of less complicated investigations up to 10.4 % in the group of the most complex ERCPs. Instead of procedure time, which was measured in the HOUSE classification, Torun focused on success rates between the groups of ERCPs with different complexity and found a linear relationship between the groups of ERCPs with different complexities (1st degree 99.3 %, 2nd degree 97.2 %, 3rd degree 86.7 % and 4th degree 46.7 % success rates). This new classification seems promising regarding measuring and comparing results from different endoscopic centers more fairly, but compared to the HOUSE classification, it lacks the ability to plan endoscopic resources as it does not include any such parameters—for example, procedure time for every single ERCP investigation, which was included in the HOUSE classification.

Table 7: Classification according to Torun: *Torun, S., et al., Turk J Gastroenterology, 2016, Mar; 27(2): 187-91.*

Grade 1	Grade 2	Grade 3	Grade 4
Stent exchange	Stone <10mm	Stone >10mm Minor papilla	Migrated pancreatic stents
Stent removal	Biliary leakage	Migrated biliary stent	Pancreatic stone >5 mm
	Extra hepatic stricture	Pancreatic-ERCP Hilar strictures	Intrahep stone Pseudocyst
	Prophylactic pancreatic stent	Sph. Oddi Dysf.	Necrosectomy Ampullectomy Prev GBY op
		Spyglass	Prev Whipple Spyglass EHL

1.5 Complications in ERCP

1.5.1 Post-ERCP pancreatitis (PEP)

PEP is the most common complication after ERCP and is most often mild to moderate, but it can occasionally be severe with subsequent organ failure.

The definitions of PEP used are those defined by Cotton *(Cotton, P. B., et al., 1991)*, where a mild PEP was characterized by abdominal pain, an amylase elevated three times the normal value and a need for a hospital stay of two to three days. A moderate PEP was defined as a condition that required hospitalization for 4-10 days. Finally, severe pancreatitis required more than 10 days in the hospital, showed signs of complications locally in the pancreas (e.g., necrosis, pseudocysts) or systemically (e.g.,

multiorgan failure) or required surgical or percutaneous interventions. Note that an already existing pancreatitis (before the ERCP) can confuse the definition of PEP and affect the PEP rates when this issue is studied. Also, an isolated amylase elevation without symptoms can be interpreted as a PEP and thus make postoperative complications rates difficult to study and even impossible to compare between different series.

The PEP rate was reported in unselected cases to be around 3.5 %, where mild and moderate PEPs represent about 90 % of all the cases (45 % each), and only 10 % developed into a severe PEP *(Andriulli, A., et al., 2007).* Similar findings were seen in the Swedish National GallRiks Registry *(Enochsson, L. et al., 2010)*, where the overall PEP frequency was 2.7 % in this unselected database of patients, but the PEP rate rose to 5.3% when the pancreatic duct had been cannulated compared to only 1.8 % if only the bile duct was cannulated. There was also a higher PEP frequency at the high-volume centers (3.7 %) compared to middle- and low-volume centers (2.4 %), indicating a case mix where more complex procedures were performed at the high-volume centers.

The exact mechanism of how PEP occurs is not known, but a long list of risk factors is known, where some depend on the patient, some on the endoscopist and some on the type of intervention. A previous PEP in the patient´s history elevated the odds of a PEP by more than five times, whereas women or patients with a suspected sphincter Oddi dysfunction had two and a half times elevated odds for a PEP. A difficult cannulation, contrast injection to the pancreatic duct or a pancreatic sphincterotomy all increased the odds of PEP approximately three times *(Andriulli, A., et al., 2007, Freeman, M. L, et al., 2001).* However, the type of contrast (high vs low osmolality) injected into the pancreatic duct did not affect the risk for developing PEP *(George, S., et al., 2004).*

Freeman also demonstrated *(Freeman, M. L., et al., 2001)* that chronic pancreatitis had a protective effect on the risk of PEP and finally found no difference if the procedure was performed on a bile duct of a small diameter or a dilated one, neither could he demonstrate any differences between high- and low-volume centers in PEP rates or whether or not a biliary sphincterotomy was performed *(Freeman, M. L., et al, 2001).* Younger age (<60 years) is another risk factor associated with an elevated risk for PEP *(Cheng, C. L., et al., 2006)*; this is probably due to a more atrophic and less reactive pancreatic glandulae in older age compared to younger patients.

Table 8. Riskfactors for PEP*: Dumonceau, J. M., et al., Prophylaxis of post-ERCP pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - updated June 2014. Endoscopy 2014; 46 (9): 799-815.*

a)Patient-related risk factors

	OR (95 %CI)	**Relative risk**
SOD	1.9 (1.4 – 2.6)	8.6 % vs. 2.5 %
Female	3.5 (1.1 – 10.6)	4.0 % vs. 2.1 %
Previous pancreatitis	2.5 (1.9 – 3.1)	6.7 % vs. 3.8 %
Younger age	1.1 – 2.9	6.2 % vs. 2.6 %
Previous PEP	8.7 (3.2 – 23.9)	30 % vs. 3.5 %
No chronic pancreatitis	1.9 (1.0 – 3.5)	4.0 % vs. 3.1 %
Normal bilirubin level	1.9 (1.2 – 2.9)	4.2 % vs. 1.4 %
Non-dilated bile duct	-	3.8 % vs. 2.3 %

b) Procedure-related risk factors

Cannulation>10 minutes	1.8 (1.1 – 2.7)	3.8 % vs. 10.8 %
Pancreatic guidewire passage	2.8 (1.8 – 4.3)	2.9 % vs. 9.5 %
Pancreatic contrast injection	2.2 (1.6 – 3.0)	3.3 % vs. 1.7 %
Precut sphincterotomy	2.3 (1.4 – 3.7)	5.3 % vs. 3.1 %
Pancreatic sphincterotomy	3.1 (1.6 – 5.8)	2.6 % vs. 2.3 %
Biliary balloon-sphincter dil.	4.5 (1.5 – 13.5)	9.3 % vs. 2.6 %
Failure of CBDS clearance	3.4 (1.3 – 9.1)	1.7 % vs. 1.6 %
Intraductal Ultrasound	2.4 (1.3 – 4.4)	8.4 % vs. 2.8 %

1.5.2 Infectious complications to ERCP (cholangitis, abscess, sepsis)

Very often stasis of the bile duct is the problem when an ERCP is undertaken, resulting in infected bile as part of the disease and not always as a direct complication to the ERCP. On the other hand, an infectious complication can be a direct consequence of an incomplete drainage of a bile duct segment but where the ERCP procedure per se contaminates the bile with gut bacteria. Finally, cholangitis can occur due to a failed cannulation that does not allow the bile ducts to be drained, resulting in a manifest sepsis or abscess formation. Altogether, these different situations make the figures of infectious complications in ERCP difficult to interpret and can vary between different series in relation to the inclusion criteria for post-ERCP infection complication rates. However, has there been an attempt by Cotton *(Cotton, P. B., et al., 1991)* to define cholangitis, where a mild cholangitis was defined as a temperature over 38 °C for 24-48 hours. A moderate cholangitis was defined as lasting for at least three days of in-hospital care or requiring a repeat ERCP or PTC for drainage of the bile ducts. Finally, a severe cholangitis corresponded to a septic shock or a cholangitis requiring a surgical intervention.

Cholangitis is reported to occur in about 0.5 %-5 % after ERCP *(Christensen, M., et al., 2004, Masci, E., et al., 2001),* depending on the patient groups and whether or not failure of complete drainage has been recorded as a complication. The cholangitis may proceed into abscesses of the liver or to manifest sepsis. Hilar tumors and patients with primary sclerosing cholangitis (PSC) are considered to be more prone to develop infectious complications because the risk of leaving undrained areas of the bile tree is greater since these diseases are multilocular (PSC) or affect multiple bile ducts (hilar tumors).

The treatment of cholangitis is otherwise quite straightforward: antibiotics are administered intravenously, and additional drainage is performed via ERCP or PTC to localize and treat undrained areas of the bile tree, if needed.

Prophylactic antibiotics to prevent complications after ERCP are still used at many endoscopic centers. Two recent meta-analyses studying prophylactic antibiotics in ERCP *(Bai, Y., et al., 2009, Brand, M., et al., 2010)* reached different conclusions. The first, which was performed by Brand *(Brand, M., et al., 2010)*, stated that prophylactic antibiotics have a role in complicated ERCPs, especially when drainage is not reached, whereas Bai *(Bai, Y., et al., 2009),* who performed the other meta-analysis, reached the conclusion that prophylactic antibiotics cannot prevent cholangitis at all.

1.5.3 Duodenal perforations

Duodenal perforation occurs in less than one percent of the ERCPs *(Christensen, M., et al., 2004, Freeman, M. L., et al., 1996, Vandervoort, J., et al., 2002, Wang, P., et al., 2009, Williams, E. J., et al., 2007)* and is usually retroperitoneally located and most often does not require any operation but can be treated with antibiotics. However, some of the perforations are intra-abdominal and more often require an operation, and the clinical challenge is to provide an early identification of these patients who would otherwise deteriorate rapidly if not for the operation. A CT scan is often of great help, but the free air outside the gut lumen frequently seen after ERCP does not always require operation, so the assessment will ultimately be clinically based. Stapfer presented a four-point classification *(Stapfer, M., et al., 2000)* according to the management required to manage these complications, where the first class needs operation, and the class with the highest number almost always could be treated conservatively.

Lately, the therapy arsenal for duodenal perforations has been extended with the possibility to temporarily deploy a covered SEMS in the bile duct as an alternative to surgical exploration, hereby minimizing the leakage *(Artifon, E. L. et al., 2015).*

A classification of the perforation´s severity is also established, where a mild perforation was defined as a possible or very slight leak that could be treated conservatively and requiring less than three days in the hospital and a moderate perforation requiring 4-10 days in the hospital, whereas a severe perforation was defined as requiring more than 10 days in the hospital or a need for a percutaneous drainage or a surgical intervention *(Cotton, P. B., et al., 1991).*

1.5.4 Post-sphincterotomy hemorrhage

Bleeding of clinical significance occurs in about 1-3 percent of ERCPs *(Cotton, P .B., et al., 2009, Freeman, M. L., et al., 1996, Masci, E., et al., 2001)*, depending on the definition of bleeding, and is more frequent for a precut sphincterotomy or if an obstruction of the papilla of Vateri is present *(Masci, E., et al., 2001)*. Other risk factors for bleeding include coagulopathy or anticoagulation therapy, on-going cholangitis, low case-volume of the endoscopist or detectable bleeding during the EST *(Freeman, M. L., et al., 1996).*

Also, regarding this specific complication, a definition of the different stages of the severity of the bleeding has been made by Cotton et al. *(Cotton, P. B., et al., 1991)*, where mild bleeding was defined where the patient did not require blood transfusions compared to a moderate bleeding, where the patient needed up to four units of blood, or severe bleeding, where the patient required five units of blood or more or an angiographic or surgical intervention.

The treatment modalities in a postoperative sphincterotomy bleeding are similar to the ones used in any upper gastrointestinal bleeding, like endoscopic injection therapy with

adrenalin or applying endoscopic clips. As an initial measure to stop the bleeding, often a balloon is inflated at the sphincterotomy site to gain initial hemostasis so further interventions can be undertaken if necessary. An increased use of SEMS inserted in the distal bile duct has been used as a temporary method to compress the bleeding site to achieve hemostasis.

If endoscopic and pharmacological methods fail, more invasive measures can be used like angiographic coiling of the gastro-duodenal artery or open surgery to gain hemostasis through a duodenotomy.

1.5.5 Other complications

Additional different but more seldom occurring complications have been described after ERCP, both systemic and of more local types related to the procedure in the duodenum. Endoscopic perforations of the instrument could occur and must be treated depending on their localization and seriousness. Perforations caused by endoscopic stents have also been described *(Christensen, M., et al., 2004).* The SEMS may also cause an obstruction of the cystic duct leading to cholecystitis, which can be treated like any cholecystitis with operation or cholecystostomy.

A special complication for ERCP is the so-called “Winnie-the-Pooh syndrome” referring to when a stone is grasped in a stone catcher basket and stuck inside it, and there is no possibility to remove neither the stone nor the basket out of the bile duct. Sometimes, the patient needed to have surgery to remove both the stone and basket with the ERCP instrument in place during the operation. However, this issue has now been solved, since modern stone catcher baskets can be taken apart at the distal end, distal to the stone, giving the operator the opportunity to get the basket out but leaving the stone in situ to be handled later.

General complications (e.g., cardiac or pulmonary) could occur like in any operation and is described in less than one percent of the ERCPs *(Christensen, M., et al., 2004).* Also, respiratory complications are described due to the stress to the cardiopulmonary system from the intervention or as an effect of pulmonary aspiration during the procedure and happens in about one and a half percent of the ERCPs *(Christensen, M., et al., 2004).* Finally, thromboembolic events must be mentioned and are reported in 0.7 % of the patients undergoing ERCP, such as cerebrovascular events and pulmonary embolism.

1.6 Prophylactic measures to ERCP to avoid postoperative complications

1.6.1 Pancreatic stents

Pancreatic stents are thought to improve the drainage of the pancreatic juice after the ERCP and hereby reduce the risk of PEP. In the guidelines from the European Society of Gastrointestinal Endoscopy (ESGE) from 2014, the recommendations are to use a prophylactic pancreatic stent in all high-risk and mixed-case groups of ERCPs, since it diminishes the risk of PEP and almost eliminates the risk of severe PEP *(Dumonceau, J. M., et al., 2014).*

This statement was based on previous meta-analyses, for instance, the one from Singh from 2004, where five trials with 481 patients showed an increased OR of 3.2 if no pancreatic stent was used with a risk of PEP of 15.5 % compared to 5.8 % if a stent was deployed in the pancreatic duct *(Singh, P., et al., 2004).* Similar results were found in a meta-analysis by Choudhary and co-workers *(Choudhary, A., et al., 2011),* where a reduction in PEP from 17.8 % to 8.8 % (OR 0.22, 95 % CI 0.12-0.38) was demonstrated if

a pancreatic stent was used prophylactically, corresponding to a NNT of 8 stents to avoid one PEP.

In another meta-analysis by Mazaki and co-workers based upon 14 studies and more than 1,500 patients *(Mazaki, T. et al., 2014),* an overall RR of 0.39 (95 % CI 0.29-0.53) for PEP was shown if prophylactic pancreatic stents were used, and an even lower RR for severe PEP was seen (RR 0.26, 95 % CI 0.09-0.76). Similar findings were noted by Fan and co-workers in 2015 *(Fan, J. H., et al., 2015)* in a further meta-analysis with over 1,600 patients that demonstrated a reduction in PEP rates from 10.4 % to 4 % if pancreatic stents were deployed prophylactically in high-risk ERCPs, corresponding to an OR of 0.35.

Yet another meta-analysis *(Vadala di Prampero, S. F., et al., 2016)* studied the effect of prophylactic pancreatic stents in 12 RCTs including 1,269 patients and found an OR of 0.28 (95 % CI 0.8-0.42). Altogether, one can conclude that this issue is well studied with overwhelming results that advocate the use of prophylactic pancreatic stents, especially in difficult ERCPs.

The largest separate study often included in the meta-analyses is by Sofuni and co-workers. *(Sofuni, A., et al., 2011)*, where 426 patients were randomized to either achieve a prophylactic pancreatic stent or not, demonstrating a reduction in the PEP rates if pancreatic stents were used (15.2 % vs 7.9 %, p=0.021); in the ITT analysis, however, the significant difference disappeared.

In the recommendations from the ESGE from 2014, where prophylactic pancreatic stents are advocated *(Dumonceau, J. M., et al., 2014)*, the guidelines suggest a 5-Fr pancreatic stent to be used. This finding was supported by the meta-analysis of Afghani from 2014 *(Afghani, E., et al., 2014)*, where the 5-Fr stent was described as superior to the 3-Fr stent, whereas the type of stent seemed to be of less importance (e.g., straight,

pigtail, flanged). However, only two studies were included in the meta-analysis, that actually directly compared 5-Fr to 3-Fr stents *(Chahal, P., et al., 2009, Zolotarevsky, E., et al., 2011)* and these studies did not demonstrate any differences in adverse events rates, and the conclusion that 5-Fr stents are better was based only on indirect evidence where the complication rates of 5-Fr and 3-Fr stents have been compared to no stent at all. The absolute complication rate figures have then been compared, and from these figures the conclusion has been drawn that 5 Fr stents are better in reducing complications after ERCP. Consequently, more studies are required with direct comparisons of different stent sizes in prospective, randomized trials.

Another advantage of the 5-Fr stent that is often mentioned is its easier placement, since it does not require a special guidewire for deployment *(Cha, S. W., et al., 2013).*

Regarding the length of the prophylactic pancreatic stents, Chahal and co-workers *(Chahal, P., et al., 2009)* recommended shorter stents since these reduced the need for a repeat endoscopy to remove the stent (98 % vs 88 % spontaneous dislodgement). This study also demonstrated a lower PEP rate in the 5-Fr group compared to the 3-Fr stents, although this difference was not significant.

Further aspects of the effect of prophylactic pancreatic stents are discussed more thoroughly later in this thesis and in Paper 2.

1.6.2 Pharmacological treatment with NSAID as PEP prophylaxis in ERCP

Rectally administered NSAID reduces the risk of PEP in both high- and low-risk procedures, and this has been demonstrated in several meta-analyses *(Dai, H. F., et al., 2009, Ding, X., et al., 2012, Sethi, S., et al., 2014, Sun, H. L., et al., 2014, Yaghoobi, M., et al., 2013, Yuhara, H., et al., 2014).* The guidelines from ESGE *(Dumonceau, J. M., et al., 2014)* therefore recommend 100-mg indomethacin or diclofenac given rectally before or after

the ERCP and has been reported to be used in an increasing part of the ERCP procedures over time.

In a randomized controlled trial from 2012 by Elmunzer and co-workers, published in New England Journal of Medicine *(Elmunzer, B. J., et al., 2012)*, the PEP rate was not only diminished from 16.9 % to 9.2 % ($p<0.005$) when using indomethacin compared to placebo, but it was also reducing the part of severe PEPs from 8.8 % to 4.4 % ($p=0.03$). NSAIDs administered through other routes than rectally seem to have no effect in preventing PEP nor does a lower dose seem to have a PEP-protective effect.

Seven meta-analyses have been published on the subject of NSAID-prophylaxis in ERCP since 2009 *(Dai, H. F., et al., 2009, Ding, X., et al., 2012, Kubiliun, N. M., et al., 2015, Sethi, S., et al., 2014, Sun, H. L., et al., 2014, Yaghoobi, M., et al., 2013, Yuhara, H., et al., 2014)* and they all demonstrate significant beneficial effects on PEP rates with reductions of ORs between 0.44 and 0.57, where the absolute PEP rates were lowered from between 10.3 % and 16.8 % to 5.1 % and 8.9 %. These studies also report a NNT with rectally administered NSAID to avoid one PEP between approximately 11 and 34 patients (for details, see Table 9).

Table 9: Prophylactic NSAID meta-analyses since 2009. *Dumonceau, J.M., et al., Prophylaxis of post-ERCP pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy, 2014; 46(9): 799-815.*

Author	Year	n	PEP NSAID	PEP placebo	OR (95 % CI)	NNT
Dai	2009	1300	8.9 %	16.8 %	0.46 (0.32 – 0.65)	NA
Ding	2012	2269	8.0 %	13.9 %	0.57 (0.38 – 0.86)	17
Yaghoobi	2013	1470	5.1 %	10.3 %	0.49 (0.34 – 0.71)	20
Sun	2013	1846	6.4 %	16.0 %	0.45 (0.34 – 0.61)	NA
Yuhara	2014	1981	7.8 %	16.0 %	0.55 (0.43 - 0.72)	NA
Sethi	2014	2133	6.6 %	15.1 %	0.44 (0.34 - 0.57)	11

1.6.3 Other pharmacological treatment in avoiding PEP

1.6.3.1 The use of **octreotide** and **somatostatin** as prophylaxis against PEP has not been generally recommended in ERCP but only in selected cases due to lack of evidence, discordant data and a high NNT to avoid complications. A meta-analysis of 18 RCTs and over 3,000 patients *(Zhang, Y., et al., 2009)* could not demonstrate any benefits in reducing PEP rates. A subgroup analysis of higher doses of octreotide (>0.5 mg), however, showed a significant odds ratio drop (OR 0.45) in PEP rates. Another meta-

analysis by Omata and co-workers *(Omata, F., et al., 2010)* could not show any benefits in using octreotid in conjunction with ERCP, whereas somatostatin reduced the risk of PEP (OR 0.52, 95 % CI 0.30-0.90), especially when given in high doses or as a bolus injection in high-risk ERCPs. In summary, octreotide and somatostatin cannot be generally recommended as a PEP prophylaxis in ERCP due to the heterogeneous documentation and high NNT to avoid one PEP.

1.6.3.2 Protease inhibitors (gabexate, ulinastatin) cannot not be recommended as PEP prophylaxis in ERCP as none of them showed any significant benefits from published meta-analyses *(Dumonceau, J. M., et al., 2014).*

1.6.3.3 Glyceryl trinitrate (GTN) has been used as an agent in trying to reduce PEP rates but has been proven useless if administered transdermally; however, it may have an effect if given sublingually but is not generally recommended in ERCP by the ESGE *(Dumonceau, J. M., et al., 2014). A* meta-analysis from 2013 *(Ding, J., et al., 2013)* including 2,649 patients in 12 RCTs found that it lowered the overall PEP risk (RR 0.67) after ERCP, but unfortunately it did not exhibit an effect for moderate and severe PEP. A further subgroup analysis showed that the most effective administration form was sublingually as compared to transdermal and topical applications.

1.6.3.4 Drugs not shown to prevent from PEP and therefore not recommended

Botulinum toxin, lidocaine, nifedipine, epinephrine (perhaps in diagnostic ERCPs), antioxidants (like allopurinol, acetylcysteine, beta-carotene), heparin, interleukin-10, anti-inflammatory drugs (other than indomethacin and diclofenac) like pentoxyfelline,

semapimod, acetylhydrolase and finally glucocorticoids are all substances without sufficient evidence to be recommended as prophylaxis in ERCP-therapy.

1.6.4 Prophylactic antibiotics in ERCP

Prophylactic antibiotics are still commonly used adjacenct to ERCP as prophylaxis against infectious complications, although the evidence for such a strategy is quite weak. In 1999, Subhani and co-workers published a review article *(Subhani, J.M., et al., 1999)*, where they proposed that antibiotics should be administered in these ERCPs where biliary drainage could not be achieved, which they calculated to be about 10 % of the ERCPs (90 % cannulation rate). But, they estimated that in this subgroup of ERCPs, about 80 % would benefit from prophylaxis, justifying a general recommendation for prophylaxis in this group. After that, only three meta-analyses have been reported on the subject of prophylactic antibiotics in ERCP; they each reached different conclusions regarding the effect of prophylaxis against complications. The first was by Harris in 1999 *(Harris, A., et al., 1999)* and the second was from Bai in 2009 *(Bai, Y., et al., 2009),* where the latter reported no benefit from prophylactic antibiotics on the frequency of postoperative cholangitis in uncomplicated ERCPs, and therefore they did not recommend general prophylaxis with antibiotics in ERCP.

The third meta-analysis was a Cochrane analysis from 2010 by Brand *(Brand, M., et al., 2010)*, where the authors concluded that prophylactic antibiotics reduce the RR of cholangitis (RR=0.5, 95 % CI 0.33-0-91) and that of bacteremia (RR=0.5, 95 % CI 0.33-0.78), but in the random effects meta-analysis only the effects on bacteremia remained significant. Also, no effect on the postoperative mortality was seen nor was there any effect on the adverse postoperative events. Their conclusion from these risk reductions is that antibiotics might be beneficial in reducing complications but not obviously in

uncomplicated ERCPs; they also recommend further research for these patients where biliary access cannot be achieved and propose that antibiotics then perhaps could be given during or after these ERCP procedures when cannulation fails. One problem with the included studies was that many of them were performed without placebo control and were hence not blinded. Most of the studies included were also small and performed with different antibiotics, and the latest included study was from 2006 *(Llach, J., et al., 2006)*, whereas most of the studies were from the 1990s. For example, the study from Niederau *(Niederau, C., et al., 1994),* who randomized 50 patients to receive either cefotaxim or no antibiotics at all, found differences only in the bacteremia rates between the groups and recommended prophylactic antibiotics only to patients with biliary stasis, where all the adverse events occurred.

Another study included in the meta-analyses is the one by Räty *(Raty, S., et al., 2001)*, who prospectively randomized 321 patients to receive cephtazidime or nothing and demonstrated significant beneficial effects on both cholangitis rates (4.4 % vs 0 %) and PEP rates (9.4 % vs 2.6 %), recommending antibiotics in all ERCPs. A final study worth mentioning, because of its larger size (n=551), is the one from van den Hazel *(van den Hazel, S. J., et al., 1996)*, which was also from the 1990s and placebo controlled. This group reached the opposite conclusion and did not recommend prophylactic antibiotics (piperacillin), since the cholangitis rates were similar in the groups whether or not they had been randomized to achieve piperacillin (4.4 % vs 6.0 %).

A large study by Cotton et al. *(Cotton, P. B., et al., 2008)* that was not included in the above mentioned meta-analyses also demonstrated an unchanged frequency of infectious complications, as antibiotics successively were phased out during the study period. They compared the later ERCP procedures where no prophylactic antibiotics were administered to the historical control ERCPs where prophylactic antibiotics were

used and showed no differences in postoperative complications; they thus advocated for a limited use of prophylactic antibiotics in ERCP.

Although prophylactic antibiotics are widely used in ERCP, one must conclude that the evidence for their efficacy is quite limited, since the studies included in the meta-analyses are quite old, and the results of the meta-analyses are contradictory. On the other hand, the guidelines from ESGE from 1998 *(Rey, J. R., et al., 1998)* were liberate and advocated prophylactic antibiotics in all ERCPs, but are not recommend as PEP-prophylaxis in the ESGEs Guidelines from 2014 *(Dumonceau, J. M., et al., 2014)*. The lack of conformity in using prophylactic antibiotics has led to a practice where many centers use prophylactic antibiotics in cases, where bile duct drainage cannot be achieved, something which cannot always can be predicted. Subsequently, antibiotics are given in difficult ERCPs with an elevated assumed risk for non-drainage (e.g., hilar tumors, PSC, or other intrahepatic diseases). This strategy was presented by Kager *(Kager, L. M., et al., 2012)* as a practical way to deal with how to use prophylactic antibiotics in ERCP. This is, in a way, an implementation of Brand´s meta-analysis *(Brand, M., et al., 2010)* in clinical praxis and a way to establish a policy for how to use prophylactic antibiotics in everyday ERCPs when scientific evidence is insufficient.

A retrospective series by Ishigaki and co-workers from 2015 *(Ishigaki, T., et al., 2015)* compared 605 patients in two groups with and without antibiotics regarding cholangitis and PEP rates. In the group given prophylactic antibiotics, the PEP rate was 4.3 % versus 4.9 % in the group where no antibiotics were administered (p=0.72); there were also no differences in the risk of developing cholangitis (prophylactic antibiotics 1.7 % vs no antibiotics 2.0 %, p=0.99).

Finally, Hauser and co-workers *(Hauser, G., et al., 2017)* prospectively randomized 272 patients to achieve either rectally administered sodium diclofenac plus placebo

intravenously (mimicking antibiotics) or intravenous antibiotics plus placebo rectally administered (mimicking sodium diclofenac) and compared the PEP rates between these groups. They found that the PEP rates were lower in the group receiving rectally administered sodium diclofenac (8.5 %) compared to the group who received antibiotics (14.7 %); however, the difference was not significant (p=0.17), but the results indicate that prophylactic antibiotics could be questioned as a general routine in ERCP.
In conclusion, the evidence for using prophylactic antibiotics in every ERCP is limited, and the recommendation should be to use prophylactic antibiotics in the cases where the risk of incomplete drainage of the bile ducts is high or not achieved at all. The subject of prophylactic antibiotics is further discussed adjacent to Paper 1 later in this thesis, but in summary more randomized studies including modern antibiotics and updated endoscopic settings are required to settle the issue of how to use prophylactic antibiotics in ERCP.

1.6.5 Electrosurgical current

Blended diathermy should be preferred to pure-cut diathermy, especially in patients with an increased risk of bleeding. However, the type of diathermia does not affect the risk of developing PEP *(Verma, D., et al., 2007).*

1.6.6 Double guidewire cannulation

When access is only achieved to the pancreatic duct during an ERCP cannulation, it has been suggested that this guidewire should be left in place in the pancreatic duct and a second guidewire introduced to obtain access to the biliary tract. This issue has been subject to a recent Cochrane analysis by Tse and co-workers *(Tse, F., et al., 2016)*, who concluded that this technique increases the risk of PEP, but this could perhaps be managed by deployment of a pancreatic stent. However, the doublewire technique in

this meta-analysis was not shown to be superior to continued conventional cannulation or precut sphincterotomy, and its place among cannulation techniques is hereby questioned, but despite this, is still recommended in the ESGE-recommendations from 2016 *(Testoni, P. A., et al., 2016)* in combination with a prophylactic pancreatic stent.

1.6.7 Carbon dioxide (CO2)

Carbon dioxide is recommended by the ESGE *(Dumonceau, J. M., et al 2014)*, since it reduces post-ERCP procedural abdominal pain, but otherwise it does not affect the complication rates after ERCP.

1.6.8 Balloon dilatation

The ESGE *(Dumonceau, J. M., et al 2014)* does not recommend sphincter Oddi dilatation as a routine procedure instead of sphincterotomy, since it has a higher risk of developing PEP but could be used as an alternative in selected cases, for instance, when the risk of bleeding is increased. **Large balloon dilatation (<20 mm)** after sphincterotomy should be reserved for selected difficult common bile duct stones and seems to be associated with fewer bleedings but similar PEP rates as conventional stone extraction methods *(Feng, Y., et al., 2012).* However, much of the evidence in this issue seems to be collected from retrospective studies.

2. AIMS

2.1 Paper 1 (The role of antibiotic prophylaxis in routine ERCP)

Primary aims: To evaluate the effect of prophylactic antibiotics in routine ERCPs on overall complication rates.

Secondary aims: To study the effects of prophylactic antibiotics in routine ERCPs on different subgroups of complications with special regard to infectious and septic ones; also, to investigate the complication rates in relation to prophylactic antibiotics of the most common indications of ERCP.

2.2 Paper 2 (The impact of prophylactic pancreatic stenting on PEP rates)

Primary aims: To study if prophylactic pancreatic stents reduce complications (especially PEP rates), when the pancreatic duct is inadvertently cannulated during ERCP and to investigate what size of the pancreatic stent that has the best results.

Secondary aims: To evaluate the risk for complications (especially PEP) in ERCP, where the pancreatic duct has been inadvertently cannulated compared to where it was not.

2.3 Paper 3 (The HOUSE Classification: A novel ERCP complexity grading scale)

Primary aims: To establish a new ERCP complexity grading scale and validate it in relation to postoperative complication rates, especially PEP, and to introduce and implement a novel instrument for better predicting postoperative complications in ERCP.

Secondary aims: To validate the HOUSE classification in relation to the procedure time of the ERCP per HOUSE-class and thereby to introduce an instrument for time scheduling of ERCP procedures for a better opportunity in planning endoscopic clinical activity.

2.4 Paper 4 (Preoperative biliary drainage by plastic stents or SEMS)

Primary aims: The primary outcome measure of the study was to quantify the colony-forming units/ml (CFU/ml) of bacteria in bile harvested during surgical exploration of resectable periampullary tumors.

Secondary aims: To investigate the number of preoperative stent dysfunctions, grade the intraoperative macroscopic inflammation in the hepatico-duodenal ligament, study the occurrence of adverse events after endoscopic stenting, investigate the surgical difficulties during the pancreatic resection and finally to demonstrate the incidence of postoperative complications.

3. PATIENTS AND METHODS

3.1 Paper 1 (The role of antibiotic prophylaxis in routine ERCP)

Patients and methods

3.1.1 Study design

A nationwide population-based study was performed to study all patients undergoing ERCP from May 1, 2005 to June 30, 2013 who were registered in the national GallRiks Registry and to investigate the complication rates in relation to whether or not prophylactic antibiotics were given.

3.1.2 The GallRiks Registry database

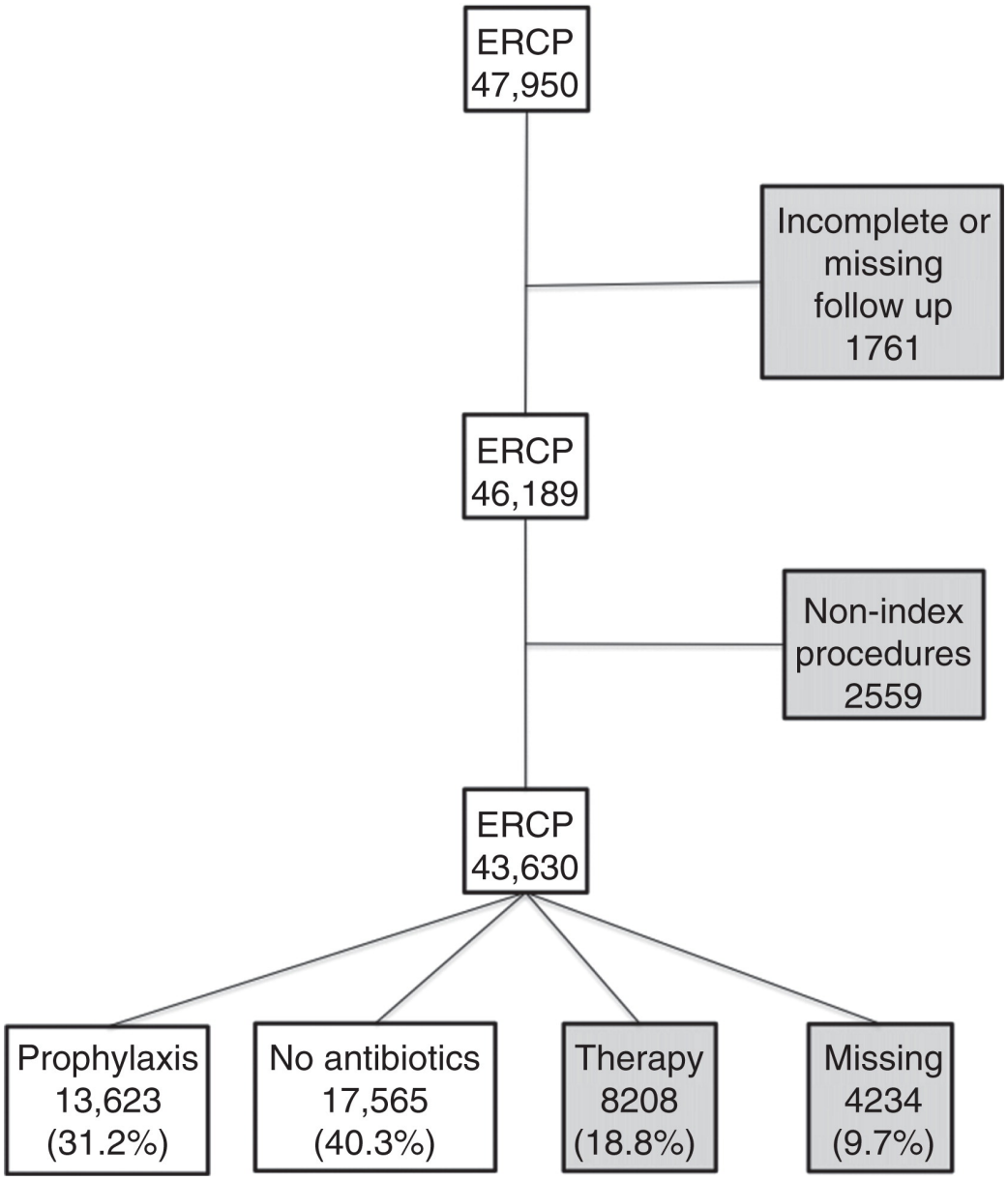
The register was established in 2005 by the Swedish Surgical Society and supported by the Swedish Board of Health and Welfare *(Enochsson, L., et al., 2013)*. The aim of the registry was to reach a complete coverage of registration of all gallstone surgery and ERCPs in Sweden, including the adverse events of the procedures performed. The registry is web-based, and all intraoperative complications of the ERCPs are registered online by the ERCP-performing doctors. The 30-day overall adverse effects are registered by a local coordinator who is a non-physician. Both general complications and more ERCP specific complications like pancreatitis, cholangitis, hemorrhage and perforation are registered. The administration of antibiotics adjacent to the ERCP is registered as therapy, prophylaxis or as no antibiotics administered at all, but the type of antibiotics and the doses are not available to register in GallRiks. Other compulsory data that are registered in the GallRiks database include patient characteristics, ERCP

indications, mode of admission, type of anesthesia, cannulation technique, diagnostic findings, therapeutic measures, procedure time and intraoperative complications.
The GallRiks Registry is continuously validated through independent external reviewers who compare the data in GallRiks to the patients´ medical record, and there has been an over 97 % concordance in these comparisons *(Enochsson, L., et al., 2010).* Since the start of the registry in 2005, there has been an increasing proportion of ERCPs included in the register; present coverage consists of about 90 % of all ERCPs performed in Sweden.

3.1.3 The Study Base

We studied the patients registered in the GallRiks database between May 1, 2005 and June 30, 2013 undergoing ERCP, but the procedures that were not index-ERCPs (the first ERCP procedure during that treatment episode) were excluded. Furthermore, patients with incomplete registrations in GallRiks or with ongoing antibiotic treatment were also excluded (Figure 2).

Figure 2. The profile of ERCP procedures included in the analysis in Paper 1; Prophylactic antibiotics in ERCP: *Olsson, G., et al. The Role of Prophylactic Antibiotics in Routine ERCP investigations. Scand Journ Gastroenterology, 2015; 50: 924-31.*



3.1.4 The variables and outcome measures

A postoperative ERCP complication was defined as any adverse event that caused a reoperation or any other reintervention, antibiotic treatment, blood transfusion or other causes that prolonged the hospital stay or the recovery of the patient. PEP was defined

according to the consensus definition of Cotton et al. *(Cotton, P. B., et al., 1991).* A hemorrhage was defined as bleeding that caused a significant decline in the patient´s hemoglobin level with a need for blood transfusions or requiring any reintervention. A postoperative infection was defined as symptoms requiring postoperative antibiotics. The variables studied were the use of antibiotics adjacent to the ERCP, where data were collected from the GallRiks Registry where antibiotics were registered as either prophylactic or therapeutic without any information in the registry, that is, on neither the type of antibiotics nor on the doses. The patients with therapeutic antibiotics were excluded from the study, since the aim of the trial was to investigate prophylactic antibiotics only.

3.1.5 Statistical analysis

JMP version 9.0.0 *(SAS Institute, Cary, NC, USA)* was used for the statistical analysis. Descriptive data were presented as mean or median values for continuous variables and as percentages for categorical variables. In the latter case, the Pearson´s Chi^2 was used for calculation unless the numbers included were low, in which case Fisher´s exact test was used instead.

To identify confounding factors, the variables influencing the postoperative complication risks were analyzed with multivariate logistic regression analysis, where each variable was introduced one by one and tested in univariate and multivariate models according to the purposeful selection of Hosmer et al. *(Hosmer, D. W., et al., 1978).* The models were tested for multicollinearity and modification effect and then assessed using the Homer-Lemeshow goodness-of-fit test. The effects of the variables are presented as odds ratios (OR) with 95 % confidence intervals (CI). The level of statistical significance was defined as $p \leq 0.05$.

Age and procedure time were treated as continuous variables in the model, although they were then dichotomized (≤ or >70 years, ≤30 or > 30 minutes). ASA classification was also dichotomized (ASA 1-2/ASA 3-4) as well as cannulation, use of antibiotics and sphincterotomy (yes or no). Finally, hospital volume of ERCP was dichotomized into high and low volumes.

3.2 Paper 2 (The impact of prophylactic pancreatic stenting on PEP rates)

Patients and methods

3.2.1 Study design

A nationwide population-based study was performed to study all patients undergoing ERCP from January 1, 2006 to December 31, 2014 who were registered in the national GallRiks Registry. This study was carried out to investigate the PEP rates in relation to whether or not, and what type of, prophylactic pancreatic stent that had been deployed.

3.2.2 The GallRiks Registry database

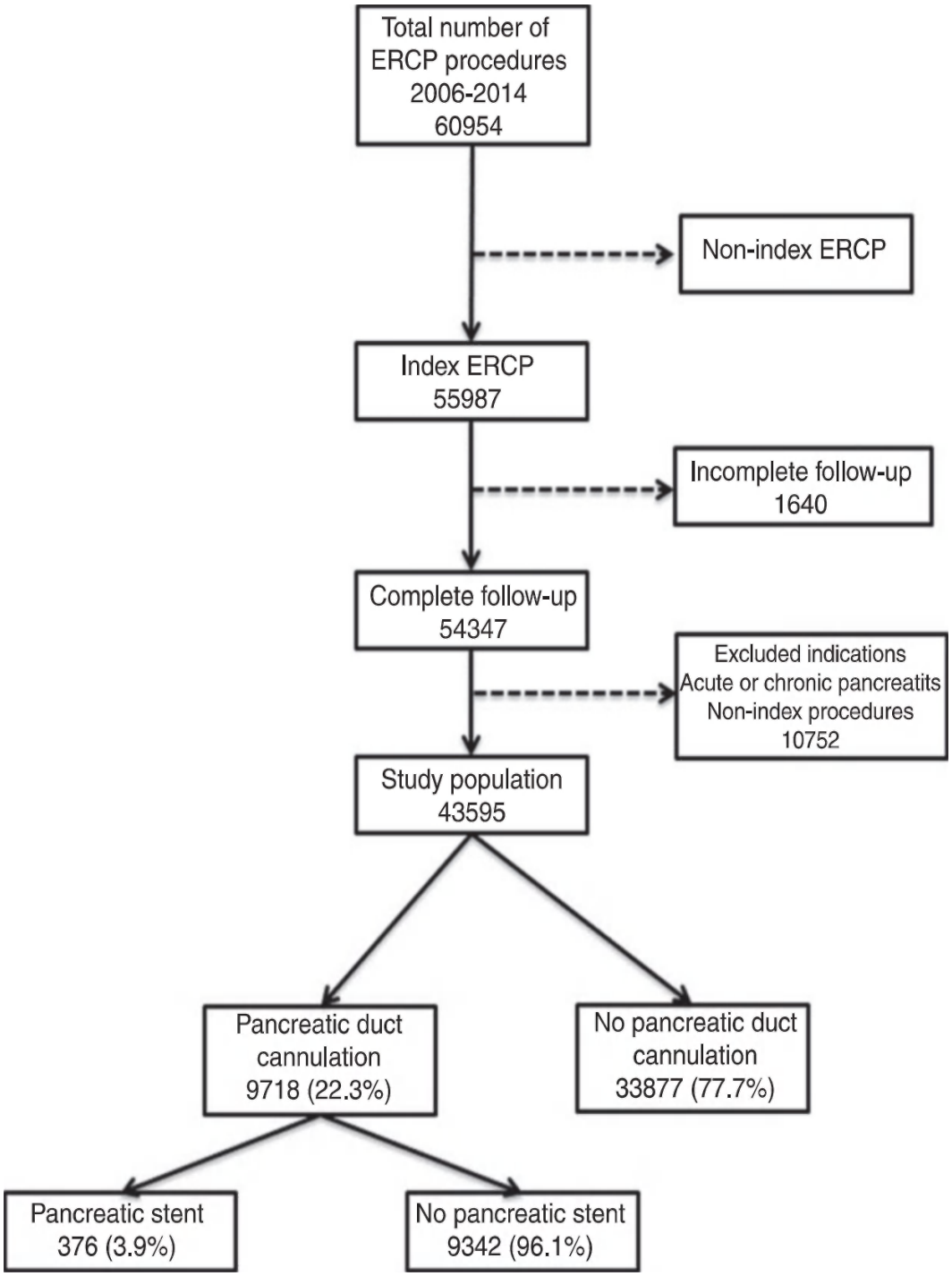
The Swedish National Registry for Gallstone Surgery and ERCP (GallRiks) was established in May 1, 2005 as a validated registry of cholecystectomies and ERCP procedures *(Enochsson, L., et al., 2013, Rystedt, J., et al., 2014)*. The aim of the registry was to obtain a complete database including demographics and patient characteristics, indication and treatment methods as well as outcome using an online registration platform. For patients undergoing an ERCP, procedure-related information includes bile and/or pancreatic duct cannulation, whether sphincterotomy was performed and any additional diagnostic or therapeutic procedures. Intraprocedural adverse events are

registered by the endoscopists performing the ERCPs. At the 30-day follow-up, all medical records are reviewed, and post-procedural adverse events are reported online in the registry by a local non-physician coordinator appointed at the respective units. GallRiks includes data from almost all Swedish hospitals performing ERCP. Matching GallRiks data with the Swedish National Patient Registry in 2014 showed that 88 % of performed ERCP procedures in Sweden at that stage were registered in GallRiks. The data are regularly validated by an independent audit group that compares register data to in-patient records. There was a complete match between registry data and patient medical records in 98 % of patients with a 100 % concordance for bile duct injuries *(Rystedt, J., et al., 2014).*

3.2.3 The Study-base

All patients undergoing ERCP between January 1, 2006 and December 31, 2014 were enrolled for the study, but the ERCP procedures that were not index-ERCPs (i.e., the first ERCP during the treatment episode, within 30 days) and those with missing data or incomplete follow-ups were excluded from the study. Furthermore, only patients for whom the intention, as documented by the indication for the investigation, was a selective cannulation of the bile duct (i.e. no intention to cannulate the pancreatic duct) were included (Figure 3).

Figure 3: The profile of endoscopic retrograde cholangiopancreatography (ERCP) procedures included in the analysis of Paper 2: *Olsson, G., et al., The impact of prophylactic pancreatic stenting on post-ERCP pancreatitis: A nationwide, register-based study. UEG-Journal 2017; 5(1): 111-18*



3.2.4 The variables and outcome measures

The outcomes studied were general intra- and post-procedural adverse events and specifically ERCP-associated adverse events like cholangitis, pancreatitis, perforation and bleeding. A postoperative ERCP complication was defined as any adverse event that caused a reoperation or any other reintervention, antibiotic treatment, blood transfusion or other causes that prolonged the hospital stay or the recovery of the patient. A PEP was defined according to the consensus definition by Cotton et al. *(Cotton, P. B., et al., 1991),* and a hemorrhage was defined as bleeding that caused a significant decline in the patient´s hemoglobin level with a need for a transfusion or any reintervention. A postoperative infection was defined as the patient requiring postoperative antibiotics due to symptoms interpreted as infectious. Intraprocedural adverse events were defined as bleeding, extravasation of contrast, perforation or any other reason for the ERCP being prematurely terminated.

Postprocedural adverse events were defined as any of the abovementioned complications during the 30-day follow-up period that required some form of medical or surgical intervention. The variables studied were firstly the insertion of a pancreatic stent (PS) and secondly pancreatic cannulation, which was defined as deep or superficial cannulation of the pancreatic duct with subsequent contrast injection.

3.2.5 Statistical analysis

Statistical analysis was performed using JMP 9.0.0 *(SAS, Cary, NC, USA)*. Comparisons of patient and procedure characteristics were presented in contingency tables with pairwise differences analyzed with Pearson's Chi^2 test and presented as *p* values. The association between pancreatic duct cannulation and the risk of adverse events, as defined above, were analyzed using multivariable logistic regression modelling.

Variables that were statistically significant in univariate analysis were included in the multivariate model as described by Hosmer et al *(Hosmer, D. W., et al., 1978).* In the multivariate analysis, the outcome was adjusted for age (dichotomized into more or less than 70 years), gender, comorbidity (dichotomized into ASA score of 1-2 and ASA ≥3), urgent or elective procedures, indication and previous sphincterotomy. Similar regression modeling was used on the subgroup of patients with a pancreatic duct cannulation, analyzing adverse effects depending on whether or not the placement of a pancreatic stent was made. In a final sub-analysis, patients receiving PS were dichotomized into two groups, depending on whether the total PS diameter was >5 Fr or ≤5 Fr as well as dichotomized into two groups depending on the length of the single PS (>5cm or ≤5cm) and analyzed for adverse events. The models were tested for multicollinearity and modification effect and were finally assessed for goodness of fit. The effects of the analyzed variables were presented as odds ratios (OR) for adverse events with 95 % confidence intervals (CI).

3.3 Paper 3 (The HOUSE Classification: A novel ERCP complexity grading scale)

Patients and methods

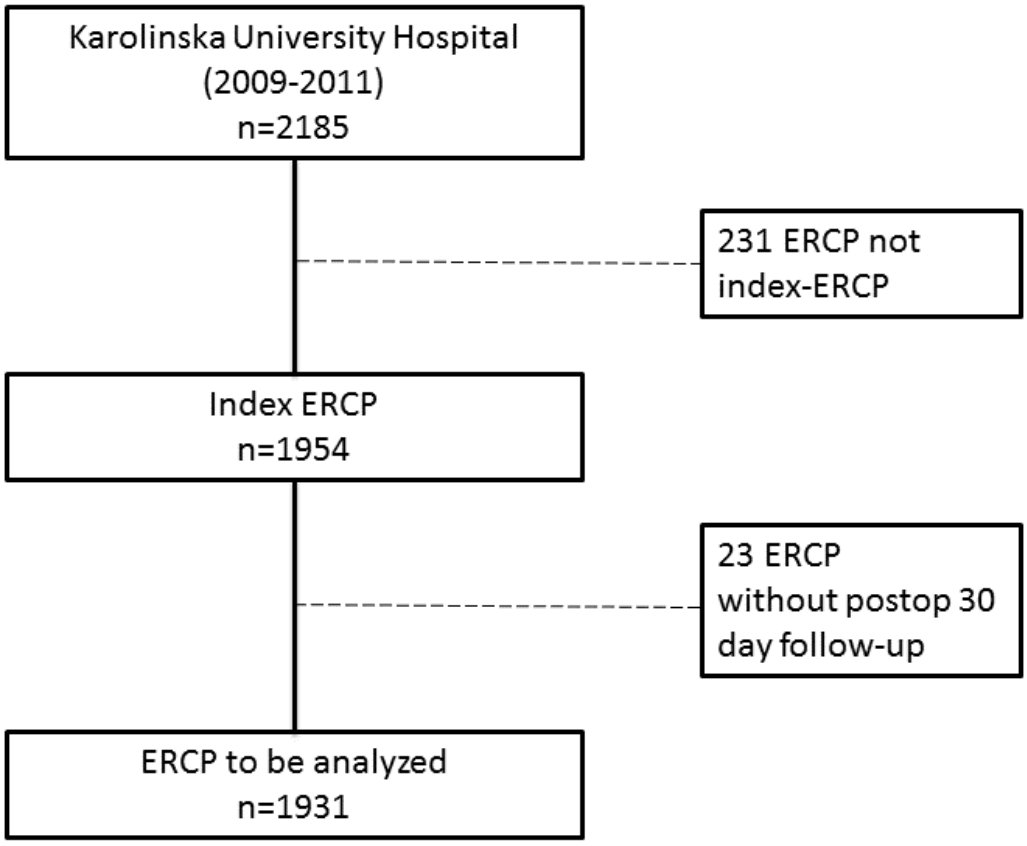
3.3.1 Design and data collection

Data were collected retrospectively from reviews of the medical records of patients being subject to ERCPs at Karolinska University Hospital, Huddinge, between 2009 and 2011. Data from these cohorts of patients representing three years of ERCP procedures at Karolinska University Hospital, Huddinge, Stockholm, Sweden, regarding the

complexity of the ERCP procedure, were gathered and divided into three classes called HOUSE classes 1-3.

Furthermore, the procedure time, the general postoperative complications and the PEP rates of the ERCP procedures were noted. The GallRiks Registry of the patients included was also investigated with special regard to the postoperative complication rates in general as well as to the PEP rates specifically. Details of the GallRiks Registry are described above in Paper 1 (The role of antibiotic prophylaxis in routine ERCP) and Paper 2 (The impact of prophylactic pancreatic stenting on PEP)

Figure 4. A flow chart depicting the respective ERCP procedures included in the analyses (HOUSE Classification): *Olsson G., et al., The HOUSE-Classification; a novel ERCP complexity grading scale. BMC Gastroenterology 2017; 17:38*



3.3.2 The establishment of the HOUSE classification and the division of ERCP procedures into three different classes in relation to their complexity

Initially, the HOUSE classification was developed and launched into clinical practice to gain financial reimbursement and control of the increasing costs for endoscopic devices used as well as the prolonged procedure times required to complete the expanding complexity of ERCP examinations done at the Karolinska University Hospital, Huddinge, Stockholm, Sweden, which over time has evolved into a national tertiary-referral center for advanced endoscopy in Sweden. Concomitantly, there was a continuous demand for

an establishment of a more accurate system for comparisons between different centers, both regarding results as well as post-procedural complication rates. The well-merited opinion was that with more complex procedures, the risk became greater that the results were marred by higher complication rates. The higher complexity of the case-mix of the procedures performed at Karolinska University Hospital was also, apart from the risk of higher complication rates, assumed to lead to higher costs per procedure, and there was a desire from the research group to gain economical control over this development.

The original database was scored in classes based on the perceived complexity of each procedure and classified into three groups, where group one represented the least complex procedures and group three represented the most complex ones. One of the aims of the grading was that HOUSE class 1 procedures would represent the least complex routine procedures as represented by those being performed at every hospital performing ERCP in Sweden (e.g., extraction of common bile duct stones, relief of obstructive jaundice due to periampullary tumors, intraoperative rendezvous ERCP procedures). The HOUSE class 2 represents the technically more advanced procedures mainly performed at the county hospitals, such as ERCP for intrahepatic stones, multiple metal and plastic stenting and ERCP for primary sclerosing cholangitits. The HOUSE class 3 represents ERCP procedures that demand extra resources like intraductal cholangioscopy double-balloon ERCP for Roux-en-Y operated patients or confocal endoscopy, which are all procedures that are performed at the tertiary referral-centers.

The database of the HOUSE classification was then compared with corresponding data from the GallRiks´ database concerning complications in general and pancreatitis rates in particular (Table 10).

The classification is referred to as the HOUSE classification, which is an abbreviation of the first letter of the name of the hospital (Huddinge) followed by the first letters of the creators' names (Olsson, Urban, Swahn, and Enochsson). The outcomes of the different ERCP procedures were also classified according to the established classification systems for ERCP procedures, i.e., the Cotton complexity grading of endoscopic procedures (see Table 3) *(Cotton, P. B., et al., 2011).*

Table 10. The HOUSE classification

The HOUSE classification	ERCP procedures
HOUSE 1	Diagnostic ERCP, EST, CBDS, Single Stent, Brush cytology, Intraoperative rendezvous ERCP
HOUSE 2	Intrahepatic stone, Multiple stents Pancreatic ERCP, PSC or liver TX, Intrahepatic interventions, Prophylactic pancreatic stent, "Caged" papilla, ERCP with ESWL
HOUSE 3	Pancreatic sphincterotomy and lithotripsy, Spy-Glass, Mother-Baby Scopy, EHL, Multiple pancreatic stents, Papillectomy, Confocal endoscopy, PTC- or EUS-rendezvous. Billroth-2 op, Roux-en Y, Whipple op, , Gastric-Bypass-op, ERCP via enteroscopy.

3.3.3 Variables and outcomes

The outcomes studied were general intra- and post-procedural adverse events and specifically PEP. A postoperative ERCP complication was defined as any adverse event

that caused a reoperation or any other reintervention, antibiotic treatment, blood transfusion or other causes that prolonged the hospital stay or the recovery of the patient. PEP was defined according to the consensus definition by Cotton *(Cotton, P. B., et al., 1991).*

Another outcome that was studied was the procedure time (minutes) of the ERCP; this represented a measurement of the resources required for that very specific investigation.

Furthermore, a final outcome that was studied was the cannulation success rate of each ERCP procedure; this was used as a surrogate marker for how difficult a certain investigation would be.

3.3.4 Statistical analysis: Descriptive data for cannulation success rates, patients suffering complications (or not) and procedure times were displayed using mean for continuous variables or percentages for categorical variables. General postoperative complications and ERCP specific complications (cholangitis, perforation, pancreatitis and postoperative bleeding) were calculated within each HOUSE class and compared using Pearson´s Chi^2 test with HOUSE class 1 used as a reference group. Differences in mean procedure times between the different HOUSE classes were analyzed using Student´s t-test. A p-value ≤ 0.05 was regarded as significant. Statistical analyses were carried out using JMP® version 12.1.0 (64-bit) *(SAS Institute, Cary, NC, USA)*.

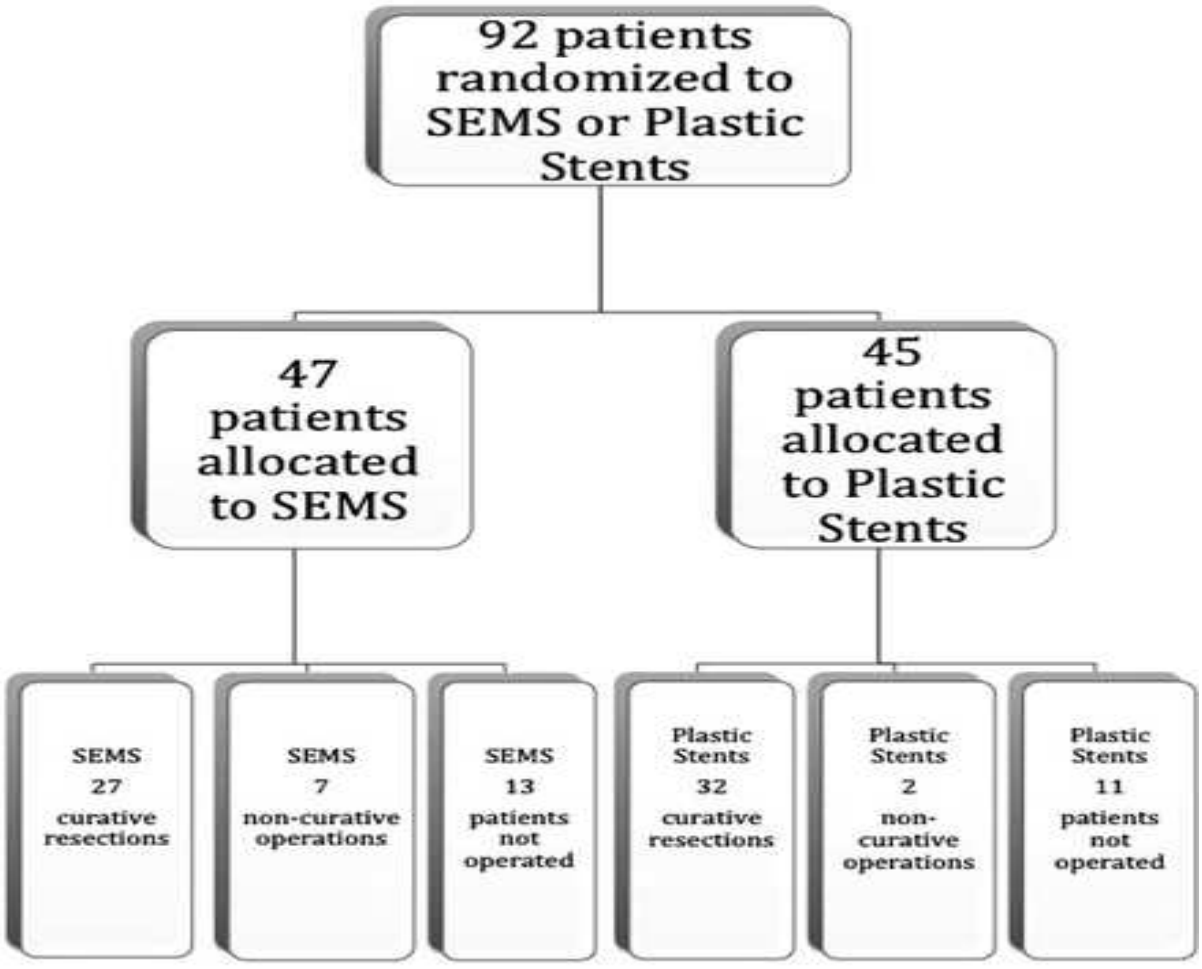
3.4 Paper 4 (Preoperative biliary drainage by plastic stents or SEMS)

Patients and methods

3.4.1 Design and data collection

A prospective, randomized controlled trial was performed including patients with extrahepatically induced jaundice (bilirubin ≥49) caused by periampullary tumors, which were presumed to be resectable at the time of the ERCP-procedure. Those patients were, after a successful cannulation of the bile duct, randomized to either receive a self-expandable metal stent (SEMS) or a plastic stent. An unsuccessful cannulation or a previous stenting were exclusion criteria as well as an inoperable patient or an unresectable tumor found during the preoperative investigational work-up before the ERCP. Tumors found to be irresectable after the ERCP remained in the study (intention to treat analysis, ITT).

Figure 5. Flow chart depicting the allocation of presumably resectable periampullary tumors to respective study group (SEMS vs plastic stents). *Olsson, G., et al., Preoperative biliary drainage by plastic or self-expandable metal stents in patients with periampullary tumors: results of a randomized clinical study. Endoscopy International Open, 2017.*



The primary outcome of the study was the amount of bacteria (colony-forming units/ml, CFU/ml) found at the operation in bile collected from the bile duct and/or the gallbladder during the pancreatico-duodenectomy. Secondary outcomes were preoperative adverse events, such as stent dysfunction or stent exchange, perioperative technical difficulties as judged by the operating surgeon in creating the anastomoses or the grade of inflammation in the hepato-duodenal ligament during the operation and also measured more objectively through operational time and perioperative blood loss. Other secondary outcomes were the histopathological grade of inflammation in the bile duct and the grade of sinus histiocytosis in lymph glandulae in the hepato-duodenal ligament harvested during the operation as a marker of the foreign body reaction caused by the preoperatively inserted stent. Final secondary outcomes studied were the rates of postoperative complications after the pancreatico-duodenectomy and time in the ICU and hospital.

3.4.2 Logistic protocol

After informed consent was given before the ERCP procedure, the patients were randomized in blocks of ten patients to receive a SEMS or a plastic stent. The patients were then discussed in multi-disciplinary conferences and those found resectable and operable were offered pancreatico-duodenectomy within six weeks. Patients with locally advanced borderline tumors were offered neo-adjuvant oncological therapy, and those responding were subsequently operated later than six weeks after the inclusion in the study.

Before the initial endoscopy and before the pancreatico-duodenectomy, blood tests (ASAT, ALAT, ALP, bilirubin, white blood cell count, CRP) were sampled to monitor liver function and grade of inflammation.

Cholangitis and cholecystitis were defined according to the Tokyo guidelines *(Takada, T., et al., 2013)* and pancreatitis according to the definition by Cotton et al. *(Cotton, P. B., et al., 1991).*

A standardized protocol was completed adjacent to the ERCP with clinical and laboratory data as well as information of the tumor characteristics.

3.4.3 Endoscopic procedure and stent insertion

After cannulation of the bile duct, the patient was randomized to achieve either a covered SEMS (*Permalume silicone interior covered platinol stent*, *Boston Scientific, Natick, MA, USA*) or a conventional plastic stent. The endoscopist decided what size of SEMS to use depending on the clinical findings (e.g., length of stricture), but most commonly a 6-cm SEMS was used (n=37) with a diameter of 10 mm when fully expanded, whereas the plastic stents that were mostly used were 10 Fr in diameter and 7 cm in length (n=35).

3.4.4 Surgical procedure

The patients found operable/resectable were offered a standard pancreatico-duodenectomy, where bile was sampled at the beginning of the operation for bacterial cultures from the bile duct and/or the gallbladder and was transferred to a culture media to allow for bacteria growth. The amount of bacteria in the bile was measured in colony-forming units/ml (CFU/ml). The surgical findings were classified by the surgeon in a three-level scale in an attempt to quantify how difficult it was to extract the stent from the bile duct, to dissect the hepato-duodenal ligament (grade of inflammation) and to create the anastomoses between the gut, stomach, pancreas and bile duct. Finally, a ring of the bile duct from the transection line of the resection was sent for

histopathological examination to quantify the grade of cholangitis (mild, moderate or severe) in the bile duct caused by the stent; a lymph node was also harvested from the hepato-duodenal ligament and investigated for sinus histiocytosis, which is a marker of foreign body reaction that represents another measurement of the grade of inflammation caused by the stent. The patients were postoperatively monitored in an ICU according to standard protocols until they were ready to be transferred to a surgical ward. Postoperative complications were registered and complications like pancreatic fistula were defined according to the ISGPF criteria *(Bassi, C., et al., 2005)* and delayed gastric emptying according to ISGPS *(Wente, M. N., et al., 2007).* All complications were recorded and defined according to the Clavien Dindo classification *(Dindo, D., et al., 2004)*. The patients were followed up 4-6 weeks after the operation (after discharge from the hospital) with an outpatient appointment.

3.4.5 Sample size estimation

The required number of enrolled patients was estimated to be able to detect a 30 % lower CFU/ml count in the SEMS group with a probability of 95 % and a power of 80 %. In order to achieve this, a minimum of 60 matched patients needed to be surgically explored and have bile samples collected. Thus, given the expected number of withdrawals due to the findings meeting the exclusion criteria during the subsequent preoperative workup, at least 90 patients had to be randomized.

3.4.6 Statistical analysis

The data were analyzed using the statistical software JMP 9.0.0 *(SAS Institute, Cary, NC, USA)*. The demographics and clinical characteristics, endoscopic adverse events, per-

and postoperative findings and complications are reported as means or medians and ranges or as number of cases and percentage of the total. The results of the bacterial cultures are reported as medians and interquartile ranges (IQR) as well as total sum of CFU/ml across all cases. Categorical data were tested with Pearson´s Chi^2 test or Fisher's exact test when appropriate. When calculating the differences between means, the Student's t-test was used for data with a normal distribution. For numerical values not normally distributed, the Wilcoxon Rank-Sum Test was used. P-values <0.05 were considered significant.

4. RESULTS

4.1 Paper 1 (The role of antibiotic prophylaxis in routine ERCP)

Results

4.1.1 Basic characteristics

There were 47,950 ERCP procedures performed between May 1, 2005 and June 30, 2013 registered in the GallRiks Registry. After exclusion of those procedures with incomplete registrations (n=5,995), those with on-going antibiotic therapy (n=8,208) and those ERCPs not being index procedures (n=2,559), 31,188 ERCP procedures remained for the study regarding antibiotic prophylaxis. Of these ERCP procedures, 13,623 (44 %) received prophylactic antibiotics, and 17,565 (56 %) did not. These two groups were similar concerning sex distribution, ASA classification and proportions of procedures performed urgently or electively. However, the patients receiving prophylactic antibiotics were 1.5 years younger than the ones not given prophylaxis (65.9 vs 67.4 years, $p<0.0001$). For details, see Table 1 in Paper 1.

4.1.2 Risk factors for adverse events in ERCP

There were no differences in postoperative adverse events, ASA class, hospital volume or gender; also, the complication rates were not affected by whether or not the bile duct was cannulated or if a sphincterotomy was performed during the ERCP.

The only indication of the ERCP that demonstrated an increased OR for adverse events in the multivariate analysis was jaundice (OR 1.11, 95 % CI 1.02-1.21). The highest elevation of the OR for complications was seen in the ERCP procedures lasting for more than 30 minutes (OR 1.54, 95 % CI 1.43-1.65), where the complication rate rose from

10.7 % to 15.8 % after 30 minutes and those where the pancreatic duct was cannulated (OR 1.34, 95 % CI 1.24-1.44) where the adverse events increased from 12.0 % to 16.4 %. Patient age below 70 years elevated the OR for adverse advents with 26 % (OR 1.26, 95 % CI 1.18-1.35), and the OR reduction for adverse events when antibiotics were given prophylactically was also 26 % (OR 0.74, CI 0.69-0.79) when the confounding factors found in the multivariate analysis had been compensated for. For details, see Table 2 in Paper 1.

4.1.3 The effect of prophylactic antibiotics in ERCP generally

The overall reduction of adverse events after the ERCP procedure was 2.6 % (from 14.2 % to 11.6 %, $p<0.0001$) if prophylactic antibiotics were administered, which corresponds to a 26 % OR reduction of complications after potential confounders have been compensated for in the multivariate analysis.

4.1.4 The effect of prophylactic antibiotics in ERCP in the subgroup of the three most common ERCP indications

To achieve a more representative picture of the ERCP procedures performed at an average mid-volume hospital, we performed a subgroup analysis of the three most common indications of ERCP (i.e., CBDS, malignancy and jaundice), which contained 21,893 ERCP procedures.

Here, we found a similar reduction in overall adverse events (OR 0.76, 95 % CI 0.70-0.82) if antibiotics were given, and there also was a significant reduction in septic complications (OR 0.85, 95 % CI 0.73-1.00) in the prophylaxis group. For details, see Table 3 in Paper 1.

However, the most pronounced reduction of complications was seen in the group when the indication for the ERCP was jaundice, where the overall adverse events were reduced with 32 % (OR 0.68, 95 % CI 0.60-0.78) in the multivariate analysis, corresponding to a 3.8 % complication reduction (15.3 % vs 11.5 %) in absolute figures, and the septic complications were reduced with 24 % (OR 0.76, 95 % CI 0.58-0.97) from 3.6 % to 2.9 %.

We also found a general complication reduction when prophylactic antibiotics were given in the group where CBDS was the indication of the ERCP. This was not as enhanced as in the jaundiced group but more in line with the odds reduction seen in the general study population (OR 0.77, 95 % CI 0.68-0.87). For details, see Table 4 in Paper 1.

4.1.5 Comments

The main finding of this paper was that we found a significant reduction of 2.6 % (14.2 % vs 11.6 %) in overall adverse effects if prophylactic antibiotics were administered adjacent to the ERCP procedure. However, this figure must be put in relation to the negative side effects of antibiotics (e.g., the development of antibiotic resistance or side effects for the patients). Although an OR reduction for adverse events of 26 % was demonstrated, if antibiotic prophylaxis was given in conjunction with the ERCP, the number of patients still needed treat to avoid one complication was 38, which cannot justify a policy of giving every routine ERCP antibiotics prophylactically. These findings are in line with a previous meta-analysis by Bai from 2009 *(Bai, Y., et al., 2009)*, which does not recommend prophylactic antibiotics in general.

Another finding of our study is that patients with jaundice seem to have a special beneficial effect from prophylactic antibiotics with an OR reduction of 32 % when

antibiotics are given in this group with a 24 % OR reduction on the septic complications. This corresponds well to the meta-analysis by Brand from 2010 *(Brand, M., et al., 2010)*, which states that prophylactic antibiotics seem to reduce cholangitis, especially in the patients where drainage of the bile duct cannot be completely achieved and suggests that prophylactic antibiotics could be reserved for these patients. The problem is that this situation of undrained bile ducts cannot be anticipated prior to the ERCP when the antibiotics should be administrated, and perhaps prophylactic antibiotics could be given to these patients with a higher risk of unsuccessful complete drainage, such as patients with hilar strictures or primary sclerosing cholangitis.

A major problem of the findings of the previous meta-analyses on the subject of prophylactic antibiotics in ERCP is that the number of randomized studies is limited *(Brandes, J. W., et al. 1981, Byl, B., et al., 1995, Llach, J., et al., 2006, Lorenz, R., et al., 1996, Niederau, C., et al., 1994, Raty, S., et al., 2001, Sauter, G., et al., 1990, Spicak, J., et al., 2001, van den Hazel, S. J., et al., 1996)*. Most of the studies were small, the results conflicting and most of the studies were from the 1990s with the latest study conducted in 2006 *(Llach, J., et al., 2006)*. Therefore, in conclusion, more randomized studies are needed that include modern antibiotics and modern endoscopic settings to resolve the issue of when prophylactic antibiotics should be administered in ERCP.

One strength of our study is the low risk of selection bias, since it is based on data from a national registry, representing all types of endoscopic centers performing ERCP with different volumes of patients and endoscopists with different experiences. Additionally, the procedures were undertaken on a great variety of patients with various different indications for the ERCP procedure – from common, less complicated ones to rare, complex ERCPs. The risk of random error is also small in a study of this size, as is the

risk of systematic errors since the register includes 90 % of all ERCPs performed in Sweden.

Another strength of the study is the GallRiks Registry´s good validity with a match with the patient records of more than 97 % *(Enochsson, L., et al., 2013, Rystedt, J., et al., 2014),* minimizing the risk for misclassification.

There also seems to be a good correlation regarding the basic characteristics between the groups receiving prophylactic antibiotics compared to the groups that were not given prophylactic antibiotics, regarding gender, ASA and age, although the age differed slightly between the groups (65.9 vs 67.4 years, $p<0.0001$). Parameters are often significantly different in large, national, register-based studies like this (mass significance), but when looking at its clinical significance, the difference between 66 years and 67.5 years probably has a very modest effect on the outcome studied.

We also identified other risk factors for ERCP related adverse events in our study. Many of them were known from previous studies *(Freeman, M. L., et al., 2001, Freeman, M. L., et al., 1996)* (e.g., the time of the ERCP procedure [>30 minutes], which increases the risk for complications). Of course, it is not the time itself that affects the complication rates but the things being performed during the longer procedure. It is probable that these 30 minutes contain multiple cannulation attempts, guidewire passages to the pancreatic duct and an over-representation of more precut sphincterotomies in this group, where time represents a surrogate marker for other events that represent the real risk factors for postoperative complications.

Lower age (<70 years) is another factor that was found to increase the risk of complications in our study, which is an opposite phenomena compared to many other surgical interventions. We interpret this by stating that younger people have a more

viable pancreas, thereby they are more reactive when being subject to an ERCP and have a higher risk for developing a PEP.

Another well-known risk factor in ERCP, which we also confirmed in this study, is cannulation of the pancreatic duct *(Freeman, M. L., et al., 2001).* We also noticed a slightly elevated complication risk in patients with jaundice prior to the ERCP, but we did not manage to demonstrate any differences in adverse events whether or not the bile duct was cannulated. We also could not identify any differences in complications depending on case volume of the center performing the ERCPs, which speculatively could be explained because larger centers have more endoscopists, which reduces the number of investigations per endoscopist; also, larger centers have more trainees, which may increase the risk of complications, and larger centers also handle more complex cases, which may result in more adverse events.

There are also weaknesses of register-based studies. Since they are not randomized, there is always a risk for confounding factors, and there might be factors that are unknown and thereby cannot have been compensated for in the multivariate regression analysis. There is also a risk of case-mixing within the study population—for example, the endoscopist may be more prone to give antibiotics if he suspects the ERCP to be more complicated. A final consideration is the long inclusion period of the study (2005-2013). This time period encompasses technical development and the introduction of new antibiotics, and these factors must also be taken into account when interpreting the results of the study.

In conclusion, our study shows that prophylactic antibiotics reduce the risk of adverse events by 2.6 %, but this is not sufficient to make a general recommendation

for their use in every ERCP, since the NNT (38 patients) is too high to justify the potential side effects induced by antibiotics and the risks of developing bacterial resistance to avoid one single complication in the 38 patients who need to be treated.
More prospective, randomized, controlled trials with modern antibiotics in modern endoscopic settings are needed, especially in the group of patients where complete biliary drainage cannot be achieved to ultimately define the role of prophylactic antibiotics in ERCP.

4.2 Paper 2 (The impact of prophylactic pancreatic stenting on PEP-rates)

Results

4.2.1 Basic characteristics

Between January 1, 2006 and December 31, 2014, a total of 60,954 ERCP procedures were registered in the GallRiks Registry. Those procedures that were not index procedures (i.e., first ERCP during that treatment episode within 30 days) or that had an incomplete registration were excluded, leaving 54,437 ERCPs in the study group. Since the intention of the study was to evaluate the effect of prophylactically deployed pancreatic stents, we further excluded those procedures where the indication was pancreatitis, assuming that the intention of these procedures was to purposefully cannulate the pancreatic duct. The remaining procedures (n=43,595) formed the study base, in which the effects of pancreatic cannulation and pancreatic stent deployment were investigated. The most common indications for the ERCP procedures were the following: suspected common bile duct stone (n=16,493, 38 %), obstructive jaundice

(n=11,802, 27 %), malignancy (n=5,534, 13 %), cholangitis (n=4,567, 10 %) and stent dysfunction (n=2,803, 6 %). For details see Table 1 in Paper 2.

Pancreatic cannulation occurred in 22.3 % (n=9,718) of the study base, which was interpreted as accidental, as the indication was a disease in the biliary tract, as mentioned above. 70 % of the procedures were performed acutely and 30 % electively, and there was a slight female dominance among those patients (53 %); there were also slightly more patients over 70 years than under (54 %). For details, see Table 1 in Paper 2.

Of the patients who had a pancreatic cannulation, only 3.9 % (n=376) received a pancreatic stent, presumably prophylactically, whereas 96.1 % did not (n=9,342) receive a pancreatic stent.

4.2.2 The effect on adverse events of an accidental pancreatic cannulation

If the pancreatic duct was not cannulated during the ERCP procedure, the risk of pancreatitis was 2.6 %, but this increased to 7.9 % ($p<0.0001$) if it was cannulated, which corresponds to a three-fold increased OR (OR 3.07, 95 % CI 2.77-3.40) in the multivariate analysis, where the confounding factors of age, gender, comorbidity, indication, urgent procedure and previous sphincterotomy were compensated for. Both the intraoperative (2.5 % vs 4.1 %, $p<0.0001$) and postoperative (13.1 % vs 16.9 %, $p<0.0001$) adverse events were increased when the pancreatic duct was cannulated, which corresponds to a 52 % (OR 1.52, 95 % CI 1.35-1.73) and 44 % (OR 1.44, 95 % CI 1.35-1.54) increase of the OR in the multivariate analysis, respectively. Finally, a pancreatic cannulation was not associated with an increased risk of perioperative hemorrhage during the ERCP (1.4 % vs 1.2 %, $p=0.16$). For more details, see Table 2 in Paper 2.

4.2.3 The effect on adverse events when inserting a prophylactic pancreatic stent

There were no differences in postoperative complications (16.5 % vs 16.9 %, p=0.82), risk of pancreatitis (8.0 % vs 7.9 %, p=0.93) or risk of bleeding (1.6 % vs 1.4 %, p=0.71) when a pancreas stent was used after a pancreatic cannulation had occurred during the ERCP procedure. However, strangely enough, there was an association to intraoperative adverse events; that is, there was a higher risk for perioperative complications in the pancreatic stent group (8.2 % vs 4.0 %, p<0.0001) compared to the group not receiving a pancreatic stent, corresponding to a more than two-fold increase of the OR (OR 2.28, 95 % CI 1.52-3.31), which is further discussed in the comments in the next chapter in this thesis and in Paper 2.

4.2.4 The effect on adverse events of different sizes and lengths of prophylactic pancreatic stents

We also compared different sizes of pancreatic stents (≤5Fr (n=241) vs >5 Fr (n=135)) regarding adverse events and found no significant differences in overall intra- and postoperative complications; there was also no difference in the risk of intraoperative hemorrhage when a pancreatic stent was inserted. However, there was an almost four-fold elevation of the OR for PEP when a pancreatic stent with a diameter ≤5Fr was used compared to using stents with a diameter of >5Fr (OR 3.58, 95 % CI 1.40-11.07). PEP occurred in 10.4 % in the ≤5Fr-stent group compared to only 3.7 % in the >5Fr-stent group (p=0.02). By adding the parameter length of the pancreatic stent (≤5cm vs >5cm) to the study, the risk of pancreatitis was decreased further in favor of the longer and thicker stents, where the PEP risk was only 1.4 % compared to 9.4 % (p=0.025) if the

stents were both ≤5cm and ≤5Fr. For further details of these results, please see Tables 4 and 5 in Paper 2.

4.2.5 Comments

One important finding in this study was that we demonstrated a more than three-fold increase in the OR (OR 3.07) for developing PEP if the pancreatic duct had been cannulated during the ERCP procedure (7.9 % vs 2.6 %, p<0.0001), which is in line with previous studies *(Cotton, P. B., et al., 2009, Cotton, P. B., et al., 1991)*. The other major finding of the study was a decreased risk of developing PEP if larger diameter pancreatic stents were used (3.7 %, >5Fr-stent) compared to thinner ones (10.4 %, ≤5Fr-stent, p=0.02). Additionally, the PEP-risk was further reduced (to 1.4 %) if a longer stent was used (>5 cm) in combination with the larger diameter (>5Fr). However, these findings should be interpreted with caution, since the number of patients actually receiving a pancreatic stent was very low (n=376) compared to the complete study base, as the vast majority of cases were excluded, and those uncertainties are reflected in the very wide confidence intervals received. However, it is important to generate hypotheses of the type of prophylactic pancreatic stents that should be preferred, since previous studies have come to opposite suggestions for which stents to use. For instance, in a randomized controlled trial, Chahal and co-workers *(Chahal, P., et al., 2009)* preferred short, 5-Fr stents to long, 3-Fr stents because the former had fewer adverse effects and the longer 3-Fr stents more often needed a repeat ERCP for stent extraction. The problem with this study was that both the lengths and the diameters of the stents varied between the groups, making it difficult to interpret the actual cause of the differences (i.e., the length or the diameter of the stent).

On the other hand, Pakh and co-workers *(Pahk, A., et al., 2011)* could not find any differences in complication rates between 4-Fr and 5-Fr stents in a randomized controlled study, whereas the opposite was found by Rashdan *(Rashdan, A., et al., 2004)*, who claimed that thinner stents were superior to thicker ones.

All studies were reviewed in a meta-analysis by Afghani *(Afghani, E., et al., 2014)*, where he concluded that prophylactic 5-Fr stents were better than 3-Fr stents, but the protective effect of the stents larger than 5 Fr still needs to be studied prospectively, as there is certainly a risk that our findings of the lower adverse event rates in the group of stents over 5 Fr might be confounded by the fact that the endoscopists were more prone to deploy a thicker stent if he demonstrated a wide pancreatic duct during the ERCP. Also, in this group of patients, there is a risk that there might be an over-representation of cases of chronic pancreatitis, which has a protective effect on PEP *(Iorgulescu, A., et al., 2013)*, confounding the results in this group by giving a false low rate of PEP caused by the over-representation of chronic pancreatitis rather than the pancreatic stent itself.

On the other hand, there are major strengths associated with our study. These strengths include a large sample size, which minimizes the risk for selection bias. Also, GallRiks is a well-validated registry that exhibits a 97.3 % match with the patients´ medical records in previous studies *(Enochsson, L., et al., 2013).* This minimizes the risk for misclassification of the ERCP procedures and the adverse events. However, there could still be misclassification harbored in the study, since what we have investigated is the pancreatic cannulations actually recorded in the GallRiks Registry as opposed to the ones actually taking place. Therefore, there could be inadvertent pancreatic cannulations missed by the endoscopists or cannulations not recalled by the endoscopist at the time of the registration (recall bias).

The ERCP procedures included in the GallRiks Registry are also representative for the wide clinical spectrum of ERCP investigations performed in Sweden, since it is generated from all types of endoscopic centers and registered by endoscopists with different experiences; this ensures that the ERCP procedures in GallRiks represent a wide variety of everyday clinical settings. Currently, about 90 % of all ERCPs performed in Sweden are registered in GallRiks. These conditions nearly completely remove the risk of systematic errors.

Naturally, there are also weaknesses associated with the study. For example, the assumptions we made that the pancreatic stents deployed in the study were prophylactic may be incorrect. We could not extract the exact intention of the pancreatic stent from the registry but only assumed this from the indication of the ERCP procedure (directed towards the bile duct). Therefore, any access to the pancreatic duct under these circumstances would be accidental and thereby any stent deployed in the pancreatic duct in this situation would have a prophylactic purpose.

There also is a methodological consideration that must be taken into account, that is, many patients were excluded from the original study base, and few patients were left to study. This is reflected in the broad confidence intervals generated when studying the effects of the pancreatic stents.

The risk of confounding by indication must also be mentioned as a shortcoming of the study and could thus be an explanation of the findings of higher intraoperative adverse events rates in the group receiving a pancreatic stent compared to those who did not. We do not have any explanation other than that the endoscopists were more prone to deploy a pancreatic stent when the ERCP procedure was difficult; this is reflected as an increase in the intraoperative adverse event rate, which is not caused by the stent

deployment per se but is just an effect of confounding that is not compensated for in the multivariate analysis.

Another potential weakness of the study is the long inclusion time (2006-2014). This time period includes changes in radiological and endoscopic techniques as well as indications for an ERCP procedure. The introduction of the MRI technique significantly changed the indications for diagnostic ERCP procedures, which have almost vanished. Today, almost all ERCPs are therapeutic, and this has changed the complication panorama. On the other hand, the endoscopic instruments and devices have improved technically, which might have affected complication rates in a positive way. A final feature that has been introduced in conjunction with ERCP is the use of rectally administered prophylactic NSAIDs adjacent to the procedure, which is also known to reduce PEP rates postoperatively. This use was only sporadically used at the time of the beginning of the study in Sweden, but it has gradually increased in use over time. This parameter was not included in the GallRiks Registry previously and has most definitely affected the complication rates. Without it, it would be impossible for us to study this outcome variable previously. However, this parameter is now introduced in the GallRiks Registry, and it is available to investigate or compensate for in future studies. So ideally, it would have been better to perform the study over a shorter time span to include this parameter throughout the entire time period; however, this would, on the other hand, have minimized the number patients included in the study.

A further limitation of the study is that neither the brand nor the type of pancreatic stent (apart from length and diameter) were registered in the GallRiks Registry, and hence factors like pigtail flanges on the stent could not be studied.

In conclusion, our study has demonstrated that the PEP risk was increased in the ERCP procedure where the pancreatic duct was cannulated, which is in line with previous

knowledge *(Cotton, P. B., et al., 2009, Cotton, P. B., et al., 1991)*. We have also demonstrated a decreased risk of PEP if longer pancreatic stents with larger diameters were used, which also correlates to previous findings. For example, the recent meta-analysis *(Afghani, E., et al., 2014)* advocates 5-Fr to 3-Fr stents for PEP prophylaxis, and this is also the recommendation of the ESGE *(Dumonceau, J. M., et al., 2014).* What our study adds to previous knowledge is that even longer or larger-diameter stents might reduce the PEP rates further, but these findings must be interpreted with caution because of the non-randomized setting of our study. Still, our results must be seen as an interesting and hypothesis-generating work, which might spur future randomized studies to compare different sizes of prophylactic pancreatic stents in a standardized setting to finally solve the issue of finding the ideal prophylactic pancreatic stent.

4.3 Paper 3 (The HOUSE Classification: A novel ERCP complexity grading scale)

Results

4.3.1 Basic characteristics

Between 2009 and 2011, 2,185 ERCP procedures were registered in the GallRiks Registry and were performed at the Karolinska University Hospital, Huddinge, Stockholm, Sweden. After exclusion of non-index procedures and those with incomplete registrations, 1,930 ERCPs remained in the study population. From these investigations, information was gathered from the patient records and the GallRiks Registry. The ERCP procedures were divided into three groups called HOUSE classes 1-3. In the HOUSE 1 group (the least complex procedures), there were 924 procedures, whereas 541 procedures were allocated to HOUSE 2 and 266 were included in the HOUSE 3 class (the

most complex procedures). There were more women in the class HOUSE 1 (53.4 %) and more men in the class HOUSE 2 (58.6 %). In HOUSE 3, the gender distribution was more even (48 % females). The patients in HOUSE 2 were younger (53 years) than in the HOUSE 1 and 3 (64 and 56 years, respectively). On the other hand, the patients in HOUSE 2 were healthier (58 % ASA 1-2) compared to HOUSE 1 and 3 (65 % and 67 % ASA 1-2, respectively).

The most common indications for the ERCP procedure in the HOUSE 1 group were common bile duct stones (36 %), malignancy (15 %), obstructive jaundice (14 %) and scheduled controls (11 %). In the class HOUSE 2 scheduled controls and "other indication" (16 % each) were the most common indications, followed by primary sclerosing cholangitis (14 %), chronic pancreatitis and jaundice (10 % each). Finally, in HOUSE 3, the indications "other" (32 %), primary sclerosing cholangitis (17 %) common bile duct stones (13 %), chronic pancreatitis (11%) and malignancy (9%) were the most common. For more detailed information, please see Table 2 in Paper 3.

4.3.2 The complication rates, cannulation success rates and procedure times of the HOUSE classification

There was a lower cannulation success rate in HOUSE 1 (91%)—which is a parameter used in the GallRiks Registry as a quality marker—compared to HOUSE 2 (96 %) and 3 (95 %).

The mean procedure time for an ERCP procedure was 40 minutes in HOUSE 1, which was significantly shorter than in HOUSE 2 (65 minutes) and 3 (106 minutes) (see Table 3 in Paper 3).

Postoperative complications occurred in 12.6 % of the total study population, where pancreatitis represented the most common complication (4.9 %) followed by postoperative bleeding (2.5 %). Infections with abscesses were less common (0.8 %). Intraoperative complications were seen in 4.2 % in the total group where extravasation of contrast (1.8 %) and intraoperative hemorrhage (1.2 %) were the most common.
When comparing the complication rates between the HOUSE classes, we demonstrated a significantly higher overall postoperative complication rate in the class HOUSE 2 (16 %) and HOUSE 3 (13 %) compared to class HOUSE 1 (11 %, p=0.03). This was also the case regarding the PEP rate, which was only 3.4 % in HOUSE 1 compared to 7.0 % and 6.8 % in HOUSE 2 and 3, respectively (p=0.0016). We found no significant differences between the HOUSE classes when investigating postoperative bleeding or abscesses.
Regarding the intraoperative overall complications, we found no differences in the rates, whereas the complication "extravasation of contrast" was higher in HOUSE 2 and 3 (3.0 % each) compared to 0.9 % in HOUSE 1 (p=0.0027).
For further details on the results, see Table 4 in Paper 3.

4.3.3 Comments

In this study, we created and validated a new complexity grading scale for ERCP procedures intended for resource planning at endoscopic centers. Additionally, the classification could work as an aid in finding ERCPs with an increased complication risk, making it possible to intensify prophylactic measures in these procedures. The HOUSE classification could also be used for educational purposes and make outcome-comparisons between different endoscopic centers more fair and reliable.

In the validation, we found a good correlation between the different HOUSE classes and the overall complication rates and the risk of PEP (with an increasing risk for both) in the HOUSE 2 and 3 classes.

Additionally, we demonstrated a good correlation between the procedure time and the HOUSE classes with a shorter procedure time in HOUSE 1 (40 minutes) compared to HOUSE 2 (65 minutes) and HOUSE 3 (106 minutes), making the HOUSE classification a good instrument for planning endoscopic resources.

There has been a need for a modern and validated ERCP complexity grading scale since the previous classifications have either been outdated or have not been validated, and the HOUSE classifications fulfills both these requisites.

The classification presented by Cotton et al. *(Cotton, P. B., et al., 2011)* was not validated but was solely eminence based, where experienced endoscopists decided what class they considered a certain endoscopic procedure to be and ranked it in a four-level scale, and the median values of the experts' opinions were grouped into classes 1-4.

Another ERCP complexity grading scale was created by Schutz in 2000 *(Schutz, S. M., et al., 2000),* but this scale has now become outdated since it contained classes defined by whether the ERCP was diagnostic or therapeutic, where the former procedures have nearly been abandoned after the introduction of the MRI technique; this makes the scale difficult to implement in modern practice. This scale was validated, but correlation between the different classes was found only in the success rates of the procedure and not in the complications rates; therefore, this scale could not be used for anticipating complications.

The Morriston Hospital Grading Scale, which was launched by Ragunath *(Ragunath, K., et al., 2003)*, was mainly introduced for educational purposes, but this scale has also become outdated since it also deals with diagnostic ERCPs, which, as mentioned, have

been subsequently abandoned. Additionally, this scale could not demonstrate any differences in the complication rates after ERCP but only in the success rates of the procedures and also only for the trainees and not for the supervisors; therefore, this hampers the grading scale.

In 2016, Torun and co-workers *(Torun, S., et al., 2016)* presented a new ERCP complexity grading scale completely independently of the introduction of the HOUSE classification, which was also validated in relation to success and complication rates. It showed linear relationships between the four groups into which the ERCP procedures were classified. Although the classification demonstrated this relationship between the classes compared to success and complication rates, it lacked the relation to procedure times included in the HOUSE classification, which makes Torun´s classification impossible to use as a resource planning instrument at endoscopic centers in contrast to the HOUSE classification.

In light of the previous classifications, the HOUSE classification offers a modern complexity grading scale and takes into account all types of current ERCP procedures. It is also well validated in relation to both complications and procedure times. The GallRiks Registry was validated by matching data with the patients´ medical records *(Enochsson, L., et al., 2013, Rystedt, J., et al., 2014),* and the data must be considered valid with a low risk of misclassification. However, this risk cannot be fully excluded since there is always the risk that some of the data introduced into the register could involuntarily have been missed by the endoscopist or forgotten if the registration was completed after the investigation (recall bias), especially if the documentation in the register occurred a long time after the ERCP procedure took place.

There are also other limitations of the study, including that the scale is “constructed by man” and the division of the groups were made almost completely arbitrary. Therefore,

it is difficult to argue why certain procedures were categorized into a certain group and how the borders between the groups were chosen. Originally, the division was made from an economical aspect in an attempt to gain control over the costs at the endoscopic center at Karolinska University Hospital, Huddinge, Stockholm, Sweden, and this classification was then extrapolated to the complexity grading scale, assuming that more devices and time spent on a procedure corresponded to more complex procedures.

A major weakness of the HOUSE classification, when used for resource planning, is the fact that some of the obstacles occurring during an ERCP procedure cannot be anticipated. An altered surgical anatomy such as a previous Billroth 2-operation or Roux-en-Y reconstruction could be easily foreseen, but other conditions (e.g., a difficult cannulation due to a small papilla) are difficult to identify before the ERCP procedure, and this hampers the HOUSE classification in its applicability for resource planning. For this shortcoming, we have found no solution.

Another limitation of the study was a significant risk of selection bias as the study was performed at an endoscopic tertiary national referral center, where more complex procedures were over-represented, and this might skew the panorama of postoperative complications. Additionally, a tertiary center educates many ERCP trainees, which also might increase the risk for complications and prolong the procedure time. These aspects must be considered before the classification can be implemented in a non-referral endoscopic center and might warrant possible additional modifications and validations of the HOUSE classification.

In conclusion, this study presents a newly constructed validated ERCP complexity grading scale that can be implemented in clinical praxis as an instrument for resource planning at endoscopic centers, in educational endoscopic training programs or used as

an aid in identifying high-risk ERCP procedures and thereby enabling targeting of necessary prophylactic measures. The HOUSE classification might, however, warrant further evaluation and validation before it is introduced in clinical praxis at non-referral endoscopic centers, as a different panorama of indications and ERCP procedures might exist there.

4.4 Paper 4 (Preoperative biliary drainage by plastic stents or SEMS in patients with assumed resectable periampullary carcinoma)

Results

4.4.1 Preoperative patient, tumor and stent function characteristics

92 patients with presumably resectable periampullary tumors were randomized to either achieve a SEMS or a plastic stent. 47 patients were allocated to the SEMS group, and 45 patients to the plastic stent group. Eventually, 27 patients in the SEMS group were curatively operated upon, 13 were not operated upon and 7 underwent palliative surgery. In the plastic stent group, 32 patients had a curative resection, whereas 11 patients were not operated upon and 11 patients had a non-curative operation, like an explorative laparotomy or a surgical bypass without a resection.

When comparing patient characteristics in all of the operation patients (curatively and non-curatively, n=34 in each group), more men received a plastic stent (67 %), but this difference was not significant. We also did not detect any differences in other patient characteristics, including weight, age, morbidity or bilirubin level when the stenting occurred. The C-reactive protein level (CRP) was significantly higher in the SEMS group (20 mg/ml vs 9 mg/ml, p=0.01), but the clinical importance of this difference should be small.

The features of the tumors regarding size, stage, grade of differentiation and type of origin (pancreatic, biliary, papillary or duodenal) did not differ between the SEMS and plastic stent groups. Also, the pancreatic texture of the glandula did not differ between the groups (hard, soft or intermediate) when the anastomosis was created according to the surgeon´s clinical opinion during the operation.

There were significantly higher rates of stent dysfunction (27 % vs 11 %, p=0.05) and stent exchanges (24 % vs 8 %, p=0.05) in the plastic stent group compared to the SEMS group in the group of all patients randomized (n=92), but there was no difference found in the risk of cholecystitis, cholangitis or pancreatitis between the groups.

There was an increased risk of preoperative stent dysfunction (21 % vs 6 %, p=0.15) and stent exchange (18 % vs 3 %, p=0.11) in the plastic stent group, in those patients who were operated on, but in this smaller group, the difference did not reach statistical significance. On the contrary, the preoperative stent exchange rate in the curatively operated patients was significantly lower among those patients who had received a SEMS (19 % vs 0 %, p=0.03), and the risk of stent dysfunction was also lower among the patients who had received a SEMS (22 % vs 4 %, p=0.06); however, this latter finding, was not statistically significant.

In the patients that underwent an operation, whether curatively or not, there were no differences in the risk of developing cholangitis or in the bilirubin or CRP levels recorded preoperatively. There were also no differences in the use of prophylactic antibiotics, the frequency of failed cannulations, previous sphincterotomized patients or the rate of precut sphincterotomies used when comparing the SEMS and plastic stent groups.

For further details, see Tables 1 and 2 in Paper 4.

4.4.2 Perioperative bacteriological, histopathological and clinical findings

The amount of gut bacteria in the bile collected during the operation was identical in the SEMS and plastic stent groups (100.000 CFU/ml), but the total amount of all bacteria was higher in the SEMS group (131.000 vs 110.000 CFU/ml, p=0.44); this difference was not significant. The most common bacteria found in the bile in both stent groups were species of Klebsiella, followed by Alpha streptococcus and Enterococcus. A complete list of the bacteria present in the bile cultures is presented in Table 3 in Paper 4.

There were no differences in the operation times nor in the perioperative bleeding between the plastic stent and SEMS groups. There were also no differences in the proportion of total pancreatectomies (compared to Whipple) or in the proportion of vascular resections performed adjacent to the pancreatico-duodenectomy between the groups. The time from the endoscopic stenting to the operation was similar between the two groups as well as the procedure times, the intraoperative bleeding, the time in ICU and the total hospital stay.

The surgeons' subjective intraoperative estimations of how much inflammation was present in the hepato-duodenal ligament showed no differences between the plastic stent and the SEMS groups. There were also no differences in the difficulties in creating the anastomoses or in extracting the stents from the bile duct irrespective of stent type present. When a ring-shaped specimen intraoperatively harvested from the bile duct was investigated histopathologically, no difference could be detected in the degree of cholangitis, but when investigating the foreign body reaction sinus histiocytosis specifically, in the lymph nodes in the hepato-duodenal ligament, this was significantly higher in the plastic stent group (26 % vs 7 %, p=0.05) compared to the SEMS group.

4.4.3 Postoperative complications

The overall complication rates in the patients with any operation (curative or non-curative) were higher in the patients receiving a plastic stent (68 %) compared to the SEMS group (50 %). This was also the case in the group of patients operated curatively (72 % vs 52 %), but none of these differences reached statistical significance (p=0.14 and p=0.11, respectively). The risk of developing a specific surgical complication among those patients with any operation (curative or non-curative) was higher in the plastic stent group (50 %) than in the SEMS group (35 %), without reaching statistical significance (p=0.22), and the difference was even smaller in the subgroups of patients curatively operated (53 % vs 44 %, p=0.51). In the group of all patients who underwent an operation, the risk for anastomotic leakage was higher in the plastic stent group (12 %) than in the SEMS group (2.9 %); this difference also was non-significant. Further on, nearly similar results were seen in the curatively operated group regarding anastomotic leakage in favor of the SEMS group (12 % vs 3.7 %, p=0.36). On the other hand, the infectious complications in patients with any operation (curative or non-curative) were more common in the SEMS group (29 % vs 15 %, p=0.14), but the difference was less enhanced in the curatively operated patients (SEMS 22 % vs 16 % plastic stent, p=0.51); again, none of the differences were significant. There were also more postoperative bleedings in the plastic stent group (9 % vs 3 % in all operated patients and 9 % vs 4 % in the curatively operated patients), but once more these results were statistically non-significant. To summarize, the other complications (i.e., delayed gastric emptying, reoperation, wound dehiscence, postoperative antibiotics used and cardiopulmonary complications) were too rare to compare, or they showed no mentionable numerical

differences (and thus no statistically significant differences) between the groups (For details, see Table 5 in Paper 4).

4.4.4 Comments

The main finding in this prospective randomized study comparing SEMS and plastic stents in patients with presumably resectable periampullary tumors was that the risk of stent dysfynction/exchange prior to operation was reduced if a SEMS was used (27%/24% vs 11%/8%, p=0.05). Intraoperatively, we found no technical differences for the surgeons in performing the pancreatico-duodenectomy in relation to the stent type used (no difference regarding the surgeon´s subjective findings, operational time or perioperative blood loss). There were also no differences in the amount of bacteria in intraoperatively collected bile measured in colony-forming units of bacteria per milliliter (CFU/mL). However, there was a more histopathologically enhanced foreign body reaction (sinus histiocytosis) in the lymph nodes harvested intraoperatively from the hepato-duodenal ligament in the patients receiving plastic stents compared to these receiving SEMS. Finally, we found numerical differences in the rates of overall postoperative complications in the curatively operated patients in favor of the SEMS (72% vs 52%, p=0.11) and in anastomotic leakage rates (12% vs 3.7%, p=0.36), however, these differences did not reach statistical significance.

SEMS have been previously demonstrated to be superior to plastic stents regarding patency in palliative patients not intended for a curative operation *(Zorron Pu, L., et al., 2015)* and also in the neo-adjuvant setting with locally advanced primary irresectable tumors, as these patients require several months of oncological treatment before they could be evaluated for surgery again *(Aadam, A. A., et al., 2012).* Until now, there has

been no prospective, randomized controlled trial comparing SEMS to plastic stents in patients with primary resectable periampullary tumors; instead, there are only retrospective series.

A meta-analysis *(Crippa, S., et al., 2016)* of these retrospective studies (n=704), which of course methodologically must be interpreted with caution, did however demonstrate a higher risk for a reintervention with a new ERCP procedure due to stent dysfunction if a plastic stent was used preoperatively compared to if a SEMS was used (15 % vs 3 %, $p<0.0001$). This meta-analysis also showed a higher risk of developing a pancreatic fistula postoperatively in the plastic stent group compared to the SEMS group (12 % vs 5 %, $p=0.04$); both findings are in line with our results, but our results represent the first data gained from a prospective RCT.

It is important to note that in Sweden, almost all patients while awaiting curative pancreatic surgery during the preoperative diagnostic work-up period receive some kind of biliary drainage, although several previous studies have shown negative effects on the postoperative results with an increased risk of postoperative complications if a preoperative stenting is performed *(Chen, V. K., et al., 2005, Fang, Y., et al., 2013, Sewnath, M. E., et al., 2002, van der Gaag, N., et al., 2010).* The most often cited study on this subject is the one by van der Gaag and co-workers from 2010, which was published in New England Journal of Medicine *(van der Gaag, N., et al., 2010)* and showed an increased risk of adverse events if a preoperative decompression of the bile duct was used compared to up-front surgery (74 % vs 39 %, $p<0.01$). However, this study was not performed with modern SEMS but with plastic stents or sometimes even with PTC drains. Therefore, a randomized controlled trial is needed to compare SEMS and up-front surgery.

In Sweden, preoperative decompression of the bile duct is mostly used for logistic reasons, while the patient is on the waiting list for surgery at a tertiary center and while the diagnostic work-up is in progress, minimizing the risk for cholangitis or coagulopathy. This is why some of the patients received a preoperative bile duct decompression with a lower threshold regarding the indication of the stenting than is usually recommended.

The strengths of our study are that the data are collected prospectively, and the patients are randomized to either receive a SEMS or a plastic stent. This reduces the risk for selection bias, and this study is the first study where this was performed prospectively in this clinical situation (preoperative in resectable periampullary tumors).

There seem to be no major differences in the preoperative demographics of the patients, neither in the tumor characteristics (e.g., tumor stage, tumor differentiation, histological types) nor in the laboratory test apart from C-reactive protein (CRP), which was 9 mg/ml in the plastic stent group compared to 20 mg/ml in the SEMS group. This difference is clinically modest but statistically significant in our study.

Another strength of the study is that it was performed at a large national tertiary endoscopic center with only experienced endoscopists; this minimizes the risk of variation in the technical quality of how the ERCP procedures were performed. On the other hand, many of the ERCP procedures were performed at a teaching hospital, where many endoscopic trainees are present performing the ERCP procedures, which might have affected the outcome. But, since the study was performed as an RCT, the effects should be equal in both groups. Also, there is a risk that the ERCP procedures performed at a national tertiary referral endoscopic center may not be representative of ordinary ERCP procedures, as more technically demanding ERCPs are performed here compared to regular endoscopic centers. This might also skew the results, but again, because this

study was performed in a prospective randomized manner, no differences should appear between the groups.

A final strength of our study is that the patients remained in the group to which they were randomized. This intention-to-treat design gives the study a higher validity.

Among the downsides of the study is that the primary outcome was chosen to be the amount of bacteria in intraoperatively collected bile; when the study was set up, and the power calculation of the study was based on this. This led to the negative effect that the study probably became underpowered regarding the secondary outcomes, such as clinical symptoms and perioperative complications. Another shortcoming was that the outcome, especially the amount of bacteria in CFU/mL, turned out to be equal between the groups, and that this parameter had a low clinical value, not corresponding to the clinical symptoms and outcome. Retrospectively, when knowing the results from the study and considering the study design critically, instead it would have been better to monitor perioperative complications as the primary outcome, but this fact could of course not be anticipated when starting the study. Perhaps the difference in overall postoperative complication rates then would have reached statistical significance, and even some of the subgroups of complications (e.g., anastomosis leakage) might have differed statistically significant between the stent type groups. However, a shortcoming of the results of the subgroup of anastomotic leakage was that the type of leakage could not be clearly distinguished from which anastomosis it emanated. Therefore, this group might represent a case-mix of different complications (e.g., pancreatic fistulae, bile leakage). Additionally, there was probably also a large overlap from this group of anastomotic leakages to the group of infectious complications, which might represent the effect of an infected fluid collection arising from a previous leakage.

A further weakness of the study was that it was not completely double blind. Although the study was blinded to the patients and staff at the surgical wards, the endoscopist was aware of the stent type used, which might have affected the patient´s and other staff´s opinion and thereby the outcome of the study.

A risk for pancreatitis and cholecystitis has been described when using SEMS, while these were thought to block the duct orifices *(Cote, G. A., et al., 2010)*, but this was not noted in our study, although the frequency of these complications was slightly higher in the SEMS group. But, again, these events were too rare to gain statistical significance, if present at all.

The stent dysfunction rate was higher in the plastic stent group as well as the stent exchange rate, but the latter may not be a good measure of outcome, as the endoscopist may be more prone to exchange a plastic stent, since this is cheaper and easier to remove than the more costly SEMS; this fact may also have biased the results.

Another aspect that must be considered is the surgeon´s subjective evaluation of the operational findings regarding difficulties in extracting the stent, creating the anastomosis and estimating the grade of inflammation in the hepato-duodenal ligament. These, of course, were highly subjective although we tried to classify them into a more objective three-leveled scale. Anyhow, we could not detect any differences. Also, there were no differences in procedure time or in the amount of perioperative blood loss, both representing more objective measurements of technical difficulties during the operation. On the contrary, there was a higher grade of foreign body reaction (sinus histiocytosis) in the lymph nodes in the hepato-duodenal ligament in the plastic stent group, and altogether, this strongly suggests that SEMS do not jeopardize the operation technically. Rather, it could even be more advantageous to use.

A final consideration of this study is the long enrollment period (2007-2014) during which endoscopic instruments and devices have experienced development, which may have also affected the outcome over time.

In conclusion, this study gives clear evidence that SEMS could be used preoperatively in resectable periampullary tumors. This is a clear advantage for patients, since the resectability is not always known at the time of the biliary decompression. By using a SEMS directly, this might avoid the morbidity of unnecessary repeat ERCP for stent exchanges.

However, there was no difference in the amount of bacteria in the bile collected during the operation—this was the primary outcome of the study—but when studying the secondary outcomes of clinical advantage of using SEMS in resectable periampullary tumors, these were threefold and present in both the pre- and intraoperative phases as well as in the postoperative period. Preoperatively, the advantage was demonstrated in the study by a statistically significant lower risk for stent dysfunctions and need for stent exchanges. Intraoperatively, the SEMS show no evidence of disadvantages affecting the operation technically – neither through the subjective findings of the surgeon nor by prolonging the operational time or increasing the amount of blood loss during the pancretico-duodenectomy. Finally, postoperatively, we demonstrated a lower risk of overall complications and risk of anastomotic leakages if SEMS were used; the lack of statistical significance regarding the postoperative complications is likely due to underpowering of the study.

5. GENERAL DISCUSSION

When the interventional ERCP techniques of sphincterotomy and endoscopic stenting were introduced in the seventies, this new development reduced the complication rates, since the number of open operations could be reduced and be replaced by this new, minimally invasive method. Although the ERCP instruments and devices have improved over time, ERCP is still marred with considerable morbidity, and further measures must be undertaken to reduce these complication rates as much as possible.

A correct indication for the ERCP (and not performing unnecessary procedures) is one important factor that can reduce complications. The introduction of the MRI technique represented a great breakthrough in reducing the number of diagnostic ERCPs, thereby reducing complications. Another important factor in reducing complications is a good educational system to secure the skills of future endoscopists and to maintain competence among active ERCPists. Guidewire cannulation represents another example of a basic ERCP technique that reduces the complications and increases the chance of getting access to the bile duct and is recommended by the ESGE *(Dumonceau, J. M., et al., 2014).*

Finally, an important prophylactic measurement in reducing ERCP complications is the use of rectally administered NSAIDs (indomethacin or diclofenac), which fortunately has increased during the last years. It significantly reduces the risk of PEP, and is recommended in ESGEs guidelines *(Dumonceau, J. M., et al., 2014)* to be administered to all patients undergoing ERCP – both in high- and low-risk cases.

5.1 When should prophylactic antibiotics be used in ERCP?

In modern society, a growing problem of bacterial resistance to antibiotics is seen, which should be considered in medicine when using antibiotics, especially in a prophylactic setting. It is therefore important to have sharp indications for prophylactic antibiotics in ERCP, but defining when prophylactic antibiotics should be administrated in ERCP is difficult. There are two modern meta-analyses *(Bai, Y., et al., 2009, Brand, M., et al., 2010)* on the subject, and they reach different conclusions. Bai *(Bai, Y., et al., 2009)* suggested that antibiotic prophylaxis should not be used routinely, as it did not reduce the risk of cholangitis, but they also warranted more studies in the ERCPs where biliary drainage could not be achieved. On the contrary, Brand *(Brand, M., et al., 2010)* claimed in a Cochrane analysis that the effect of prophylaxis was less evident in routine ERCPs, and they also suggested to reserve the prophylaxis for those patients where decompression of the bile ducts could not be achieved; they also speculated whether perhaps the antibiotics could be administered postoperatively if no bile duct access was reached during the ERCP procedure. Our study gave similar results as these meta-analyses, that is, a modest reduction in complications if antibiotics were used prophylactically (14.2% vs 11.6%) but with a number needed to treat of 38 patients to avoid one postoperative complication. According to our considerations, these results do not justify a general recommendation to use prophylactic antibiotics in all ERCP procedures. We later found a greater effect on the reduction of complications in the group of patients with jaundice (15.3% vs 11.5%), which is also in line with the findings in the meta-analyses mentioned above, with a number needed to treat of 26 patients to avoid one adverse effect in this subgroup, which might justify a more generous recommendation of antibiotic prophylaxis in these particular ERCP procedures.

One way could be to administer the antibiotics postoperatively in these ERCP procedures where no biliary access is gained to reduce the administration of antibiotics, but more studies are warranted. Until this problem is solved, we will be directed to use a strategy where we estimate the risk in a certain indication of the ERCP procedure for not achieving biliary drainage; if this risk is sufficiently high, this will guide us, when to use prophylactic antibiotics.

5.2 When and which type of prophylactic pancreatic stents should be used in ERCP?

Prophylactic pancreatic stents reduce the risk of developing PEP, but they have historically not been frequently used in ERCP in Sweden. Not only do the stents reduce the PEP rates, but they also seem to almost eliminate the risk of severe PEP, and they are recommended in ESGE guidelines *(Dumonceau, J. M., et al., 2014)* in high-risk ERCP procedures. One problem is finding the appropriate definition for a high-risk ERCP procedure; currently, Halttunen and co-workers *(Halttunen, J., et al., 2014)* suggested the rule of "5-5-2", where the different separate figures represent an ERCP procedure with either five attempts to cannulate the bile duct, more than five minutes of cannulation attempts or two passages of the guidewire into the pancreatic duct through which all the risk of complications increase. This may be a suitable way to decide when a pancreatic stent should be deployed. This definition of a difficult cannulation was currently also adapted by the ESGE (*Testoni, P. A., et al., 2016).*

Another issue, apart from the indication of a prophylactic stent, is which type of stents that should be preferred as the golden standard. In a recent meta-analysis *(Afghani, E., et al., 2014),* it was demonstrated that 5-Fr stents performed better than 3-Fr stents in reducing complications and were also easier to deploy in the pancreatic duct. This meta-

analysis also speculated about whether flanged or unflanged stents were better, but this was less obvious, and they only concluded that there was no difference between those two types. They interpreted this finding as suggesting that the diameter is the important issue and not the flanges. However, there is an increased risk for a repeat ERCP to remove the flanged stents, which is also the case for the longer stents. So, all together, the recommendation must be to use a short, unflanged 5-Fr stent for prophylaxis, which is in line with the ESGE recommendation *(Dumonceau, J. M., et al, 2014).* Another aspect of prophylactic pancreatic stents is the time that the stents should be in place in the pancreatic duct and how the dislodgement of the stent should be controlled. Here, the ESGE recommend five to ten days stenting *(Dumonceau, J. M., et al, 2014)* and a control so that retained stents can be removed.

Our contribution in the field of prophylactic pancreatic stenting is that we have investigated the effect on PEP of even larger stents (>5Fr, >5 cm) in a national population-based registry. We found that these may reduce the PEP rates further, but these findings must be confirmed through future RCTs. Therefore, presently the recommendation of prophylactic pancreatic stenting is to use short 5-Fr stents in high-risk procedures, preferably defined through the "5-5-2-rule" described above.

5.3 Why should an ERCP complexity grading scale (The HOUSE Classification) be implemented in clinical praxis?

ERCP is one of the most advanced endoscopic procedures that is performed today, but the complexity between different procedures varies considerably; therefore, it is desirable to introduce a new ERCP complexity grading scale. Firstly, this scale can function as a resource-scheduling system at endoscopic centers, when planning for the right amount of time for an ERCP procedure, the right endoscopic competence and that

the correct devices are present. Secondly, the scale can be used for targeting prophylactic measures towards more complex procedures—for example, a higher level of postoperative control or a more liberal indication for perioperative prophylactic measures during the procedure. This new HOUSE classification can also be used for educational purposes in finding the right level of difficulty of the ERCP procedure in relation to a certain level for the trainee in an endoscopic training fellowship. Finally, the HOUSE classification can be used for economical billing when transferring money between different healthcare systems or as an instrument to make comparisons of complications and research results more reliable and fair between different endscopic centers.

An endoscopic complexity classification system introduced by Cotton *(Cotton, P. B., et al., 2011)* is hampered by a lack of validation and is solely eminence based, whereas the HOUSE classification is validated in relation to procedure time, for resource planning possibilities and to complication rates and is able to direct prophylactic measures towards the ERCP procedures with higher complication rates.

Another classification presented recently in 2016 *(Torun, S., et al., 2016*), launched completely independently to the HOUSE classification, seems promising since it demonstrates a good correlation to success- and complication rates, but lacks the HOUSE classification´s correlation to procedure time and could thereby not be used for resource planning.

Former ERCP classifications *(Madhotra, R., et al., 2000, Ragunath, K., et al., 2003, Schutz, S. M., et al., 2000)*, although validated, have been outdated, since both radiological (MRI) and endoscopic techniques have developed, making those classifications difficult to apply to modern ERCP procedures.

The HOUSE classification presented in our study represents a modern ERCP complexity classification that is applicable in modern endoscopic praxis. It is validated in relation to both procedure time for resource planning, to complications in general and to PEP rates in particular and could be used as an aid to anticipate postoperative problems, which provides the possibility to act against them at an early stage.

5.4 What are the benefits of using a SEMS preoperatively in resectable periampullary tumors?

Several previous studies and meta-analyses *(Chen, V. K., et al., 2005, Fang, Y., et al., 2013, Sewnath, M. E., et al., 2002)* have shown that routine preoperative biliary endoscopic stenting increases morbidity by adding preoperative complications (e.g., PEP) but also by increasing postoperative complications presumably mediated through the infected bile and contaminating the inserted stent through ascending bacteria along the stents. However, many of these studies were performed with older endoscopic devices like plastic stents or sometimes even with PTC drainages of the bile duct; this may add more complications than associated with modern SEMS. For instance, this was the case in the often quoted study by van der Gaag and co-workers *(van der Gaag, N., et al., 2010),* which showed a significantly lower risk of postoperative complications in the group where the pancreatic surgery was performed up-front without any previous bile duct decompression. Despite this knowledge, most patients in Sweden diagnosed with jaundice due to periampullary tumors receive a stent preoperatively due to logistical reasons while the diagnostic work-up is in progress and while the patients wait for their operations, which are performed at a tertiary referral center often 4-6 weeks after the initial diagnosis.

Some pancreatic surgeons believe that the SEMS might induce a more severe inflammation in the hepato-duodenal ligament, jeopardizing the operation and making it more difficult to dissect the tumor and to create the anastomoses during the pancreatico-duodenectomy. This has led to a skepticism in using SEMS in potentially resectable periampullary tumors among pancreatic surgeons.

There has been a lack of prospective, randomized controlled studies comparing SEMS to plastic stents in resectable periampullary tumors until our study, but a recent meta-analysis based only on retrospective studies *(Crippa, S., et al., 2016)* showed less adverse events if SEMS were used preoperatively compared to plastic stents.

Our study, which is to our knowledge the first RCT to compare SEMS to plastic stents in the preoperative setting in periampullary tumors, clearly showed that the risk of preoperative stent dysfunction was lower in the SEMS group, thereby reducing the risk and morbidity of a repeat ERCP preoperatively for a stent exchange. Additionally, the apprehension for technical difficulties during the pancreatic operation could be dispatched in our study, since no differences were seen in operation time or blood loss during the pancreatico-duodenectomy; also, surgeons could not detect any subjective difference in technical difficulties as judged by their personal opinion of how they experienced the operation. On the contrary, the histopathological foreign body reaction (sinus histiocytosis) in the lymph nodes in the hepato-duodenal ligament was lower in the SEMS group compared to the plastic stent group, indicating a lower grade of inflammation in the SEMS group in the hepato-duodenal ligament compared to the plastic stent group.

Finally, the postoperative overall complications were lower in the group where a SEMS was used compared to a plastic stent; however, these results were not significant.

In conclusion, SEMS can always be used when the bile duct is decompressed due to a periampullary tumor, independently of the stage of the tumor, which is not always known at the time of the ERCP stenting. Resectable tumors, especially those requiring neo-adjuvant treatment before operation, will benefit through a lower risk of needing a repeat ERCP for stent exchange prior to the operation. This strategy must be recommended, since no perioperative technical problems during the pancreatic surgery were seen in our study and additionally since the postoperative complications might be lower when using the SEMS, although these results were not statistically significant. If the tumor after the diagnostic work-up turns out to be irresectable, the patient still benefits from the SEMS, as the patient in this palliative situation might avoid an unnecessary stent exchange because the SEMS has a longer patency that is longer than the life expectancy of the patient.

6. CONCLUSIONS

The following conclusions can be drawn from the data provided from our studies:

6.1 **Prophylactically administered antibiotics** in conjunction with ERCP were associated with a lower rate of infections and overall complications. The association was strongest in the group of patients where the indication for the ERCP was jaundice, where both infections and overall complications were further reduced when prophylactic antibiotics were given. However, the reduction in complications was not that high that prophylactic antibiotics could be recommended on a general basis for all ERCP procedures.

6.2 When the **pancreatic duct was accidentally cannulated** during an ERCP that intended for a bile duct cannulation, there was an increase in the overall intra- and postoperative complication rates, especially for PEP where the OR for complications was increased more than three times.

If a ≤5-Fr **pancreatic stent** was deployed in the pancreatic duct after an inadvertent pancreatic cannulation, there was an increased risk for PEP compared to if a >5-Fr pancreatic stent was used, corresponding to an almost fourfold OR increase in the multivariate analysis (OR 3.6). Furthermore, a pancreatic stent >5 cm in length further significantly reduced pancreatitis frequency compared to shorter stents.

6.3 If the three-level ERCP complexity grading scale called the **HOUSE classification** is implemented in clinical praxis, this could be used for resource planning in endoscopic centers or as a guide for a greater alertness in detecting postoperative complications in more complex procedures. Note that the HOUSE classification was validated in relation to procedure time and to the postoperative complication rates; shorter procedure times and lower complication rates, like PEP, were found in HOUSE 1 compared to the higher HOUSE classes.

6.4 In resectable periampullary tumors requiring **preoperative biliary drainage**, there were no differences in the amount of bacteria growing in bile collected intraoperatively during the pancreatico-duodenectomy between plastic stents and SEMS – this was the primary outcome of the study. Clinically, SEMS were superior to plastic stents, since they reduced the risk for preoperative stent dysfunction and decreased the stent exchanges before the operations. Also, there were no intraoperative technical downsides in those patients who had received a SEMS, since this did not jeopardize the operation, as subjectively judged by the surgeons during the pancreatico-duodenectomy (grade of

inflammation in the hepato-duodenal ligament, difficulties in stent extraction or in creating anastomoses) neither did the stent type affect the operational time nor the peroperative blood loss.

There were also no differences between the plastic stent- and SEMS groups in the grade of cholangitis in the bile duct harvested during the pancreatico-duodenectomy when this was histopathologically investigated. On the contrary, there was a more enhanced histopathological foreign body reaction (sinus histiocytosis) in the lymph nodes harvested intraoperatively from the hepato-duodenal ligament if a plastic stent had been used.

The postoperative complication rates after the pancreatico-duodenectomy was lower in advantage of the SEMS group, but these differences were not statistically significant.

7. PROPOSAL FOR FUTURE CLINICAL RESEARCH

Since ERCP is a minimally invasive method that clearly has advantages compared to open surgery, it is still plagued with significant morbidity (e.g., pancreatitis, bleeding, perforation and cholangitis), and every effort must be made to undertake measures to reduce these complications. Future research must focus on defining the procedures where prophylactic measures should be intensified to reduce adverse events using cost-benefit analyses. Desirable future studies and designs are presented below.

7.1 A multi-center, prospective, randomized study focusing on the effects of modern **prophylactic antibiotics in ERCP** with special focus on the subgroup of patients where

no complete bile duct drainage can be achieved should be considered. This subgroup of ERCP procedures may benefit the most from prophylactic antibiotics.

7.2 A multi-center, prospective, randomized study comparing **prophylactic pancreatic stent** to no stent in a national population of unselected ERCP procedures should be considered to evaluate the effects on adverse events of ERCP in this population and to define the high-risk procedure of ERCPs where prophylactic pancreatic stents are justified from a cost-benefit and morbidity perspective.

7.3 The **HOUSE classification** of ERCP complexity grading should be implemented in a non-educational endoscopic center. In this clinical setting, the scale should be validated in a prospective manner in relation to procedure time and complication rates for the different HOUSE classes.

7.4 The RCT on **preoperative stenting (SEMS vs plastic stents) in resectable periampullary tumors** should be repeated with a primary endpoint of clinically relevant parameters like preoperative adverse events and postoperative complications; a power calculation should be used to identify differences in complication subgroups (e.g., infections, anastomotic leakage).

Finally, a prospective, randomized study comparing preoperative biliary drainage with modern SEMS to up-front surgery without any preoperative bile duct decompression in resectable periampullary tumors should be completed

8. POPULÄRVETENSKAPLIG SAMMANFATTNING

I denna avhandling presenteras kunskapsläget om komplikationer till ERCP och vad som är känt som effektiva åtgärder för att minimera risken för negativa effekter av undersökningen. Dessutom redovisas resultaten av fyra vetenskapliga studier.

ERCP, dess komplikationer och åtgärder mot dessa.

Endoskopisk retrograd cholangio-pancreatografi (ERCP) är en undersöknings- och operationsmetod för att behandla sjukdomar i gallgången och bukspottskörteln. Metoden infördes i slutet av sextiotalet, först som en möjlighet att röntga gall- och bukspottskörtelgång via en undersökningsslang som fördes ner via magsäcken till tolvfingertarmen. Där kunde sedan en tunn kateter, under endoskopisk uppsikt föras in i den gemensamma gall- och bukspottskörtelmynningen, något som var revolutionerande på den tiden. Sedermera förfinades ERCP-tekniken, då man under sjuttiotalet, kunde genomföra de första små operationerna via ERCP-instrumentet genom att med en strömförande böjd tråd kunna skära upp slutmuskeln av gallgången och därigenom skapa en större öppning till gallgången genom vilken man kunde utföra sina ingrepp. Denna operation kom att kallas sfinkterotomi och de vanligaste ingreppen som nu kunde genomföras var att rensa gallgången från gallstenar och att behandla gulsot orsakad av hinder i gallgången, genom att ett plaströr kunde stoppas in i gallgången för att leda gallvätskan förbi hindret och därmed upphäva gulsoten (s.k. stentning). Införandet av ERCP-tekniken ledde till att man nu kunde undvika de öppna operationer som tidigare krävts för att behandla t ex stenar i gallgången och gulsot orsakad av tumörer i bukspottskörteln. Man hade nu lyckats sänka komplikationerna vid dessa

sjukdomstillstånd men upptäckte snart att även den nya ERCP-tekniken var behäftad med komplikationer, men som var av en ny natur.

Den vanligaste komplikationen till ERCP är bukspottskörtelinflammation (pankreatit), som uppstår ungefär efter var tjugonde ERCP-undersökning. Orsaken till denna är inte fullständigt känd, men på något sätt retas bukspottskörteln av ERCP-undersökningen och reagerar med en inflammation. Oftast blir denna lindrig och snabbt övergående men i ovanliga fall kan den leda till svåra buksmärtor och påverkan på övriga organsystem i kroppen, med långvarig sjukhusvistelse som följd, ibland krävande intensivvård. I sällsynta fall krävs till och med operationer för att rensa ut död vävnad från buken när bukspottskörteln bryter ned sig själv och omkringliggande vävnader.

Man vet att det finns vissa faktorer vid ERCP, som medför att risken för bukspottskörtelinflammation ökar i anslutning till undersökningen, där en del är patientberoende och andra är beroende av själva ingreppet. Till de patientrelaterade faktorerna hör kön och ålder, där risken är förhöjd hos kvinnor och hos yngre patienter. Till de riskfaktorer som är relaterade till själva ERCP-undersökningen hör om undersökningen varit tekniskt svår och tagit lång tid eller om kontrastvätska eller något instrument förts in i bukspottskörtelgången. Förutom att genomföra en så skonsam och tekniskt lyckad ERCP-undersökning som möjligt av en välutbildad ERCPist, kan vissa förebyggande åtgärder vidtas för att minska risken för att bukspottskörtelinflammation skall uppstå. Den vanligaste och mest förebyggande åtgärden är att patienten får ett stolpiller med ett inflammationshämmande preparat innan undersökningen. En annan viktig åtgärd som kan genomföras under ERCP-undersökningar där risken för bukspottskörtelinflammation bedöms som förhöjd, är att via ERCP-instrumentet införa ett tunt rör (stent) i den yttersta delen av bukspottskörtelgången som får sitta kvar där under några dagar efter undersökningen, för att sedan plockas bort. Man tror att detta

lilla rör, gör det lättare för bukspottet att tömma sig till tarmen och på det sättet minskas risken för bukspottkörtelinflammation.

Andra komplikationer som kan uppstå vid en ERCP-undersökning är infektion i gallgången, levern eller i andra närliggande organ. Infektion i gallgången kan dels uppstå innan ERCP-undersökningen om det blir stopp i gallgången, som då snabbt infekteras när gallflödet hämmas, dels kan den uppstå som en följd av själva ERCPn, då tarmbakterier kan föras upp under undersökningen och sedan orsaka en inflammation om inte undersökningen leder till att gallvägen kan dräneras ordentligt. De typiska symptomen för gallgångsfeber är hög feber, ofta över fyrtio grader, med frossbrytningar. Tillståndet är tacksamt att behandla då symptomen ofta snabbt viker på intravenös antibiotika, om bara gallvägarna blivit avlastade under ERCP-undersökningen. Slutligen kan två andra tillstånd nämnas, som kan uppstå efter en ERCP-undersökning. Det ena är blödning från sfinkterotomin, som uppstår då slutmuskeln av gallgången skärs upp. Denna blödningstyp kan oftast behandlas med metoder som är tillgängliga via ERCP instrumentet, t ex som injektion av adrenalin med en nål runt blödningskällan. I sällsynta fall krävs dock operation för blodstillning eller en åtgärd där man går in med en kateter via ljumsken i lårpulsådern och upp till det aktuella kärlet vid gallgången och stoppar in blodstillande material i denna pulsåder för att stoppa blödningen, s k “coiling”. Den andra komplikationen, slutligen, är att det kan gå hål på tolvfingertarmen i anslutning till ERCP-undersökningen, oftast som en effekt av sfinkterotomin och mat och tarmvätska kan då läcka ut, utanför tolvfingertarmen. Är inte hålet för stort, kan tillståndet behandlas med antibiotika, men ibland krävs en operation för att täta hålet.

Vetenskapliga studier:

Det **första delarbetet** beskriver effekterna av att ge **förebyggande antibiotika** innan varje ERCP-undersökning. Bakgrunden till ett sådant förfarande skulle vara att när man för upp en kateter i gallgångsmynningen också för upp tarmbakterier, som antibiotikan därmed teoretiskt skulle slå ut och på så vis undvika en gallgångsinflammation. Dock är kunskapsläget för en sådan generell hållning svagt och kan möjligen försvaras vid de ERCP-undersökningar där man inte lyckas avlasta gallvägarna. Det som studien visar är att man förvisso sänker risken för komplikationer med ett par procent om man ger antibiotika innan ERCP-undersökningen men för att undvika en enskild komplikation, måste man behandla 38 patienter för att undvika en komplikation. Detta medför att man utsätter 37 patienter i onödan för biverkningar till antibiotikan för att undvika EN komplikation hos EN patient samtidigt som man ökar antibiotika-trycket i samhället med alla risker det innebär för utvecklande av antibiotika-resistens mot bakterier. Detta medför i sin tur att man inte kan rekommendera antibiotika till alla patienter generellt innan varje ERCP, utan bara i utvalda fall och den framtida frågan är att ta reda på till vilka.

Det **andra delarbetet** som vi presenterar handlar om effekterna att vid ERCP-undersökningen, införa ett tunt plaströr (s k **"pancreas stent"**) i den yttersta delen av bukspottskörtelgången. Detta låter man sedan ligga kvar under några dagar och kan på så vis minska risken för bukspottskörtelinflammation efter ERCP-undersökningen. Det studien först visar är att risken för bukspottskörtelinflammation ökar trefaldigt om man under undersökningen av misstag råkar komma in i bukspottkörtel gången med ett instrument eller med röntgenkontrast. Det andra som studien visar är att risken för

bukspottskörtelinflammation kan minskas genom att ett plaströr lämnas kvar i bukspottskörtelgången efter undersökningen och ju tjockare och längre röret är desto mer minskar det risken för bukspottskörtelinflammation efter undersökningen.

I vårt **tredje delarbete** i avhandlingen redovisar vi resultaten av en utvärdering av en ny klassifikation **(HOUSE-klassifikationen)** som använts för att indela ERCP i tre grupper, utifrån deras tekniska svårighetsgrad. Klassifikationen är värderad, dels i förhållande till hur lång tid varje ERCP-undersökning tar, dels i förhållande till hur vanliga komplikationerna är i relation till dess klass i HOUSE-skalan.
HOUSE skalan introduceras för att kunna hjälpa sjukhus och ERCP-center att bättre kunna planera sin verksamhet och styra resurserna till de undersökningar som kräver mest tid och kompetens. Ett annat användningsområde för HOUSE-skalan är att den kan användas efter undersökningen för att kunna identifiera de ERCPer som kräver extra övervakning, där man genom dessa åtgärder förhoppningsvis, skall kunna upptäcka komplikationer tidigare, som kan ha uppstått under ERCP-undersökningen, och på så vis tidigare kunna åtgärda dem.

I avhandlingens sista och **fjärde delarbete** har vi jämfört effekten av **olika stent-typer som använts hos patienter med tumörer i bukspottskörteln, som senare blev föremål för kirurgi.** Traditionellt har man använt plaströr för att avlasta gulsoten som ofta uppstår då patienter drabbas av bukspottkörtelcancer, i de fall där man tror att patienten kan bli föremål för senare kirurgi, dels för att det är billigare och dels för att man haft en farhåga att de moderna metallstentarna skulle försämra möjligheterna till en lyckad operation. Å andra sidan, medför en användning av metallstent en längre funktion av stentet, vilket leder till att patienten kan undvika en onödig ERCP, och

används alltid i de fall där tumören inte kan avlägsnas genom en operation. I denna studie har vi lottat patienter som skall bli opererade för bukspottkörtelcancer till att antingen erhålla ett plast- eller metallstent, och det vi fann var att metallstentet fungerade bättre. Den främsta orsaken var att stentet fungerade bättre fram till operationen och patienten därigenom kunde undvika att behöva genomgå ytterligare en onödig ERCP undersökning. Vi fann dock även för att ett metallstent heller inte alls påverkade själva operationen negativt, utan att de patienter som genomgick operation som tidigare fått ett metallstent fick samma goda operation som de som fått ett plaststent. Den sista fördelen med att använda ett metall stent var efter operationen, då det visade sig att även komplikationerna efter ingreppet var lägre om man fått ett metallstent innan operationen, men denna sistnämnda skillnad var inte statistiskt säkerställd.

Sammanfattningsvis visar våra studier att **profylaktisk antibiotika** inte bör användas generellt vid alla ERCP-undersökningar eftersom det inte sänker risken för komplikationer tillräckligt, men att **pankreas-stent** bör användas oftare vid ERCP då undersökningen varit besvärlig, eftersom det då sänker risken för bukspottkörtelinflammation väsentligt. Vi har vidare introducerat en ny ERCP-svårighetsgrads-skala **(HOUSE-skalan)** och värderat denna i förhållande till undersökningarnas längd och komplikationsfrekvens, och den kan användas för planering och komplikationshantering vid sjukhus som genomför ERCP. Slutligen har vi visat att **metallstent** är överlägset vid behandling av gulsot hos patienter som skall opereras för bukspottkörtelcancer eftersom de fungerar bättre innan operationen, inte påverkar operationen negativt och till och med kanske minskar risken för komplikationer efter operationen.

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