Multi-society State-of-the-Art Consensus Conference on Prevention of Bile Duct Injury During Cholecystectomy

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State of the Art Consensus Conference on Prevention of Bile Duct Injury During Cholecystectomy

Saturday, October 20, 2018 • Boston, MA

PICO 4: Should **intraoperative biliary imaging** (e.g. intraoperative cholangiography, ultrasound) versus **no intraoperative biliary imaging** be used for limiting the risk or severity of bile duct injury during laparoscopic cholecystectomy?

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PICO 4

- PICO 4: Should **intraoperative biliary imaging** (e.g. intraoperative cholangiography, ultrasound) versus **no intraoperative biliary imaging** be used for limiting the risk or severity of bile duct injury during laparoscopic cholecystectomy?

  Main Outcome: Bile duct injury and severity

  Proxy outcomes: Quality of the CVS, Conversions, Complications (major/minor), Mortality

  Reviewers comments: intraoperative cholangiography/ultrasound vs no imaging

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PICO 4: Recommendation

- Intraoperative biliary imaging (in particular IOC) should be used during cholecystectomy to prevent or limit the severity of bile duct injury in patients with unclear biliary anatomy or suspicion of bile duct injury (strong, low evidence)
- We suggest the liberal use of IOC during cholecystectomy to prevent or limit the severity of bile duct injury in patients with acute cholecystitis or a history of acute cholecystitis, (conditional, low evidence)
- For surgeons with appropriate experience and training, laparoscopic ultrasound imaging is an appropriate alternative to IOC.

PICO 4: Justification

- Randomized trials have been underpowered to answer the question
- Meta-analysis of large studies favors IOC over no IOC in most of adjusted studies
- Large prospective Swedish database study showed intent to use IOC was associated with lower rate of BDI in acute cholecystitis and history of acute cholecystitis only. Other studies have shown a higher rate of BDI in patients with acute cholecystitis.
- In multiple studies, IOC use is associated with increased rate of intraoperative recognition of BDI when it occurs (quality of evidence low but is a consistent finding across multiple studies). The potential benefit is early recognition and avoidance of potentially increasing the severity of BDI.
- Laparoscopic ultrasound appears to show accurate anatomic identification but requires experience and expertise for appropriate use and interpretation of anatomy.

Randomized Trials of IOC vs No IOC:
Ford JA et al Br J Surg 2011 R-AMSTAR Score: 31.5

Table 3 Main outcomes for randomized trials of intraoperative cholangiography *versus* no intraoperative cholangiography

Reference	CBD injury		Intraoperative stones		Retained stones at follow-up		True-positive cholangiograms	False-positive cholangiograms
	IOC	No IOC	IOC	No IOC	IOC	No IOC		
Khan *et al.*[15] ($n = 190$)	0	1*	3	–	0	0†	3	0
Nies *et al.*[17] ($n = 275$)	0	1	3	–	0	4	3	1
Tusek *et al.*[18] ($n = 100$)	NR	NR	4	–	0	0	4	0
Hauer-Jensen *et al.*[19,20] ($n = 280$)	0	0	4	–	0	0	4	3
Murison *et al.*[21] ($n = 285$)	NR	NR	12	–	1‡	0	12	16
Soper and Dunnegan[23] ($n = 115$)	0	0	3	–	0	0	3	3

*Common hepatic duct injury requiring conversion to open surgery. †Three patients re-presented with abnormal liver function tests (LFTs) consistent with choledocholithiasis but ultrasonography showed no significant common bile duct (CBD) or biliary dilatation; one further patient re-presented with deranged LFTs secondary to a biliary stricture. ‡Intraoperative cholangiography (IOC) performed and reported as normal. NR, not reported.

Table 4 Main outcomes for randomized trials of routine *versus* selective intraoperative cholangiography

Reference	CBD injury		Intraoperative stones		Retained stones at follow-up		True-positive cholangiograms	False-positive cholangiograms
	Routine IOC	Selective IOC	Routine IOC	Selective IOC	Routine IOC	Selective IOC		
Amott *et al.*[16] ($n = 303$)	1*	1*	12	5	3†	5‡	12	0
Sharma *et al.*[22] ($n = 167$)	NR	NR	10	7	0	0	10	1

*Intraoperative cholangiography (IOC) performed. †None had successful IOC. ‡One negative IOC, one failed IOC, and IOC not indicated in three. NR, not reported.

There were 2 major BDIs in 1715 patients.

Overall BDI rate was 0.2% and major BDI rate 0.1%.

Randomized Trials of IOC vs No IOC in Lap Chole

Study	N	BDI IOC	BDI No IOC
Khan et al	190	0	1
Nies et al	275	0	1
Tusek et al	100	NR	NR
Hauer-Jenson et al	280	0	0
Murison et al	285	NR	NR
Soper et al	115	0	0
Arnott et al	303	1	1
Sharma et al	167	NR	NR
Ding et al**	371	1	1
Total	2086	2	4

**Not reviewed in Ford et al

Systematic Review of Randomized Trials of IOC vs No IOC: Ford et al Br J Surg 2011 R-AMSTAR Score: 31.5

- Mortality: N=4 trials.
  - 5 deaths in the IOC group and 3 in the non-IOC group
  - None of the deaths were directly attributable to surgery
- Morbidity: N=5 trials
  - One of open cholecystectomy showed higher morbidity rate in the IOC group (14.8% versus 5.8%) – Hauer-Jensen.
  - Another study showed a slightly higher rate of wound sepsis in the IOC group (7.6% versus 5.2% - Murison 1993.
- Summary:
  - Level 1 evidence for IOC was of poor or moderate quality
  - No robust evidence to support or abandon the use of IOC to prevent retained CBD stones or bile duct injury.
  - They also concluded that further small trials were **not** recommended.

Systematic Reviews:

Buddingh KT et al Surg Endosc 2011; 25: 2449-2461.

R-AMSTAR Score: 24

- Systematic review of articles that looked at bile duct visualization techniques for the prevention of BDI during lap chole
- Population based studies > 10,000 pts; most from 1990's
- Studies prone to bias and confounders as they relied heavily on administrative data or very heterogeneous groups.
- In some cases, IOC could have been performed only because a BDI was suspected or observed. As result, the number of BDIs that were identified when IOC was used could have been higher than the true incidence.

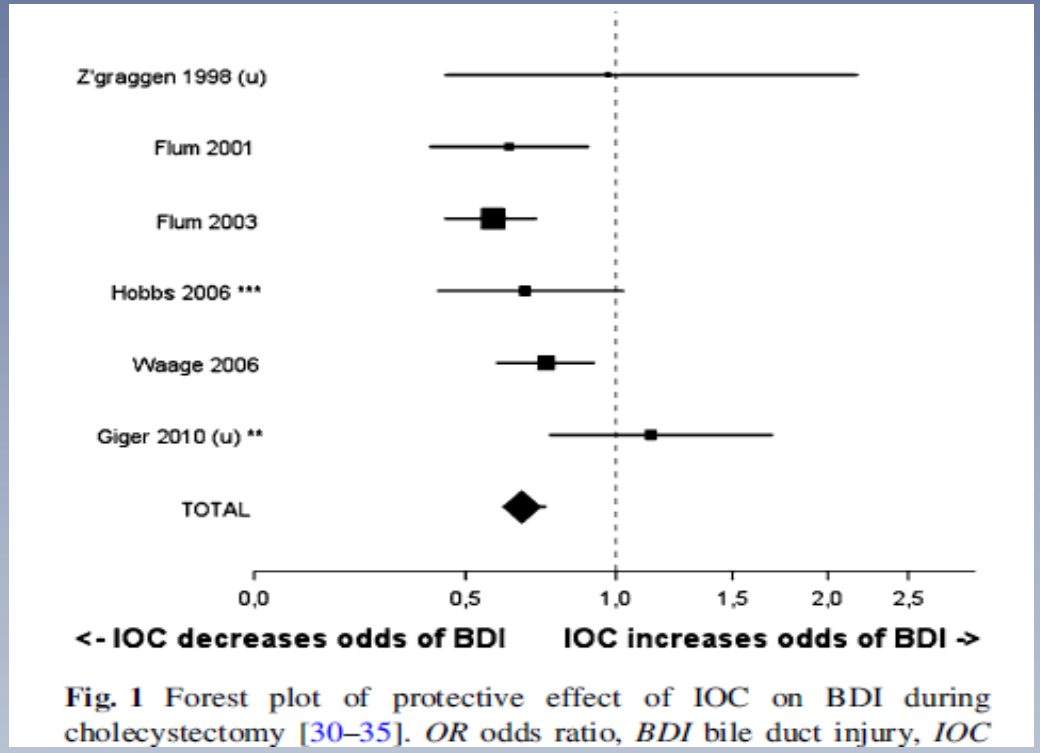
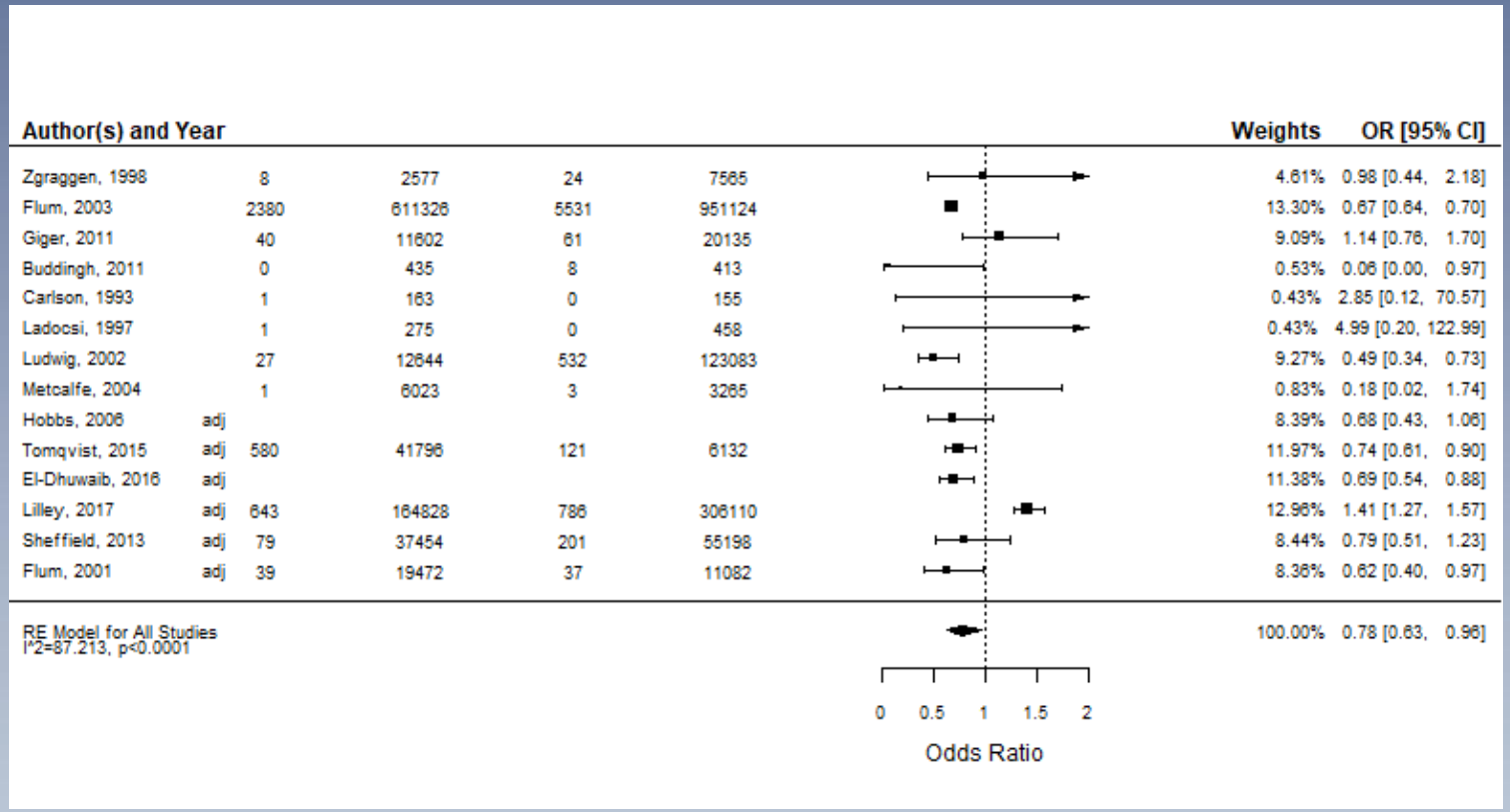


Fig. 1 Forest plot of protective effect of IOC on BDI during cholecystectomy [30–35]. *OR* odds ratio, *BDI* bile duct injury, *IOC*

Forest Plot of Protective Effect of IOC

PICO 4: Meta-analysis IOC vs No IOC and BDI

- Analysis of 14 large studies of mostly administrative data of 2,540,700 cholecystectomies
- Studies at mod-high risk of bias
- Odds Ratio for IOC vs no IOC and BDI:
  - Overall: 0.78 (0.63-0.96)
  - Adjusted: 0.81 (0.62-1.07)



Selective intraoperative cholangiography and risk of bile duct injury during cholecystectomy

B. Törnqvist[1], C. Strömberg[1], O. Akre[2], L. Enochsson[1] and M. Nilsson[1]

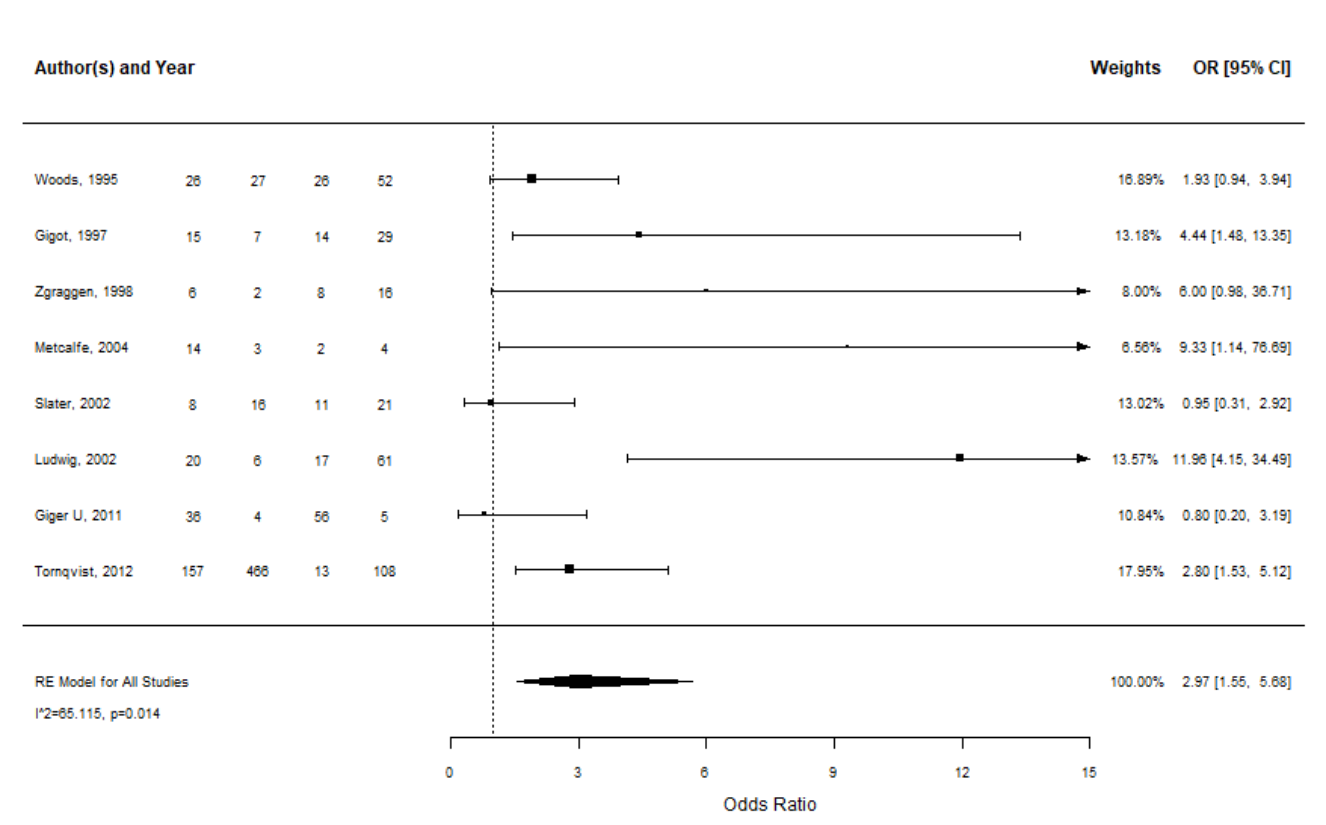
- Swedish Gallriks prospective database study of 51,404 cholecystectomies
- Intent to use intraoperative cholangiography assoc. *reduced* risk of BDI in acute cholecystitis and Hx acute cholecystitis

Group	Adjusted Odds Ratio	Adjusted Odds Ratio w/ instrument variable
All patients	0.76 (0.62, 0.93)	0.80 (0.62-1.04)
Acute cholecystitis	0.44 (0.30, 0.63)*	0.50 (0.32-0.77)*
History acute chole	0.59 (0.35, 1.00)*	0.70 (0.37-1.34)*
No acute cholecystitis	0.97 (0.74, 1.25)	1.06 (0.75-1.49)

Tornqvist B et al. BMJ; 2015; 102: 950-958

Meta-analysis of IOC vs No IOC and Diagnosis of BDI Intraoperatively

- Meta-analysis of 8 studies of 1256 BDI's comparing IOC vs no IOC and intraop recognition of injury
- Odds ratio: 2.92 (95% CI 1.55-5.68) favoring IOC (p=0.014)



Laparoscopic Ultrasound Studies
Systematic Review: Buddingh KT et al Surg Endosc 2011; 25: 2449-2461. R-AMSTAR Score: 24

- Success rate of LUS and IOC both over 90% (Machi 1999)
- Retrospective cohort study (Biffl) found 11 BDIs in 594 cases without LUS vs 0 in 248 cases with LUS. (p =0.04).
- Prospective multicenter cohort study by Machi (2009) reported no BDI and only 3 bile leaks in 1381 patients.
- Conclusions: US shows excellent results in delineating biliary anatomy

PICO 4 Summary of Judgments

CRITERIA	SUMMARY OF JUDGEMENTS						IMPORTANCE FOR DECISION
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large	Varies	Don't know	**HIGH**
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial	Varies	Don't know	**LOW**
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High	No included studies		**LOW**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			**MODERATE**
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies / Don't know	**MODERATE**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes	Varies	Don't know	**MODERATE**
FEASIBILITY	No	Probably no	**Probably yes**	Yes	Varies	Don't know	**MODERATE**

PICO 4: Recommendation

- In patients with uncertainty of biliary anatomy or suspicion of bile duct injury during laparoscopic cholecystectomy, we recommend that surgeons use intraoperative biliary imaging (in particular intraoperative cholangiography) to mitigate the risk of bile duct injury (strong recommendation, low certainty of evidence).

- In patients with acute cholecystitis or history of acute cholecystitis, we suggest the liberal use of intraoperative cholangiography during laparoscopic cholecystectomy to mitigate the risk of bile duct injury (conditional recommendation, low certainty of evidence)

- Surgeons with appropriate experience and training may use laparoscopic ultrasound imaging as an alternative to IOC during laparoscopic cholecystectomy.

Vote on PICO 4 Recommendation

State of the Art Consensus Conference on Prevention of Bile Duct Injury During Cholecystectomy

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PICO 5

PICO 5a: Should **intraoperative infrared biliary imaging** versus **IOC biliary imaging** be used for limiting the risk or severity of bile duct injury during laparoscopic cholecystectomy?

PICO 5b: Should **intraoperative infrared biliary imaging** versus **white light biliary imaging** be used for limiting the risk or severity of bile duct injury during laparoscopic cholecystectomy

Main Outcome: Bile duct injury (incidence or change in severity)

Proxy outcomes: Quality of the CVS, Conversions, Complications (major/minor), Mortality

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PICO 5: Recommendations:

- Current evidence is insufficient to make a recommendation regarding use of near infrared cholangiography for identification of biliary anatomy during cholecystectomy compared to intraoperative cholangiography or white light.

- The evidence should be reassessed once results of the large randomized trial are available (NCT02702843)

PICO 5: Type B Recommendation:

- Near infrared cholangiography should be assessed in large trials compared to white light and/or intraoperative cholangiography with risk stratification and risk adjustment. In particular, this technology should be studied in difficult cholecystectomy patient populations that includes those with acute cholecystitis or a history of acute cholecystitis, severe chronic cholecystitis, and obese patients.

PICO 5: Justification:

- Multiple small studies, most are not comparative
- Comparative studies though small suggest a trend toward enhanced identification of CD and CBD with NIRC compared to IOC
- Studies are inconclusive regarding the additional benefit of infrared cholangiography in comparison to conventional white light.
- Studies are not risk adjusted and NIRC inadequately studied in higher risk populations (obese patients, acute cholecystitis)
- Large randomized industry sponsored trial (NCT02702843) completed – results pending

PICO 5: Overview

- Systematic reviews – 5
- Randomized controlled trials: 0
- Prospective cohort studies: 11
- Retrospective cohort studies: 0
- Case series: 2

Systematic Review 1:
Vlek SR et al Surg Endosc 2016: R-AMSTAR-29

- Most studies examined were prospective cohort studies and highly subject to bias
- Most studies did not compare ICG visualization intraoperatively to conventional white light
- The population studied were heterogeneous. For studies that looked at both complicated and uncomplicated gallstone disease, biliary visualization was pooled for these.
- Different definitions for uncomplicated and complicated gallbladder disease were used between the studies.
- Other considerations for use of ICG verses IOC. IOC costs more, has greater radiation exposure, higher technical failure, potentially challenging perioperative logistics, and risk of biliary injury from cannulation. ICG can provide imaging before the start of dissection and can be used multiple times without additional risk to the patient

Systematic Review 1: Vlek SR et al Surg Endosc 2016: GRADE Summary of Evidence

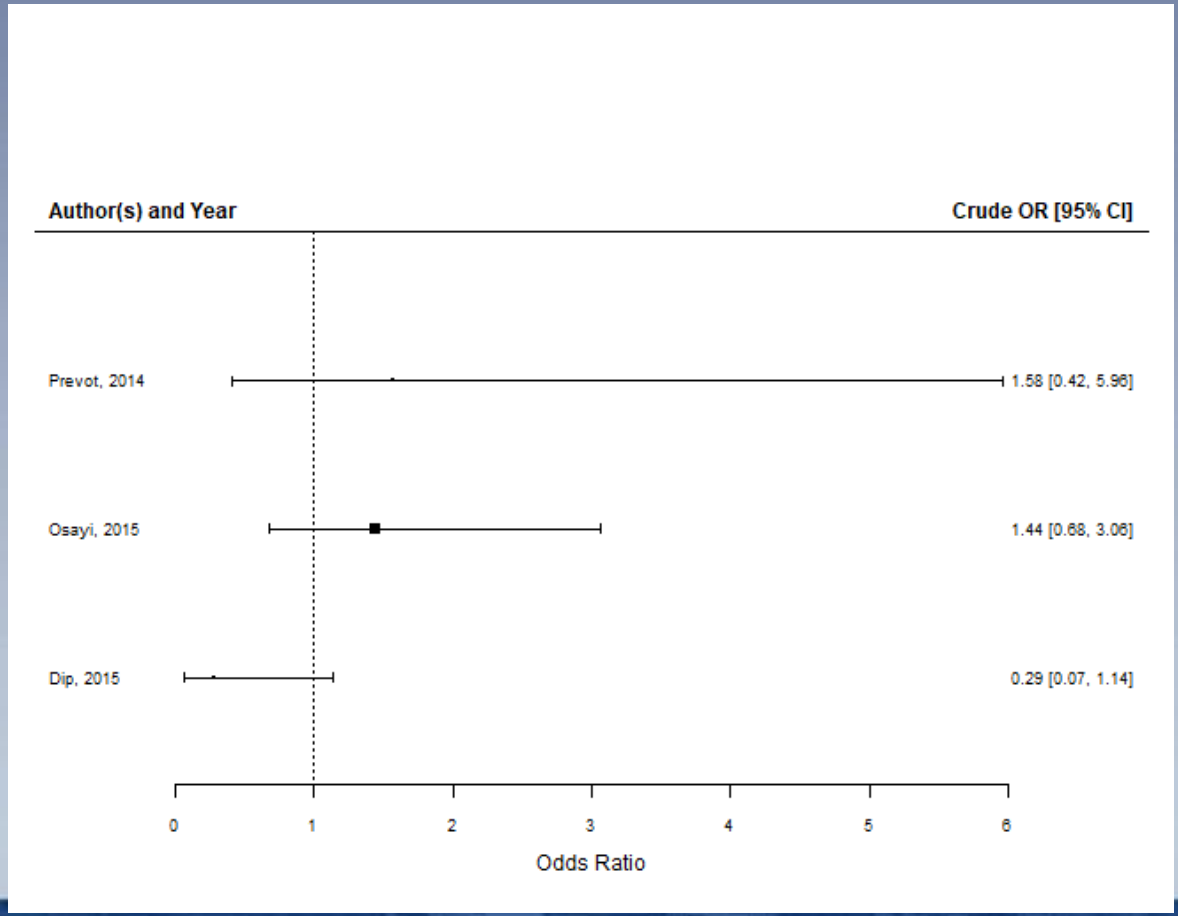
Outcomes	Anticipated absolute effects* (95% CI) Risks with IOC	Relative effect (95% CI) Risk w ICG	No Participants	Quality of evidence	Comments
Cystic duct	study population 837 per 1000	RR 1.16 (1.00-1.35) 971 per 1000 (837-1000)	430 (four observational studies)	moderate	Down graded for imprecision
CBD	study population 851 per 1000	RR 1.00 (0.97-1.03) 851 per 1000 (826-877)	430 (for observational study	moderate	Down graded for imprecision
CHD	study population 793 per 1000	RR 0.76 (0.58-1.01)603 per 1000 (460-801)	300 (3 observational studies)	low	Down graded for imprecision and serious risk of bias

Systematic Review 2:
Pesce A et al World J Gastroenterol 2015: R-AMSTAR-27

- Sixteen studies were reviewed from 2009-2014. The study populations were NIR during standard lap chole N= 11, single incision robotic cholecystectomy N= 3, multiport robotic cholecystectomy N= 1, and single incision lap chole N= 1. The only study not reviewed in Vlek is Dasalaki 184 robotic lap choles.
- Detection rates of structures (weighted averages)

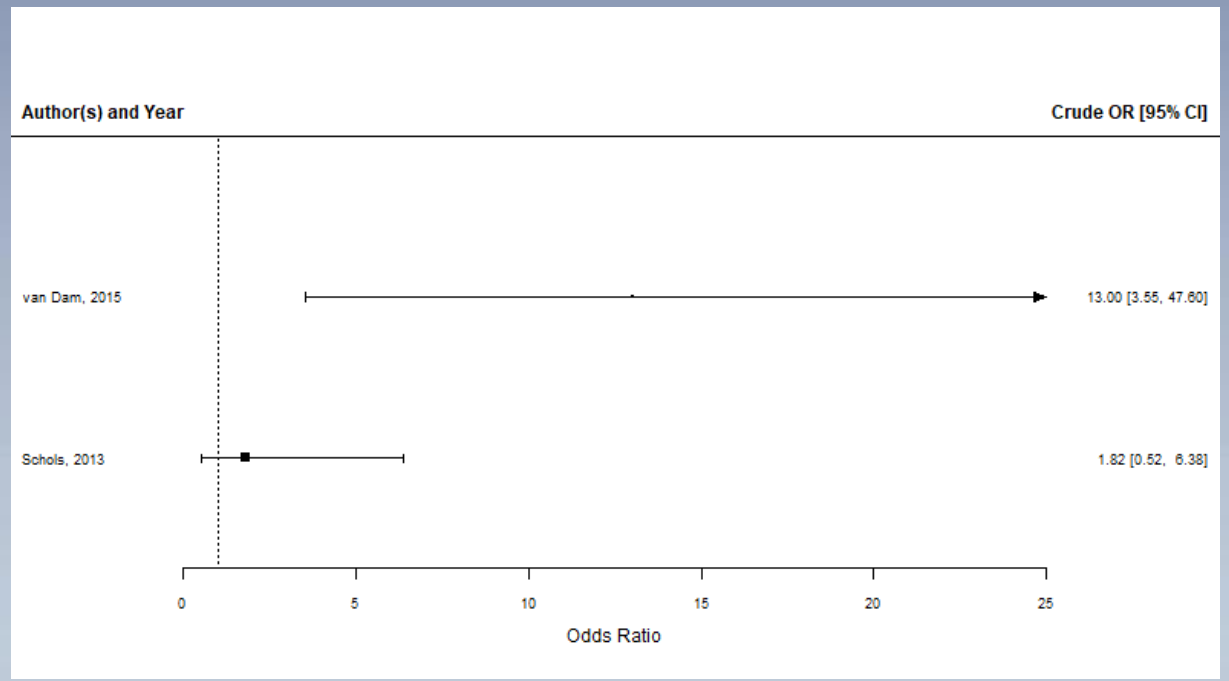
	Cystic duct	CHD	CD-CHD junction	CBD	Cystic artery
N = 590 pts	96.2 (94.7.97.7)	78.1 (74.8-81.4)	72.0 (69.0-75.0)	86.0 (83.3-88.8)	69.4 (61.8-77.1) *
Acute cholecystitis (2 studies,	91.6-94.5%	79.1-57.0%	75%^	79.1-72.0%	

WG2 PICO 5 Meta-analysis: Near-infrared cholangiography vs IOC

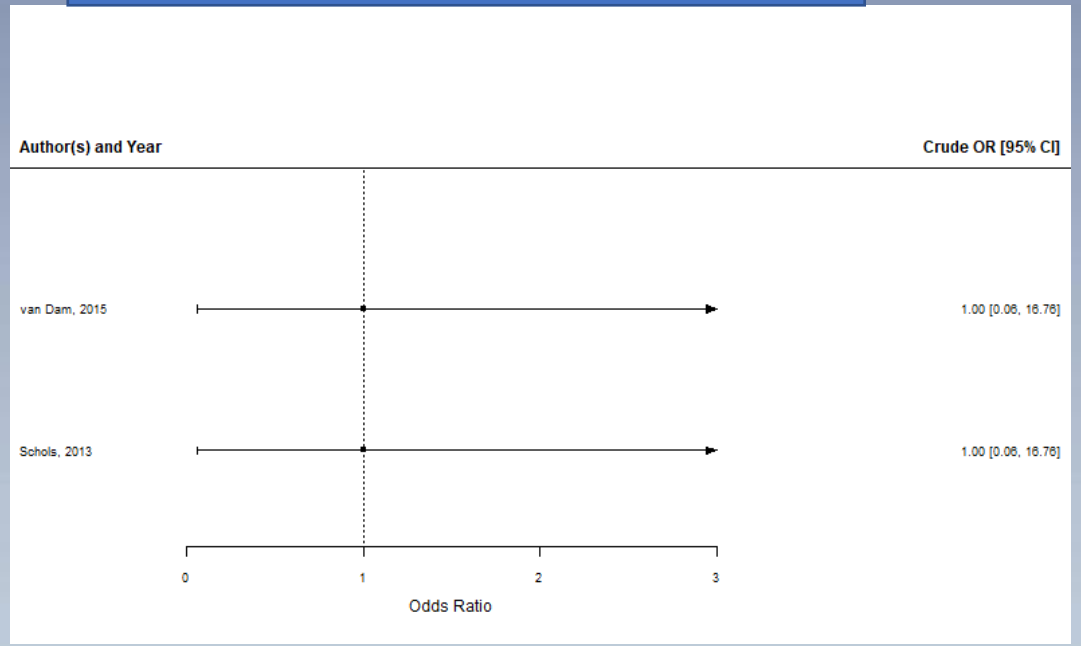


WG2 PICO 5 Meta-analysis: Near-infrared cholangiography vs White Light

Cystic Duct ID



CBD ID



Multicenter Randomized Trial (NCT02702843)

- Trial design: Prospective randomized trial to compare lap cholewith near infrared fluorescent cholangiography (NIRC) vs conventional lap chole
- Enrollment: 603 pts
- Outcomes: ID biliary structures, CVS visualization, cystic duct/artery to GB, surgical time, BDI, complications, etc
- Sponsor: Karl Storz Endoscopy

PICO 5: Summary of Judgments

CRITERIA	SUMMARY OF JUDGEMENTS					
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large	Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial	Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High	No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability		
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies / Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes	Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes	Varies	Don't know

PICO 5: Recommendations:

- Current evidence is insufficient to make a recommendation regarding use of near infrared cholangiography for identification of biliary anatomy during cholecystectomy compared to intraoperative cholangiography or white light. The evidence should be reassessed once results of the large randomized trial become available (NCT02702843)

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- Near infrared cholangiography should be assessed in large trials compared to white light and/or intraoperative cholangiography with risk stratification and risk adjustment. In particular, this technology should be studied in difficult cholecystectomy patient populations that includes those with acute cholecystitis or a history of acute cholecystitis, severe chronic cholecystitis, and obese patients.

Vote on PICO 5 Recommendation

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PICO 6 and 7

- Taylor Riall and Dana Telem

- Workgroup: Ryan Campagna, Dan Hashimoto, Chris Davis, Marie Crandall, Chantal den Bakker, Leonie van Gastel, Charles Lawrence

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PICO 6: Question

Should **surgical (complexity) risk stratification vs alternative or no risk stratification** be used for mitigating the risk of BDI associated with laparoscopic cholecystectomy?

Primary outcome: Bile duct injury

Recommendation 1

We suggest that surgeons use the Tokyo Guidelines 18 (TG18) for grading and management of patients with acute cholecystitis.

(conditional recommendation, low certainty of evidence)

Recommendation 2

During operative planning of laparoscopic cholecystectomy and intraoperative decision-making, we suggest that surgeons consider factors that potentially increase the difficulty of laparoscopic cholecystectomy (such as male gender, increased age, chronic cholecystitis, obesity, liver cirrhosis, adhesions from previous abdominal surgery, emergency cholecystectomy, cystic duct stones, enlarged liver, cancer of gallbladder and/or biliary tract, anatomic variation, biliodigestive fistula, and limited surgical experience).

(conditional recommendation, very low certainty of evidence)

Study Review

- We reviewed 18 articles, some only tangentially relevant. These included:
  - 3 systematic reviews,
  - 1 case-control study
  - 4 prospective cohort studies
  - 9 retrospective comparative cohort studies
  - 1 case series

Study Review

No article DIRECTLY addressed the PICO question by comparing the incidence of BDI when a risk stratification system was used vs. not used.

Evidence: Acute Cholecystitis Increases Risk of BDI

There is evidence to indicate that the presence of acute cholecystitis increases the risk of mortality as well as BDI, as well as evidence that this risk increases with the severity of inflammation as proposed by the TG 13/18.

Evidence: Acute Cholecystitis Increases Risk of BDI

- Best evidence is from a case-control study, derived from a population-based clinical database
- Matched 158 BDI patients to 623 controls
- One of the few studies to use the TG13 criteria to grade severity of cholecystitis

Tvornquist et al. World J Surg. 2016;40:1060–1067.

Evidence: Acute Cholecystitis Increases Risk of BDI

- The adjusted **risk of bile duct injury doubled** among patients with ***acute cholecystitis*** **(OR 1.97 95 % CI 1.05–3.72)**
- **Risk increased as inflammation increased**
  - *Tokyo grade I:* ***(OR 0.96 95 % CI 0.41–2.25)***
  - *Tokyo grade II:* ***(OR 2.41 95 % CI 1.21–4.80)***
  - *Tokyo grade III;* ***(OR 8.43 95 % CI 0.97–72.9)******
- The mortality rate was 5.4% for grade III, 0.8% for grade II, and 1.2% for grade I cholecystitis (not risk adjusted)

******The N for grade III cholecystitis was small.***

Tvornquist et al. World J Surg. 2016;40:1060–1067.

Evidence: Acute Cholecystitis Increases Risk of BDI

- Systematic review focusing on factors that make LC difficult
- Does it assess the validity of a risk stratification system in reducing BDI
- No quantitative analysis performed
- No direct results focusing on BDIs
- No provision of comparative statistics from the included studies to identify risk factors for BDIs

Hussain et al. Surg Laparosc Endosc Percutan Tech. 2011;21:211–217.

Evidence: Acute Cholecystitis Increases Risk of BDI

- Included 91 articles
  - Three meta-analyses of randomized trials
  - 5 controlled randomized trials, 8 well-designed controlled studies,
  - 13 well-designed experimental studies
  - 63 descriptive retrospective studies.
- 324,553 patients

Evidence: Acute Cholecystitis Increases Risk of BDI

- Factors associated with difficult LC:
  - Male gender, age, acute cholecystitis, chronic cholecystitis, obesity, liver cirrhosis, adhesions from previous abd surgery, emergency cholecystectomy, cystic duct stone, large liver, big gallbladder, cancer of GB and/or biliary tract, anatomic variation, biliodigestive fistula, surgical experience
- For age, gender, chronic cholecystitis, cirrhosis, abdominal adhesions, obesity, cystic duct stones, large liver/GB, surgical experience, and emergency cholecystectomy there were **no included studies that directly showed an association with BDI**

Evidence: Acute Cholecystitis Increases Risk of BDI

- Prospective Cohort Study (Switzerland) – included in systematic review
  - Evaluated 12,111 laparoscopic cholecystectomies
- BDI
  - Overall - 0.3%
  - 0.18% for symptomatic gallstones
  - 0.36% for ***acute cholecystitis*** (no p-value provided)
  - Severe chronic cholecystitis with shrunken gallbladder - 3%

Evidence: Risk Stratification Models

- Identified two risk stratification systems that grade the severity of acute cholecystitis:
  - Tokyo guidelines 2013/2018 (TG13/18)
  - AAST Emergency General Surgery Grade for Acute Cholecystitis.
- **TG are currently the only risk stratification model that risk stratified and guides management of patients with acute cholecystitis by grade (severity) of acute cholecystitis.**

Okamoto et al. J Hepatobiliary Pancreat Sci. 2018;25:55–72.

TG18 Severity Grading

The Tokyo guidelines grade descriptions of acute cholecystitis severity.

Grade	Description
Grade I (mild)	Acute cholecystitis without organ dysfunction
Grade II (moderate)	Associated with any single following conditions WBC > 180,000/mm^3 Palpable tender mass in right upper quadrant Symptoms longer than 72 hours Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)
Grade III (severe)	Associated with any organ dysfunction of the following: Cardiovascular: Hypotension requiring vasopressors Neurologic: Decreased level of consciousness Respiratory: $PaO_2/FiO_2 < 300$ Renal: Oliguria, creatinine > 2.0 mg/dL Hepatic: PT-INR > 1.5 Hematologic: Platelets < 100,000/mm^3

PT-INR, prothrombin time–international normalized ratio; *WBC*, white blood cell.

AAST Severity Grading

Table 2
AAST EGS grade descriptions of acute cholecystitis severity.

Grade	Description	Imaging	Operative
Grade I	Localized gallbladder inflammation	Wall thickening, pericholecystic fluid, nonvisualization of the gallbladder	Localized inflammatory changes
Grade II	Distended gallbladder with purulence or hydrops, necrosis/gangrene of wall noted without iatrogenic perforation	Above plus air in the gallbladder lumen, wall or biliary tree	Distended gallbladder with pus/hydrops, nonperforated wall necrosis/gangrene
Grade III	Noniatrogenic perforation with bile located to RUQ	Extraluminal fluid collection limited to RUQ	Noniatrogenic gallbladder wall perforation with bile limited to RUQ
Grade IV	Pericholecystic abscess, bilioenteric fistula, gallstone ileus	RUQ abscess, bilioenteric fistula, gallstone ileus	Pericholecystic abscess, bilioenteric fistula, gallstone ileus
Grade V	Grade IV disease but with generalized peritonitis	Free intraperitoneal fluid	Above with generalized peritonitis

RUQ, right upper quadrant.

Fig. 1. AAST EGS acute cholecystitis grade.

TG18 Management Based on Severity

- Grade I (mild) AC:
  - LC should ideally be performed soon after onset if the Charlson and ASA-PS scores suggest the patient can withstand surgery.
  - If patient cannot tolerate surgery, conservative treatment should be performed at first and delayed surgery considered once treatment is seen to take effect
- Grade II (moderate) AC
  - LC should ideally be performed soon after onset if the CCI and ASA-PS scores suggest the patient can tolerate surgery and the patient is in an advanced surgical center
  - Particular care should be taken to avoid injury during surgery and a switch to open or subtotal cholecystectomy should be considered depending on the findings
  - If patient cannot withstand surgery, conservative treatment as above and biliary drainage should be considered

Okamoto et al. J Hepatobiliary Pancreat Sci. 2018;25:55–72.

TG18 Management Based on Severity

- Grade III (severe) AC
  - Degree of organ dysfunction should be determined
  - Attempts to normalize function through organ support, alongside administration of antimicrobials
  - If patient can withstand surgery, early Lap-C can be performed by a specialist surgeon with extensive experience in a setting that allows for intensive care management
  - If patient cannot withstand surgery
    - Conservative treatment
    - Early biliary drainage should be considered if it is not possible to control the gallbladder inflammation

Controversy Over TG Severity Grading

- Hernandez et al. 2018
- Compares the AAST vs. TG18 severity grading systems for predicting:
  - Mortality (AUC 0.86 vs. 0.73)
  - Complications (AUC 0.76 vs. 0.63)
  - Need for cholecystectomy tubes (AUC 0.80 vs. 0.68), all $p<0.05$.
- Do not look specifically at BDI, nor do they propose a management algorithm based on the AAST grading or evaluate such a stratification system in reducing risk of complications or BDI

Controversy Over TG Severity Grading

- Joseph et al. 2018
- Retrospective cohort study
- 1,982 patients undergoing urgent cholecystectomy
  - 779 had an acute component on final pathology
  - TG13 missed 35% of gangrenous/acute cholecystitis
  - Only 39% of patients with an acute component were identified by TG13

PICO 6 - Limitations

- The majority of studies demonstrating and increased risk of BDI with AC do not grade the severity of cholecystitis because clinical data are not available
- The TG13/18 are currently the only risk stratification model that guides management of patients with acute cholecystitis
- In one case-control study, the severity of AC was graded according to the TG13; the risk of injury increased with increasing severity.
- The validity of TG18 model in identifying AC is controversial
- No evidence that risk stratifying management based on TG18 would have reduced that risk or changed management

PICO 6 – Summary of Judgments

DESIRABLE EFFECTS	Trivial	Small	Moderate	Large	Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**	Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High	No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**		
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies / Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes	Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes	Varies	Don't know

Recommendation 1

We suggest that surgeons use the Tokyo Guidelines 18 (TG18) for grading and management of patients with acute cholecystitis.

(conditional recommendation, low certainty of evidence)

Vote on PICO 6 A1. Recommendations

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Recommendation 2

During operative planning of laparoscopic cholecystectomy and intraoperative decision-making, we suggest that surgeons consider factors that potentially increase the difficulty of laparoscopic cholecystectomy (such as male gender, increased age, chronic cholecystitis, obesity, liver cirrhosis, adhesions from previous abdominal surgery, emergency cholecystectomy, cystic duct stones, enlarged liver, cancer of gallbladder and/or biliary tract, anatomic variation, biliodigestive fistula, and limited surgical experience).

(conditional recommendation, very low certainty of evidence)

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PICO 7: Question

Should **risk stratification that accounts for cholecystolithiasis vs no/alternate risk stratification** be used for mitigating the risk of BDI associated with laparoscopic cholecystectomy?

Primary outcome: Bile duct injury

Recommendation

A specific recommendation cannot be provided as no risk prediction models exist that incorporate the presence or absence of gallstones as a factor that increases bile duct injury or difficulty of laparoscopic cholecystectomy.

Future Studies Related to PICO 6 and PICO 7

To be discussed later:

12.B.2 We suggest the development and establishment of valid evidence for a ‘procedure difficulty score’ for laparoscopic cholecystectomy.

PICO 9

- Taylor Riall and Dana Telem
- Workgroup: Ryan Campagna, Dan Hashimoto, Chris Davis, Marie Crandall, Chantal den Bakker, Leonie van Gastel, Charles Lawrence

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PICO 9: Question

Subtotal cholecystectomy **compared to** total laparoscopic or open cholecystectomy for limiting the risk or severity of bile duct injury in patients who at the time of their operation have MARKED acute LOCAL INFLAMMATION or CHRONIC cholecystitis with biliary inflammatory fusion (BIF) of tissues and tissue contraction?

Primary outcome: Bile duct injury

Recommendation

When marked acute local inflammation or chronic cholecystitis with biliary inflammatory fusion (BIF) of tissues/tissue contraction is encountered during laparoscopic cholecystectomy that prevent the safe identification of the cystic duct and artery, **we suggest that surgeons consider subtotal cholecystectomy either laparoscopically or open depending on their skill set and comfort with the procedure** (Conditional recommendation, very low level of evidence)

Data: Group Comparison & Primary Outcome

- Only 1 article directly compared subgroups (STC vs. LC) with BDI as an outcome metric and **directly addressed question 9**
- University HealthSystem Consortium database, 2009-2013
- 1:1 propensity score match was used to compare procedural outcomes accounting for clinical and demographic factors
- STC (n=487), LC (n=131,082)
- Initial analysis STC: longer LOS, higher readmission, higher mortality
- After PS matching, NO difference was demonstrated between LC and STC (except cost which was higher for STC)

J Surg Res. 2017 Oct;218:316-3

Data: Group Comparison & Primary Outcome

- Concluded: STC Safe and feasible and can be used as an alternative to total LC in select patients.

- Limitations:
  - Confounding variables not accounted for in PS that cannot be derived from administrative database
    - Clinical heterogeneity (intraoperative details)
    - Surgeon factors (decision making, skill set, training)
    - Patient factors (e.g., duration of symptoms, previous attacks)

Data: Addressing STC

- The remaining articles:
  - One article reflected the Tokyo guidelines
  - 11 single group case series (excluded)
  - 2 retrospective comparative cohort studies
  - 1 prospective comparative cohort study
  - 2 systematic reviews.

- No cohesive end points are identified for aggregation and comparison.

- **Groups were not compared.**

Retrospective Cohort Study (n=2)

- Both single center studies (n=48 and n=3,485) conducted in the Asia Pacific in patients undergoing subtotal cholecystectomy (any approach).

- Study 1 was an as-treated and study 2 on an intent to treat basis.

- End points not comparable, populations not similar and comparison not made. The single case series had no real comparisons and did not merit inclusion.

Prospective comparative cohort study

- Prospective comparative cohort study, n=125,
- Compared traditional LC to retroinfundibular approach
- Thus the main outcome measure was not compared and groups of interest not compared.

Systematic reviews (n=2)

- The first article classified as a systematic review, 91 studies including 324,556 patients were selected for review.
- Reviewed 12 studies (n=822) patients for lap subtotal cholecystectomy.
- Conversion rate of 0.05%, and concluded with Level 2 evidence that it can be performed safely.
- No data on cumulative BDI injury. Did not compare treatment therapies, only commented on variable options. No management consensus determined.

Systematic Reviews: (JAMA Surgery, 2015)

- Systematic review: 30 studies, 1,231 patients, 72.9% lap
- Follow-up data not reported
- Due to AC 72%, cirrhosis 18%, gangrene/perf 6%, Mirizzi 3%
- Stump closure: clips, sutures, endoloop, linear stapler
- Outcomes for subtotal cholecystectomy
  - Bile leak 18% (42% fenestrating vs. 16.5% reconstituting)
  - BDI 0.08%
  - Retained stones 3.1% (12.0% fenestrating vs. 2.4% reconstituting)
  - ERCP 4.1%
  - Reop 1.8%

Elshaer M et al. JAMA Surg 2015;150:159-168.

Table. Complications Classified According to the Surgical Technique Used

Surgical Technique (No. of Studies)	Patients, No. Affected/ Total No. (%)	No. (%)								
		Hemorrhage	Subhepatic Collection	Bile Leak	CBD Injury	Retained Stones	Post-operative ERCP	Wound Infections	Reoperation	30-d Mortality
Nonremoval of posterior wall (23)[a]	1011/1151 (88.0)	4 (0.4)	30 (3.0)	205 (20.3)	1 (0.09)	33 (3.3)	42 (4.1)	19 (1.9)	20 (2.0)	5 (0.5)
Removal of posterior wall (4)[b]	140/1151 (12.2)	0	4 (2.8)	10 (7.1)	0	4 (2.8)	5 (3.6)	6 (4.3)	1 (0.7)	0
OR (95% CI)		0.9 (0.3-2.5)	1.0 (0.7-1.4)	1.[illegible] (0.9-2.[illegible])	1.0 (0.1-7.3)	1.0 (0.7-1.[illegible])	1.0 (0.7-1.3)	1.0 (0.6-1.5)	1.0 (0.6-1.5)	0.9 (0.4-2.3)
Heterogeneity *Q* value		40.6[g]	39.6	37.7	39.4	49.0[g]	31.2	25.8	34.0	33.3
Nonclosure of CD and GB stump (3)[c]	100/1161 (8.6)	1 (1.0)	19 (19.0)	42 (42.0)	0	12 (12.0)	15 (15.0)	1 (1.0)	5 (5.0)	2 (2.0)
Closure of CD and GB stump (24)[d]	1061/1161 (91.4)	3 (0.3)	16 (1.5)	175 (16.5)	1 (0.09)	25 (2.3)	32 (3.0)	28 (2.6)	16 (1.5)	3 (0.3)
OR (95% CI)		1.1 (0.4-3.0)	1.0 (0.7-1.5)	0.[illegible] (0.8-1.1)	1.0 (0.1-7.7)	1.[illegible] (0.7-1.5)	1.0 (0.8-1.4)	1.0 (0.[illegible]7-1.5)	1.0 (0.6-1.6)	1.0 (0.4-2.7)
Heterogeneity *Q* value		49.0[g]	41.8	36.2	40.1	37.2	32.2	38.8	32.5	37.8

No Difference

No Difference

Elshaer M et al. JAMA Surg 2015;150:159-168.

Meta-analysis continued

- Only comparison was laparoscopic versus open
- Laparoscopic approach (vs open) produced less risk of:
  - Subhepatic collection (odds ratio [OR], 0.4; 95% CI, 0.2-0.9)
  - Retained stones (OR, 0.5; 95% CI, 0.3-0.9)
  - Wound infection (OR, 0.07; 95% CI, 0.04-0.2)
  - Reoperation (OR, 0.5; 95% CI, 0.3-0.9)
  - Mortality (OR, 0.2; 95% CI, 0.05-0.9)

- Lap (vs. open) was associated with increased risk of bile leaks (OR, 5.3; 95% CI, 3.9-7.2)

Elshaer M et al. JAMA Surg 2015;150:159-168.

Limitations Driving Recommendation

- Lack of comparative effectiveness research
- Heterogeneity precluding comparison in current studies
  - Patient factors (e.g., clinical presentation, relevant history)
  - Clinical factors (e.g. intraoperative findings, preoperative workup)
  - Surgeon factors (e.g., training, skill set, judgement)
  - Technical factors (e.g., how STC performed, defined)
- Low incidence of BDI

Future Directions

- Comparative effectiveness research to ascertain/specify when and in whom STC is appropriate as compared to open or lap total cholecystectomy

- Education of surgeons in technique to ensure proper performance.

Recommendation

When marked acute local inflammation or chronic cholecystitis with biliary inflammatory fusion (BIF) of tissues/tissue contraction is encountered during laparoscopic cholecystectomy that prevent the safe identification of the cystic duct and artery, **we suggest that surgeons consider subtotal cholecystectomy either laparoscopically or open depending on their skill set and comfort with the procedure** (Conditional recommendation, very low level of evidence)

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