An international multi-centre appraisal of the management of acute CHOLEcystitis during the COVID-19 pandemic: The CHOLECOVID audit.

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CHOLECOVID Collaborative

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Introduction

Acute cholecystitis is inflammation of the gallbladder, typically due to gallstones [1,2]. Internationally accepted guidelines provide information on standards for diagnosis and optimum management [3,4]. In patients without major co-morbidity, laparoscopic cholecystectomy during the index admission is the recommended treatment for acute cholecystitis [5,6,7]. A meta-analysis of randomized trials demonstrated that delayed laparoscopic cholecystectomy increased the total hospital stay compared to an early laparoscopic cholecystectomy after acute cholecystitis [8]. Treatment with antibiotics may be used as a temporising option or as an attempt to control symptoms in patients who are unfit for surgery. Radiologically guided percutaneous cholecystostomy can also be a treatment option in patients who are unfit for surgery [9]. Percutaneous cholecystostomy is a recognised alternative treatment to cholecystectomy in high-risk patients and can be used as a definitive option [10,11,12]. Although evidence is limited, this option is supported by international guidelines [13]. The only randomised controlled trial to compare laparoscopic cholecystectomy to percutaneous cholecystostomy reported complications in 44 of the 68 patients (65%) in the percutaneous drainage arm compared to 8 of the 66 patients (12%) in the group undergoing surgery [14].

The outbreak of the novel coronavirus, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19), has posed a significant challenge to surgical healthcare systems across the world [15]. The World Health Organization declared a global pandemic due to SARS-CoV-2 on 12th March 2020 [16].

To cope with this unprecedented pandemic, healthcare systems across the world cut back or completely stopped elective surgery, reduced non-elective surgery and adopted non-surgical modes of treatment. In the United Kingdom, the Royal College of Surgeons of England advised that non-operative treatment options should be considered wherever possible for emergency presentations [17]. In the case of acute cholecystitis, recommended non-operative management constitutes antibiotics

alone, with percutaneous cholecystostomy in select patients [17]. Similar guidance was provided by the American College of Surgeons [18] and the Royal Australasian College of Surgeons [19].

This study is an audit of the hospital management of patients with acute cholecystitis during the time of the COVID-19 pandemic. The audit assesses treatment options and compares outcome to the reference standard of the Tokyo guidelines [3,4].

Methods

Summary

'Mini-teams' of collaborators, with members ranging from medical students and trainees/residents, to consultants, will participate at each hospital. They will retrospectively collect data on patients with acute cholecystitis during two separate data periods. Each centre will be required to complete a survey detailing their local acute cholecystitis management practices.

Design

CHOLECOVID is an international multi-centre audit.

Setting

CHOLECOVID is open to any hospital in the world that treats patients with acute cholecystitis. In order to describe local processes and resources, each site will be asked to complete an online site profile questionnaire to understand local management of acute cholecystitis. All participating centres will be required to register the study according to local regulations, evidence of which will be uploaded onto REDCap prior to commencement of data collection from each respective site.

Patients

Patients admitted to hospital with a clinical diagnosis of acute cholecystitis constitute the study population.

Definition of acute cholecystitis

Acute inflammation of the gallbladder with pain for over 24 hours, often with systemic upset (pyrexia, tachycardia), elevated white cell count (WCC), elevated c-reactive protein (CRP), and at least one imaging modality with findings characteristic of acute cholecystitis [3,4].

Inclusion criteria:

- Adult patients (greater than or including 18 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 at least one radiological test (USS, MRCP or Computed Tomography (CT))

Exclusion criteria:

- Less than 18 years of age

Data collection

Data will be collected and stored online via the Research Electronic Data Capture (REDCap) web application [20,21], hosted and managed by the University of Manchester, United Kingdom. No patient identifiable data will be uploaded or stored on the REDCap database. A designated collaborator (principal investigator - PI) and maximum of 4 co-collaborators will be identified per site, making a total of 5 collaborators at each participating site. Collaborators at each participating site will retrospectively collect data covering admissions with acute cholecystitis from the date of declaration of the pandemic for 2 months (12th March 2020 – 12th May 2020) with a 30-day follow-up period to allow estimation of 30-day mortality. Data will also be collected for a 2 month period prior to the declaration of the pandemic (September 12th 2019 – November 12th 2019) with a 30-day follow-up period to allow for comparison.

Data will be collected in the following categories:

1. Demographics
2. Diagnosis
3. Intervention

4. COVID-19 status on admission, during in-patient course and after discharge
5. Outcome

Local Project Registration

If the option is available, this project should be registered as a clinical audit or service evaluation. In some countries, it may be necessary to obtain formal research ethics approval. It is the responsibility of each local mini-team at each hospital to ensure the study is registered appropriately, according to local regulations. Confirmation of this must be uploaded to REDCap before data collection is permitted.

Possible ways to register this study include:

- Clinical audit. The audit standard used should be that of the Tokyo Guidelines 2018 for management of acute cholecystitis (Appendix B).
- Service evaluation
- Research (e.g. research ethics committee or institutional review board approvals)

Principal investigators should discuss with their head of department to expedite the approval process wherever possible, in view of the urgency of the global pandemic. Regardless of the approval pathway chosen, it should be stressed that this is an **investigator-led, non-commercial** study, which requires **no changes to normal patient care** and only **routinely available non-identifiable data** will be collected. No patient identifiable data will be uploaded or stored on the REDCap database. Patient consent does not need to be sought prior to data collection.

Ethics

The NHS Health Research Authority questionnaire (http://www.hra-decisiontools.org.uk/research/; accessed 1st May 2020) deemed that this study was not research as the participants are not randomized to different groups, there is no change in treatment or patient care and the findings cannot be regarded as wholly generalizable. The primary investigator at each site is responsible for obtaining

necessary local approvals (e.g. audit approval, service evaluation, research ethics committee or institutional review board approval). It will not be possible for collaborators to upload data to REDCap until evidence is provided by the hospital's local lead that the following approvals are in place at each centre:

1. Successful registration of CHOLECOVID study.
2. Caldicott Guardian (or equivalent) permission for data to be submitted to REDCap.

Analysis plan

Data will be reported using descriptive analysis. Comparisons between groups and to reference standards will be undertaken using appropriate non-parametric analyses.

Authorship

All local collaborators who collect and input data into REDCap will be eligible for PubMed-citable co-authorship as collaborators, providing >95% of data points are entered. Centres with >5% of missing data will be excluded from the analysis and the contributing data collectors excluded from authorship. Sponsorship through the audit approval process by a consultant does not constitute authorship, nor does inclusion of a consultants' patients in the audit serve sufficient for authorship. Authorship will be in accordance with the National Research Collaborative Authorship guidelines [24].

Expected Outputs

All data will be reported as a whole cohort. This project will be submitted for presentation at national and international conferences. Manuscript(s) will be prepared following close of the project.

Appendix A - CHOLECOVID Data Collection Proforma

SECTION ONE: BASELINE DEMOGRAPHICS	
Date of Completion of form	
Study number	
Hospital Number	(not to be uploaded to RedCAP)
Age	
Gender	☐ Male ☐ Female
Pregnant	☐ Yes ☐ No

✎	**Co-Morbidity**	**Scoring**
	Previous Myocardial Infarction	1 Point
	Congestive Heart Failure	1 Point
	Peripheral Vascular Disease	1 Point
	Previous CVA	1 Point
	Dementia	1 Point
	COPD	1 Point
	Connective Tissue Disease	1 Point
	Peptic Ulcer Disease	1 Point
	Diabetes Mellitus	1 Point (Uncomplicated) 2 Points (End-Organ Damage)
	Moderate to Severe Chronic Kidney Disease	2 Points
	Hemiplegia	2 Points
	Leukaemia	2 Points
	Malignant Lymphoma	2 Points
	Solid Tumour with Metastasis	6 Points
	Liver Disease	1 Point (Mild) 3 Points (Moderate to Severe)
	AIDS	6 Points
	Age	0 Points (40 or less Years) 1 Point (41 – 50 Years) 2 Points (51 – 60 Years) 3 Points (61 – 70 Years) 4 Points (71 or more Years)

	TOTAL CHARLSON CO-MORBIDTY INDEX	

SECTION TWO: DIAGNOSIS		
Admission Bloods		
Haemoglobin (g/L)		
WCC (x 10^9/L)		
CRP (mg/L)		
Urea (mmol/L)		
Creatinine (µmol/L)		
Alkaline Phosphatase (IU/L)		
Alanine Transaminase (IU/L)		
Bilirubin (µmol/L)		
Internationalised Normal Ratio		
Radiological Investigations		
Abdominal Ultrasound (US)	☐ Yes ☐ No	**Day post-admission:**
US Findings	☐ Gallstones ☐ Acute cholecystitis ☐ CBD Stone / biliary obstruction ☐ No acute findings	
Computed Tomography (CT)	☐ Yes ☐ No	**Day post-admission:**
CT Findings	☐ Gallstones ☐ Acute cholecystitis ☐ CBD Stone / biliary obstruction ☐ No acute findings	
Magnetic Resonance Cholangio Pancreatography (MRCP)	☐ Yes ☐ No	**Day post-admission:**
MRCP Findings	☐ Gallstones ☐ CBD Stone / biliary obstruction	
ERCP for CBD Stone	☐ Yes ☐ No	

Diagnosis & Grading			
Tokyo Diagnostic Criteria*	☐ Suspected Diagnosis	☐ Definite Diagnosis	
Tokyo Severity Grade**	☐ Grade I	☐ Grade II	☐ Grade III

*A. Local signs of inflammation (1) Murphy's sign, (2) RUQ mass/pain/tenderness

B. Systemic signs of inflammation (1) Fever, (2) elevated CRP, (3) elevated WBC count

C. Imaging findings characteristic of acute cholecystitis

Suspected diagnosis: one item in A + one item in B

Definite diagnosis: one item in A + one item in B + C

****Grade I (mild):** No organ dysfunction and mild inflammatory changes in the gallbladder

Grade II (moderate): Associated with any one of the following conditions:

(1) Elevated WBC count (>18,000/mm3)

(2) Palpable tender mass in RUQ

(3) Duration >72h

(4) Marked local inflammation (gangrenous/emphysematous cholecystitis, pericholecystic/hepatic abscess, biliary peritonitis)

Grade III (severe): Associated with dysfunction of any one of the following organs/systems:

(1) Cardiovascular: hypotension requiring treatment with dopamine ≥5 lg/kg per min, or any dose of norepinephrine

(2) Neurological: decreased level of consciousness

(3) Respiratory: PaO2/FiO2ratio <300

(4) Renal dysfunction: oliguria, creatinine >2.0 mg/dl

(5) Hepatic dysfunction: PT-INR >1.5

(6) Haematological: platelet count <100,000/mm3

SECTION THREE: INTERVENTION		
Conservative Management Only	☐ Yes ☐ No	
If yes to conservative management were antibiotics used?	☐ Yes ☐ No	
Cholecystectomy		
IP Cholecystectomy Performed	☐ Yes ☐ No	
Cholecystectomy during index admission	☐ Yes ☐ No	
Date of Surgery		
Surgical Details	☐ Cholecystectomy ☐ Subtotal Cholecystectomy ☐ Abandoned intraoperatively	
Surgical Modality	☐ Laparoscopic ☐ Laparoscopic converted to Open ☐ Open	
Postoperative complications (Clavien-Dindo grading)	☐ Grade I ☐ Grade II ☐ Grade IIIA ☐ Grade IIIB ☐ Grade IV ☐ Grade V	
Bile leak/duct injury	☐ Yes ☐ No	
Cholecystostomy		
IP Cholecystostomy inserted	☐ Yes ☐ No	
Date of Insertion		
Approach	☐ Transhepatic ☐ Transperitoneal	
Tube size (Ch)		
Tubogram	☐ Yes ☐ No	**Date:**
Complications	☐Dislodgement ☐ Bleed ☐ Occlusion ☐ Bile Leak ☐Intra-abdominal collection ☐Viscus perforation	

SECTION FOUR: Peri-operative COVID-19 STATUS **(Seven days before admission or within 30 days of admission).**			
COVID-19 Status	☐ Negative	☐ Positive	☐ Unknown
COVID-19 Diagnosis			
COVID Nasopharyngeal Swab	☐ Negative	☐ Positive	☐ Test not performed
COVID Chest CT	☐ Negative	☐ Positive	☐ Test not performed
COVID Clinical diagnosis	☐ Negative	☐ Positive	☐ Not documented
Interval between swab/CT and surgery			

SECTION FIVE: OUTCOMES	
Perioperative	
Death during index admission	☐ Yes ☐ No
Date of death during index admission (days post-admission)	
Death within 30 days of discharge	☐ Yes ☐ No
Date of death after discharge (days post-discharge)	
Length of stay (days)	
Follow-up	
Unplanned readmission within 30 days	☐ Yes ☐ No
Discharged following Conservative Management	
Number of unplanned readmissions within the follow up period	
Cholecystectomy planned	☐ Yes – booked for elective cholecystectomy ☐ No – to reassess in Outpatient Department ☐ No – definitive management ☐ Unclear from current notes
Discharged with Cholecystostomy	
Discharged with cholecystostomy	☐ Yes ☐ No
Number of unplanned readmissions within the follow up period	
Duration of cholecystomy in days (if known)	
Cholecystectomy planned	☐ Yes – booked for elective cholecystectomy ☐ No – to reassess in Outpatient Department ☐ No – definitive management ☐ Unclear from current notes ☐ Not applicable as had index admission cholecystectomy.

Appendix B - Audit Standard: Tokyo Guidelines 2018 for management of acute cholecystitis

'We propose that the treatment strategy be considered and chosen after an assessment has been made of cholecystitis severity, the patient's general status and underlying disease.

Grade I (mild) AC: Lap-C should ideally be performed soon after onset if the CCI and ASA-PS scores suggest the patient can withstand surgery. If it is decided that the patient cannot withstand surgery, conservative treatment should be performed at first and delayed surgery considered once treatment is seen to take effect.

Grade II (moderate) AC: Lap-C should ideally be performed soon after onset if the CCI and ASA-PS scores suggest the patient can withstand surgery and the patient is in an advanced surgical center. However, 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 it is decided that the patient cannot withstand surgery, conservative treatment and biliary drainage should be considered.

Grade III (severe) AC: The degree of organ dysfunction should be determined and attempts made to normalize function through organ support, alongside administration of antimicrobials. Doctors should investigate predictive factors, i.e. a rapid recovery in circulatory dysfunction or renal dysfunction after treatment is initiated, and CCI or ASA-PS scores; if it is decided that the 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 it is decided that the patient cannot withstand surgery, conservative treatment including comprehensive management should be performed. Early biliary drainage should be considered if it is not possible to control the gallbladder inflammation. (Recommendation 2, level D)'

Reference: Okamoto K, Suzuki K, Takada T, et al. Tokyo Guidelines 2018: flowchart for the management of acute cholecystitis. J Hepatobiliary Pancreat Sci. 2018;25:55-72

Appendix C – Clavien-Dindo Grading of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal post-operative course not requiring surgical, endoscopic or radiological intervention. This includes the need for certain drugs (e.g. antiemetics, antipyretics, analgesics, diuretics and electrolytes), treatment with physiotherapy and wound infections that are opened at the bedside
Grade II	Complications requiring drug treatments other than those allowed for Grade I complications; this includes blood transfusion and total parenteral nutrition (TPN)
Grade III	Complications requiring surgical, endoscopic or radiological intervention • Grade IIIa - intervention not under general anaesthetic • Grade IIIb - intervention under general anaesthetic
Grade IV	Life-threatening complications; this includes CNS complications (e.g. brain haemorrhage, ischaemic stroke, subarachnoid haemorrhage) which require intensive care, but excludes transient ischaemic attacks (TIAs) • Grade IVa - single-organ dysfunction (including dialysis) • Grade IVb - multi-organ dysfuncton
Grade V	Death of the patient

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