**Appendix 7: Guideline Question 8: Other Notable Studies on Timing of Acute Cholecystitis**

1. Roulin D et al. Early versus delayed cholecystectomy for acute cholecystitis, are the 72 hours still the rule? A randomized trial. Ann Surg 2016 ; 264: 717-722.

This RCT is the only one found that specifically compared patients having cholecystectomy on initial admission with symptoms >72hr to patients having cholecystectomy delayed for at least 6 weeks. Eighty-six patients diagnosed by TG triad were randomized. By definition all patients had moderate cholecystitis (symptoms present >72hr).

“Overall morbidity” was higher in the delayed group [6 (14%) vs 17 (39%) patients, p=0.015]. Median total length of stay (4 vs 7 days, p< 0.001) and duration of antibiotic therapy (2 vs 10 days, p < 0.001) were longer in the delayed group. Total hospital costs were lower in the early group p=0.018). There were no differences in postoperative complications. This study is too recent to have been included in most meta-analyses.

Comment: The primary endpoint “overall morbidity” was a complex variable that included failure of initial antibiotic treatment in the phase 2 group requiring emergency cholecystectomy, unplanned hospital readmission or emergency consultation while awaiting delayed LC, and 30 day postoperative complications. Demographics and comorbidities were well matched in the two groups. However the WBC count on admission was slightly but significantly higher in the delayed group 14,000/mm3 vs. 12,000/mm3(personal communication). Basically, this study supports the findings of the GRADE analysis regarding length of stay but informs that the conclusion applies to moderate grade cholecystitis. The study was not intended to inform re BDI and mortality because of size.

2 Blohm et al. The sooner the better? The importance of optimal timing of cholecystectomy in acute cholecystitis: Data from the National Swedish registry for gallstone surgery, Gallriks. J Gastrointest Surg 2017;21:33–40.

A population based study from Sweden examined the effect of timing of cholecystectomy after admission for AC on BDI, mortality and AEs. The study examined results of treatment within what is considered the early phase. No patients were discharged and readmitted for what is normally defined as delayed cholecystectomy. Significant increases in bile duct injury, adverse events, and mortality were seen in patients operated more than 4 days after admission. The optimal time for operation was within 48 hours of admission.

Comment There was no information given regarding parity of health status among the groups. Severity of acute cholecystitis was not reported.

3. Polo M et al. Acute cholecystitis-optimal timing for early cholecystectomy: A French Nationwide study. J Gastrointest Surg 2015;19:2003–2010.

A population based French study of 40,000 patients examined outcomes in patients who had cholecystectomy on the first admission. Mortality rate was higher if cholecystectomy was done on the day of admission or after day 3 and particularly high when it was done after day 5. Patients operated on day of admission had a higher risk of admission to intensive care unit than patients operated later. Likewise, intensive care admission, reoperation, and postoperative sepsis were lower when surgery was performed between days 1 and 3 than following surgery on the day of admission or after day 5. Patients operated on after day 3 and especially after day 5 were older, had more comorbidities, and were more likely to be operated on in public or private not-for-profit hospitals.

Comment The increased mortality rate on the day of admission probably reflects patients admitted with severe grade acute cholecystitis because of the correlation to admission to the ICU. The difference in results between patients operated on days 1 in 2 and those operated on after day 3 may not have been due to increasingly difficult local operative conditions with time since the two groups were unequal for age, comorbidities and facilities

4. Cao AM, et al. Early laparoscopic cholecystectomy is superior to delayed cholecystectomy for acute cholecystitis: A meta-analysis of case-control studies. Surg Endosc 2016; 30:1172–1182.

There have been many case-control studies. Cao et al published a meta-analysis of 77 such studies. They reported statistically significant reductions in mortality, complications, bile duct leaks, bile duct injuries, wound infections, conversion rates, length of hospital stay and blood loss associated with early LC.

Comment. This was a prodigious effort and as these are lower level studies, it is not surprising that there are significant criticisms. There was a large variation in what was considered to be early vs late. Two thirds of the patients in the 77 studies were derived from two papers, one of which was the study of de Mestral.126 Fewer than half of the studies used TG-triad for diagnosis and severity grading was not used.

5. Endo I, et al. Optimal treatment strategy for acute cholecystitis based on predictive factors: Japan-Taiwan multi-center cohort study. J Hepatobiliary Pancreato Sci 2017; 18: 250-257.

This international multi-centric observational studied treatment in more than 5000 patients presenting with AC stratified patients by TG severity grade. They found that the presence of jaundice, neurologic dysfunction, and respiratory dysfunction were associated with increased mortality when cholecystectomy was performed early.

Comment. This study suggests that early cholecystectomy may be performed safely in patients with TG grade 3 severity who do not have these negative predictive factors. The study also demonstrates that patients can be stratified by TG severity grade even in very large studies.