MANAGEMENT OF ACUTE CHOLECYSTITIS

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MACHO

MANAGEMENT OF ACUTE CHOLECYSTITIS
A COLLABORATIVE AUDIT

Steering group

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Lay Summary

Inflammation of the gallbladder is a common problem affecting many people in the general population and resulting in variable lengths of hospital stay. Treatment options can be non-invasive or invasive based on the severity of the disease and might include antibiotics, a drain into the gallbladder or an operation to remove the gallbladder either at the time of initial admission to hospital or after several weeks at a planned admission once the infection and or inflammation has settled down. It is clear that practices vary within different hospitals so this audit will examine exactly how we manage these patients, with a view to improving the care received by patients presenting with gallbladder disease.

Background:

10-20 % of the UK population are reported to have gallstones. Whilst many of these remain asymptomatic, symptomatic cholelithiasis presents a significant and increasing health care challenge, and now accounts for the most common acute gastro-intestinal disorder for which patients are admitted to hospital in Europe.[1]

Acute cholecystitis is the most common reported complication of gallstone disease occurring in approximately 10% of those patients with symptomatic gallstones. Acute cholecystitis should be suspected in those patients presenting with fever, severe pain located in the right upper abdominal quadrant and tenderness on palpation (Murphy's sign). Inflammation is usually the result of obstruction of the cystic duct by a stone.[2]

Whilst clinical signs are considered specific and sensitive for diagnosis of acute cholecystitis[3], supporting investigations include a raised white cell count (WCC), raised C-reactive protein (CRP) and consistent features on abdominal ultrasound (USS) which may include gallstones, a thickened gallbladder wall (>4mm), gallbladder distension, pericholecystic fluid and a positive sonographic Murphy's sign. MRCP and Computed Tomography (CT) may also support the diagnosis if applicable. [2]

Despite the increasing burden of disease, there continues to be uncertainty and a wide range of practices involved in the treatment of gallstone disease. NICE guidelines (CG188) [4] outlined several key areas for implementation with respect to cholecystitis including offering early laparoscopic cholecystectomy (LC) within 1 week of diagnosis for those patients with acute cholecystitis, utilisation of a cholecystostomy drain as a temporising measure with a view to reconsideration of LC once the patient is well enough and clearance of the bile duct.

More broadly, treatment options can be non-operative or operative. Supportive care with or without antibiotics, analgesia and intravenous fluids are commonly utilised on admission. Thereafter, early or late laparoscopic cholecystectomy should be considered. For those patients considered unfit a cholecystostomy drain is widely used, although there remains limited evidence relating to the long-term impact of this management strategy. A recent randomised trial comparing cholecystostomy versus conservative treatment in a high risk patient population demonstrated no long term benefit for the use of cholecystostomy and suggested that non-operative strategies should be minimised.[5] A Cochrane review (2013) was also unable to determine the role of percutaneous cholecystostomy based on the currently available literature.[6]

The widely accepted Tokyo Guidelines 2018 [7,8] stratify diagnostic severity grading of acute cholecystitis into recommended management flow charts. The grading systems utilised are summarised in Table 1 below.

Grade 3 (severe)	Associated with dysfunction of any one of the following organs/systems: 1. Cardiovascular dysfunction: hypotension requiring treatment with dopamine ≥5 lg/kg per min, or any dose of norepinephrine 2. Neurological dysfunction: decreased level of consciousness 3. Respiratory dysfunction: PaO2/FiO2 ratio <300 4. Renal dysfunction: oliguria, creatinine >2.0 mg/dl 5. Hepatic dysfunction: PT-INR >1.5 6. Hematological dysfunction: platelet count <100,000/mm3
Grade 2 (moderate)	Associated with any of the following: 1. Elevated WCC count (>18,000/mm3) 2. Palpable tender mass in the right upper quadrant 3. Symptoms lasting >72 hours 4. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)
Grade 1 (mild)	Acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder

Table 1: Grading of acute cholecystitis according to Tokyo 2018 criteria. (Adapted from Tokyo guidelines 2018[8])

Within the Tokyo system, Grade 2 AC is often accompanied by severe local inflammation which may make cholecystectomy technically difficult. As such, the authors recommend early LC should be considered if feasible but should take into account the patients general condition. Where the patient's condition is considered 'poor', elective cholecystectomy after improvement in the acute inflammatory process is indicated. Furthermore, the authors state that when a patient does not respond to initial medical treatment, urgent or early gallbladder drainage is required. Figure 1 shows the suggested treatment flow chart for the management of grade 2 AC.

There is a broad array of guidelines within the literature with respect to managing acute cholecystitis but practices continue to vary widely. Factors affecting current practices include surgeon skill set, theatre utility and the availability of diagnostic and therapeutic adjuncts. This audit aims to compare current practices against national and international guidelines and describe regional variation in practice and outcomes.

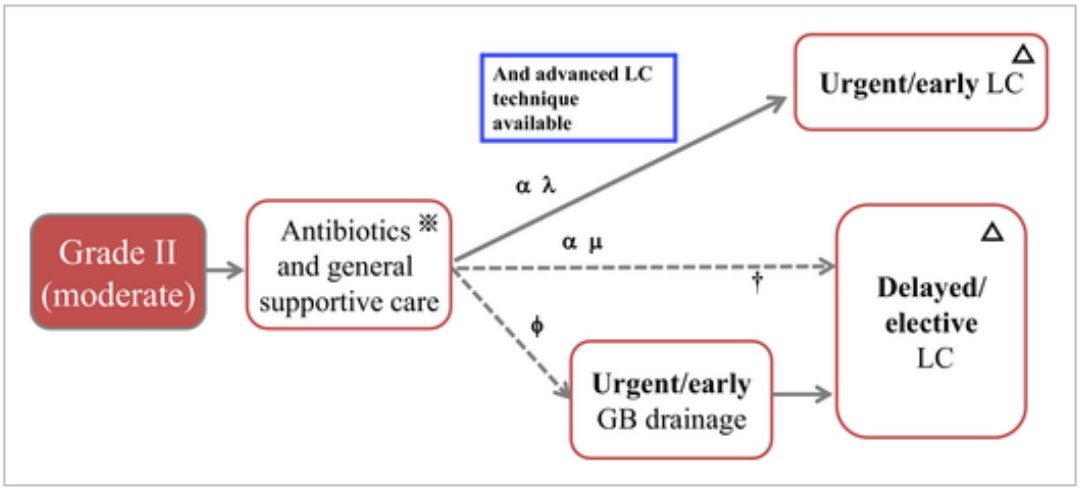

Figure 1. Management of grade 2 acute cholecystitis (Tokyo guidelines 2018[8]).

Aims:

To examine the commonly utilised practices for the management of acute cholecystitis.

Objectives

1. To examine the level of variation in the management of acute cholecystitis
2. To report patient level outcomes stratified by Tokyo severity classification
3. To report patient level outcomes based on treatment strategies
4. To establish proportion of patients undergoing definitive biliary surgery within 90 days of discharge
5. To examine the proportion of patients receiving hot lap chole or cholecystostomy (overall and at each site)
6. To report the characteristics of patients receiving each treatment strategy
7. To examine the outcomes of each treatment strategy
8. To analyse factors effecting time to LC (survival plot)
9. To produce funnel plots to depict centre level variation for each treatment group (use of treatment)
10. Utilise logistic regression outcome model to delineate mortality and complications.
11. If sufficient numbers, to report propensity matched analysis of outcomes of each treatment strategy

Primary outcomes

1. In-hospital mortality
2. In-hospital morbidity
3. Length of stay
4. Unplanned readmissions at 30-days post discharge

Audit standards and expectation:

Source	Measure	Evidence	Expectation
NICE guidance CG 188 [9]	Offer percutaneous cholecystostomy to manage gallbladder empyema when: surgery is not appropriate at presentation and/or conservative management is unsuccessful.	Documentation in patient notes	100%
NICE guidance CG 188 [9]	Reconsider laparoscopic cholecystectomy for people who have had percutaneous cholecystostomy once they are well enough for surgery.	Documentation in patient notes	100%
Pathway for the management of Acute Gallstone Disease [10] Association of Upper GI Surgeons (AUGIS)	Patients diagnosed with AC should have a LC within 72 hours of admission	Documentation in patient notes	100%
Pathway for the management of Acute Gallstone Disease [10] Association of Upper GI Surgeons (AUGIS)	Patients unfit for surgery may be treated with percutaneous cholecystostomy	Documentation in patient notes	Variable
NICE guidance CG 188 [9]	Offer early laparoscopic cholecystectomy (to be carried out within 1 week of diagnosis) to people with acute cholecystitis	Documentation in patient notes	100%
Tokyo Guidelines 2018[8]	Early LC in Grade 1 cholecystitis	Documentation in patient notes	100%

Ethics:

This is a combined audit and service evaluation. As such it does not require ethical approval. All participating units must provide evidence of registration with local audit/clinical governance structures and, permission from the Caldicott Guardian for entry of pseudoanonymised data into REDCap.

Project team structure

MACHO Steering Group

This comprises of a core group of surgical trainees and consultant general surgeons representing the White Rose Surgical Research Collaborative (WRSC). The steering group is responsible for protocol design, data handling, analysis, dissemination of results and the preparation of manuscripts. The MACHO Steering Group are responsible for the use of data resulting from this project.

Local leads

The local leads are responsible for the co-ordinating and organisation of local MACHO teams. This role should normally be filled by a Consultant Surgeon who participates in the management of acute gallbladder pathology. The local lead will sponsor the registration of the audit and ensure that collaborators act in accordance with local clinical governance and guidelines. The local leads act as a link between the local MACHO team and the MACHO Steering Group. They are the first point of contact for local collaborators and are responsible for the dissemination of information to local collaborators from the MACHO Steering Group.

Local MACHO Team

This comprises of a local lead, up to three other collaborators and one independent validator – who may be doctors, medical students, nurses or allied healthcare professionals. There is a maximum of four collaborators per local MACHO team and one validator. The local MACHO team is responsible for putting in place means of identifying all eligible patients and capturing the required data. They should also identify an independent member of the team to validate data.

Trainee Research Collaborative Leads

We are working with trainee research collaborative groups to support delivery of this project. We are liaising with leads of these groups to support recruitment of sites and trainees to for data collection.

Local Project Registration & Data governance

MACHO should be registered as a clinical audit. It is the responsibility of the local MACHO team at each site to identify a local consultant surgeon to supervise them and ensure that MACHO is registered appropriately with their trusts' clinical governance department.

The local MACHO team should seek the permission of their Trust's Caldicott Guardian in order to submit data to the REDCap system. No data should be uploaded to REDCap prior to approval from the Caldicott Guardian.

If there are any difficulties encountered with clinical audit registration, then please seek advice from either the local supervising consultant or contact a member of the MACHO steering group (contact@MACHO.org.uk or info.wrsc@gmail.com) as required.

Method:

Prior to undertaking the prospective assessment of practice, it is important to describe the settings and processes that underpin the care of patients with acute cholecystitis.

Profile of Centre

In order to describe local processes and resources, each site will be asked to complete an online site profile questionnaire when they register. (Questionnaire link: **https://docs.google.com/forms/d/e/1FAIpQLSf47gamyMsh5bovvioAU4jUwqDTQximloJdBg1ZyhNdlaA_hw/viewform?usp=sf_link**). This assesses availability of imaging, theatres, emergency rota set-up, care for increased dependency patients and access to support services.

Identification of patients

The study will take the form of a retrospective cohort audit. The cohort will be identified through local administrative coding using prescribed inclusion criteria set out below. All patients coded K80.0, K80.1, K81.0 and K82.2 using the World Health Organisation (WHO) International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)[11] will be eligible for inclusion.

Inclusion and exclusion criteria

Inclusion criteria:

- Adult patients (greater than or including 16 years of age)
- Clinical features of acute cholecystitis including right upper quadrant pain, pyrexia and/or raised inflammatory markers (WCC, CRP)
- Documented diagnosis of acute cholecystitis as demonstrated by a single radiological test (USS, MRCP or Computed Tomography (CT))

Exclusion criteria:

- Acalculous Cholecystitis
- Pregnant women
- <16 years old
- Underlying Hepatopancreaticobiliary malignancy
- Concomitant common bile duct stones

Data collection period

Retrospective patient identification will be undertaken over a 3-month period using established local administrative coding and data management systems. Those patients presenting between **1st April 2017 and 31st October 2017** will be included. Follow up to **six months** after index admission will be recorded.

Data collection procedure

At registration, the Centre lead will complete a site profile form and return this to the steering committee, along with audit and Caldicott approvals. This form is presented in Appendix A.

Data collection will be using the form presented in Appendix A. Hospital or NHS numbers will not be entered onto this form, but will be kept separately with a key sheet. It is anticipated that for each site a coding report for all patients presenting between the inclusion dates with the coding ICD K81.0 will be generated and there after further interrogation of this data set will be undertaken.

Patients will be screened for inclusion, and data collected where appropriate. Basic demographics and comorbidities (in the form of Charlson Comorbidity Index) will be recorded. This allows standardisation of comparisons between any groups. At 30-days following discharge, hospital systems should be interrogated for evidence of unplanned readmission.

Completed datasheets will be entered onto the secure REDcap system, hosted by the University of Sheffield (https://redfox.shef.ac.uk/). Access to data-entry will be via issued accounts. The REDcap data form matches the pro forma, but has an additional field capturing the collaborator ID number to allow attribution.

Data Collation

All data will be handled in accordance with the Data Protection Act 1998. Data will be collected and stored online through a secure server running the Research Electronic Data Capture (REDCap) web application (ref). REDCap allows collaborators to enter and store data in a secure system. Collaborators will be given secure REDCap project server login details, allowing secure data storage on the REDCap system. All transmission and storage of web by this system is encrypted and compliant with HIPAA-Security Guidelines the United States. Data from this study will be retained on University of Sheffield servers and will not be removed from the UK.

No patient identifiable information will be uploaded or stored on the REDCap database. Collaborators will anonymise patients by recording patient hospital numbers alongside REDCap numbers in a separate spreadsheet in order to aid the collection of data locally. This should be held on secure, password computer systems. Any files should be encrypted for added security. Collaborators may also wish to initially use a paper version of the data collection pro-forma. Paper copies of any data should be destroyed as confidential waste within the centre once uploaded to REDCap.

REDCap accounts will not be issued until evidence is provide via your hospital's local lead that the following approvals are in place at your centre:

1. (i) Successful registration of MACHO with the audit department.
2. (ii) Caldicott Guardian permission for data to be submitted to REDCap.

Training Materials

As with previous multicentre studies, we will deliver online training to ensure standardisation. This will be delivered through online presentation of project rationale, how to complete the proforma, and how to use the REDCap system for return of forms.

Pilot Study

An initial pilot study will be trialled at Sheffield Teaching Hospitals NHS Trust for the prescribed retrospective collection period before disseminated to collaborating centres. This will permit a trial of the data-collection pro forma and IT systems supporting the project.

Process results from the pilot will be reviewed at a steering group meeting. If no or minor modifications only are required, these will be made and the project will proceed as planned. Updated documents will be available from the study website. If a major issue is identified, which requires significant modification of the project, the main data collection window will be delayed to allow this to be addressed.

Local pilot

In order to overcome a learning curve in identifying patients for inclusion, data collection and using REDCap, participating centres are strongly advised to pilot patient identification and data collection prior to their formal data collection start date. Any problems encountered can then be resolved prior to formal data collection either locally or with support from the steering committee.

Full Study Period

The steering group will provide documents to facilitate local audit registration at least three months prior to commencement of the data collection period.

The study period is:

Period	Date
Case Identification and data collection period	01/06/2019-01/10/19
Validation completion date	30/12/2019

Validation

Validation will be performed on 25% of data fields for 10% of cases. The validated fields will include key demographic and outcome data. These fields are outlined in a separate document.

Analysis plan

The initial analysis will describe the cohort of patients admitted with acute cholecystitis. Comparisons between treatment groups (antibiotics alone, early LC, late LC, cholecystostomy) will be made using standard statistical tests (e.g. X^2 for categorical data, student t test for parametric continuous data). A multi-level fixed effects model will be used to compare outcomes from different centres controlling for individual patient level data and explore whether variation in treatment strategy is associated with hospital characteristics (e.g. access to interventional radiology, dedicated upper GI service, index admission LC list).

Statistical support will be obtained from Sheffield Clinical Trials Unit. A formal statistical analysis plan will be developed with this group following the pilot study.

Descriptive analysis:

Description of demographics of captured patients including gender, median age, aetiology of acute cholecystitis and management pathway will be performed. Data on complications of management will be described.

Specific results to be reported are described as in the table below;

Description	**Units of analysis**	**Reported**
Proportion of patients receiving acute LC		As percentage of all patients
Proportion of patients receiving cholecystostomy		As percentage of all patients
Time to surgery from day of admission	<2 days <7days <14 days >14 days	As percentage of all patients
Assessment of centre level variation for each treatment group		As funnel plots for each individual reporting centre.
30-day mortality		As comparison of grade of acute cholecystitis, operated vs non-operated groups and intervention vs no intervention.
In-patient morbidity		As comparison of grade of acute cholecystitis, operated vs non-operated groups and intervention vs no intervention.

Authorship

Authorship will be in accordance with the National Research Collaborative Authorship guidelines. Local MACHO team collaborators and data validators will be eligible for PubMed-citable co-authorship as collaborators, provided a validated dataset is returned by the closing data of the project. There is a maximum of four collaborators per local team and one independent validator, unless an increase in the local team is agreed in advance by the Steering Group. Centres with >5% missing data will be excluded from the analysis and the contributing local team removed from the authorship list.

Sponsorship through the audit approval process by a consultant/senior does not constitute authorship. Similarly, inclusion of a consultants' patients in the audit is not sufficient reason

for authorship. All members of the local team should participate in the process of registering the audit, identifying the data set, collecting data and ensuring >95% completeness and >98% accuracy targets are met.

Data ownership

Following analysis, each unit will receive their own raw data, and a summary of national data. This will allow comparison to local performance and enable local quality improvement work. Data will be held on the University of Sheffield REDCap server. The Steering Group anticipate the data will be made available as open access for all MACHO collaborators.

Quality assurance and Stakeholders

This protocol has been designed and adapted with the support of a number of experts in the management of acute cholecystitis. The protocol was interactively presented to the steering group either side of a pilot study, run in Sheffield Teaching Hospital NHS trust. The study protocol was refined following feedback from these meetings. The protocol has been agreed with the study stakeholders, Roux Group (formerly known as AUGISt), ALSGBI, ASGBI, and AUGIS

Expected Outputs:

All data will be reported as a whole cohort. Unit level data for comparison will be fed back to collaborators to support local service improvement.

This project will be submitted for presentation at a national or international surgical conference.

Manuscript(s) will be prepared following close of the project.

Further steps

With results from the audit, we will identify an intervention and repeat the audit post-intervention. Examples of intervention may include:

- Expedited use of cholecystostomy drains in a selected cohort of patients
- Increasing use of acute cholecystectomy on index admission for the management of acute cholecystitis.

Appendices

Appendix A

Data Collection Proforma

Date of form completion	
Study number	
Age (years)	____ years
Sex	M/F
Charlson comorbidity index	
AIDS	Yes / No
Heart failure	Yes / No
MI	Yes / No
COPD	Yes / No
PVD	Yes / No
CVA/TIA	Yes / No
Dementia	Yes / No
Hemiplegia	Yes / No
Connective tissue disorder	Yes / No
Peptic ulcer disease	Yes / No
Malignancy	No Haematologic or localised solid tumour Metastatic tumour
Liver disease	No Mild Moderate Severe
Diabetes Mellitus	No Uncomplicated End-organ damage
Warfarin	Yes / No

Admission details		
Date admitted (dd/mm/yyyy)	___/____/_____	
Blood tests	Admission	Peak
ALT		
ALP		
Bilirubin		
White cell count		
CRP		
If not on Warfarin PT		
Was there evidence of AKI?	Yes / No	
USS date	___/____/_____ N/A	
CT date	___/____/_____ N/A	
MRCP date	___/____/_____ N/A	
Early outcomes		
Date of discharge	___/____/_____	
Hospital acquired pneumonia	Yes / No	
Delirium	Yes / No	
Cardiac complication	Yes / No	
VTE	Yes / No	
Surgical site infection	No Superficial SSI Deep SSI	
Unplanned 30-day readmission	Yes / No	
Unplanned escalation of care	No HDU ITU	
Inpatient mortality	Yes / No	

Cholecystostomy data	
Date of cholecystostomy	___/____/_____ N/A
Bloods on date of or closest date prior to cholecystostomy	
ALT	
ALP	
Bilirubin	
White cell count	
CRP	
PT	
Was there evidence of AKI?	Yes / No
Approach	Transhepatic Transperitoneal Other
Tube size	
Immediate complication?	Yes / No
Further complications	Wrong site Drain falling out Vascular injury Visceral injury Chronic fistula
Check tubogram post-insertion?	Yes / No
Date	___/____/_____
Check tubogram clear?	Yes / No
Date cholecystostomy removed	___/____/_____
Number of cholecystostomy related hospital admissions in six months after index admission.	____

Cholecystectomy data	
Did patient have cholecystectomy as inpatient on index admission	Yes / No
Did patient have cholecystectomy within 2 weeks of index admission?	Yes / No
Did patient have a cholecystectomy within six months of index admission?	Yes / No
Date of cholecystectomy	___/____/_____
Approach	Laparoscopic Laparoscopic converted to open Open cholecystectomy
Bile duct injury	Yes / No
Hospital length of stay	Day case In-patient

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