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Research Paper

Management of acute cholecystitis in patients on anti-thrombotic therapy: A single center experience

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A R T I C L E I N F O

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A B S T R A C T

Background: Acute cholecystitis in patients on anti-thrombotic therapy (ATT) presents a clinical dilemma at the intersection between conflicting guidelines, specifically between timing of early operative management (OM) versus time-to-reversal of certain ATT agents. With growing recognition that nonoperative management (NOM) is associated with considerable morbidity, and evidence in the literature that early OM in patients on ATT is safe, we reviewed our own practice to examine how we addressed these conflicting guidelines.

Materials and methods: We performed a retrospective review of patients with acute cholecystitis between December 2017 and March 2022. Patients were classified as ATT or non-ATT; ATT patients were subdivided into anticoagulation (AC) and antiplatelet (AP) groups. Rates of OM were compared.

Results: 502 patients with acute cholecystitis were identified, 464 non-ATT and 38 ATT. 30 ATT patients were on AC, 7 on AP, and 1 on both. Non-ATT patients were significantly more likely to receive OM at index presentation compared to those on ATT: 89.9 % vs 63.2 % ($p < 0.05$). Subgroup analysis of the ATT group showed AP patients were significantly less likely to receive OM compared to those on AC, 12.5 % vs 77 % ($p < 0.05$).

Conclusions: At our institution, patients on ATT were significantly less likely to undergo OM for acute cholecystitis compared with non-ATT patients. Those on AC received OM significantly more than patients on AP. Further study is needed to better define the management of this growing population so that acute cholecystitis guidelines might address this issue in the future.

Introduction

Acute cholecystitis is typically managed with laparoscopic cholecystectomy (LC) at the time of presentation. In the United States (US), hepatopancreaticobiliary (HPB) conditions are the most common reason for admission to an Emergency General Surgery (EGS) service [1]. Cholecystitis is the second most common gastrointestinal condition for which patients are hospitalized in the US, resulting in as many as 200,000 admissions in a year [2]. The number of hospitalizations for cholecystitis has been increasing over time, as have the costs associated with these admissions [3].

Various practice guidelines exist for the management of acute cholecystitis in the general population [4–7]. These guidelines recommend early operative intervention (<72 h from onset of symptoms) to minimize the risk of intraoperative complications. However, in our practice, we identified a subgroup of patients where more general perioperative practice guidelines conflict with acute cholecystitis guidelines: patients on antithrombotic therapy (ATT). Among surgical patients in general, those on ATT are at increased risk of intra- and perioperative bleeding, and thus there are specific recommendations for how such patients are managed perioperatively [8]. Most notably, regarding a subgroup of ATT patients on anti-platelet (AP) agents – for which there are no reversal agents – there are specific recommendations for how long one should wait to avoid bleeding complications: 3–5 day interruption for ticagrelor, 5-day interruption for clopidogrel, and 7–10 day interruption for prasugrel. It is readily evident that these durations place AP patients with acute cholecystitis outside the 72-hour window currently recommended in acute cholecystitis management guidelines [4–7]. Depending on the indication(s) for ATT, the safety of its discontinuation, and the availability of reversal agents, OM may be delayed or withheld, leading to increased morbidity [9]. Further, given the indications for therapy, interruption of AP may be catastrophic and significantly more morbid than interruption of AC.

Therefore, the management of acute cholecystitis in patients on ATT

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presents a clinical challenge arising from conflicts between two sets of recommendations for good practice that can impact timing of LC. This dilemma is more likely to arise in the future as there has been an increase in the use of ATT – AC and/or AP for a variety of indications, a trend that is likely to continue to increase as the population continues to age [10,11]. As a potential means of reconciling this conflict, some authors advocate for OM without AP discontinuation and have presented outcomes suggesting LC can be safely performed prior to washout; however, it is unclear how this information has affected practice [12]. In this study, we seek to evaluate the current practice patterns at our institution to better understand the approaches to management for patients with acute cholecystitis on ATT.

Materials and methods

We performed a retrospective review at an academic tertiary center of all patients evaluated by the EGS team for acute cholecystitis between October 2017 and March 2022. This review involved an initial tabulation of patients in the University of Vermont EGS Database fitting these criteria, followed by more detailed evaluation of the medical records for certain subgroups of patients noted below. The classification process proceeded as follows: the patients were divided into two groups, those on ATT and those not on ATT. Only patients who presented with acute cholecystitis were included. The following entities under the umbrella of acute cholecystitis were identified: acute cholecystitis, gangrenous cholecystitis, perforated cholecystitis, hemorrhagic cholecystitis, and acute on chronic cholecystitis. Patients with choledocholithiasis, ascending cholangitis, gallstone/biliary pancreatitis, and refractory biliary colic were excluded from this study, as the time sensitivity regarding OM does not affect them. Patients who presented for elective or interval LC were also excluded. We assessed duration of biliary symptoms, management approach, and wait times until OM. Additionally, for patients on ATT, we also assessed the type(s) of ATT, their indication(s), and whether reversal was given in the cases of AC. This subset of patients also underwent a more detailed chart review to collect information about the clinical reasoning for the pursuit of nonoperative management (NOM), where applicable.

All patients were classified as having either OM or NOM. OM was defined as having been offered a (laparoscopic or open) cholecystectomy during the initial episode of care. Subtotal/partial cholecystectomy was counted as OM. If a procedure was initiated but aborted without performing a complete or subtotal cholecystectomy, the patient was included in the OM group because the management decision had already been made to proceed with an operation. Patients who were offered surgery but refused were also counted in the OM group since the management decision had already been made that OM was appropriate. NOM was defined as having received either intravenous (IV) antibiotics alone or IV antibiotics along with percutaneous cholecystostomy (PC). If at the time of first surgical evaluation no operative intervention was offered, that patient was counted in the NOM group only. Any subsequent visits for that same patient were excluded.

We also performed a subgroup analysis on the ATT group to determine the rates of OM in those on AC compared to those on AP. There was one patient who was on both AC and AP, and for the purposes of this study, this patient was counted only in the AP group.

All NOM patients, whether in the non-ATT or ATT group, underwent more detailed chart review to compare the reasons for NOM between groups. Given that the purpose of this study is to evaluate whether the decision regarding OM was affected by the presence of ATT, we parsed these patients into those who met the traditional criteria for NOM given existing guidelines [4–7]. We specified whether the decision was based on duration of symptoms >72 h or medical instability that precluded safe general anesthesia. If neither situation was met, we identified the decision as due to perception of bleeding risk.

The study was reviewed by the University of Vermont's Internal Review Board and approved along with a waiver of the requirement for informed consent. Statistical significance was set at $p < 0.05$. Chi-Squared tests were used to determine statistical significance of the differences between categorical variables. Python was used for statistical analysis along with the pandas, numpy, and scipy packages.

Results

A total of 502 patients with acute cholecystitis that met the study criteria were included – 38 were on ATT, 464 were not (non-ATT). The ATT group had 30 patients who were on AC, 7 patients on AP, and 1 patient on both AC and AP. Patient baseline characteristics are summarized in Table 1. Types of anti-thrombotic agents and their frequencies in the study group are listed in Table 2.

The overall classification schema of our cohort of patients is seen in Fig. 1. In the non-ATT group, 417/464 (89.9 %) underwent OM, while in the ATT group there was a significant reduction in the number of patients who underwent OM 24/38 (63.2 %) ($p < 0.05$). On sub-group analysis of ATT patients, those on AP were significantly less likely to undergo OM 1/8 (12.5 %) as compared to those on AC 23/30 (76.7 %) ($p < 0.05$), albeit with a small total number of patients. Analysis of the reasons for NOM is as follows:

- In the non-ATT group, 19/47 (40 %) had symptoms for >72 h prior to presentation while 28/47 (60 %) were deemed medically unstable to undergo general anesthesia.
- In the AC group, 2/7 (29 %) patients had symptoms >72 h and 5/7 (71 %) patients were medically unstable.
- In the AP group, 1/7 (14 %) patients had symptoms >72 h, 2/7 (29 %) were medically unstable, but 4/7 (57 %) would have qualified for OM based on guidelines if not for the presence of antiplatelet therapy.

For the patients who underwent OM, average time to OR was 1 day in the non-ATT group and 2 days in the ATT group. In the ATT subgroup, AC patients waited an average of 1.9 days before OR while the AP patient waited 3 days. Notably, 8/23 (34.8 %) AC patients received reversal prior to OR and the AP patient waited until complete washout prior to OR. The most common indication for AC was atrial fibrillation, while the most common indication for AP was the presence of coronary stent(s).

Discussion

While practice guidelines regarding the timing of laparoscopic cholecystectomy for acute cholecystitis are well known, we identified a potential conflict regarding recommendations for managing existing ATT therapy in those who require LC; more specifically in those patients on AP therapy. While there is existing literature demonstrating that LC can be safely performed for acute cholecystitis without waiting for the reversal of AP agents, it is unclear how this information has been incorporated into existing practice [12]. Therefore we undertook a review at our institution to establish our baseline practice.

Our study shows that the practice patterns in the management of patients on ATT differ significantly than that of the general population. Acknowledging that the overall number of patients in our cohort is small, we observed that patients on ATT are less likely to undergo OM

Table 1
Baseline characteristics:

Characteristic	Non-ATT (n = 464)	ATT (n = 38)
Age	53.5	69.6
Male	194 (42 %)	25 (66 %)
Female	270 (58 %)	13 (34 %)
BMI (mean)	31.8	30.9
ASA (mean)	2.28	2.81

Table 2
Anti-thrombotic agents and counts for ATT group.

Drug	Count
Apixaban	16
Warfarin	16
Clopidogrel	7
Rivaroxaban	4
Ticagrelor	3
Enoxaparin	2

for acute cholecystitis compared to those not on ATT. Further, those ATT patients who do undergo OM tend to wait longer before OR. Patients on AP are managed most differently in that they seldom receive OM, and when they do, their time to OR is longest due to the washout period.

One explanation for the discrepancy in care plans between non-ATT and ATT patients could be that the latter group are at higher risk of being medically unable to tolerate general anesthesia by virtue of having underlying co-morbidities that warrant the administration of these drugs. Again, acknowledging small numbers, the difference between non-ATT and AC was 60 % vs 71 %, while AP patients actually had the lowest likelihood of being medically unstable at 29 %. These results were not statistically significant.

The difference in OM rates between AC and AP can be at least partially attributed to the fact that reversal was an option for the AC patients (if not pre-emptively, then the possibility of later reversal, based on the course of the surgical procedure). The fact that it was only in the AP group that there was a number of patients who were not offered an operation for reasons other than the standard exclusion criteria of duration of symptoms or medical instability suggests that, at least in our prior practice, concern of intra−/peri-operative bleeding played a role in clinical decision making.

As the population continues to age and the use of ATT increases, the discrepancy between guidelines for the management of acute cholecystitis and those for the management of perioperative ATT will present a growing clinical dilemma. As our study shows, ATT patients are placed on different care pathways that lead to less definitive management of their disease and longer wait times for definitive management when it is offered (related to washout times, need for reversal, etc.).

Those patients in the ATT group who did not receive OM during their index presentation were typically managed with either IV antibiotics alone, or with IV antibiotics and PC. In either case, the acute cholecystitis was not definitively addressed. In the case of those treated with antibiotics alone, they are likely to have recurrent cholecystitis with frequent Emergency Room (ER) visits or hospitalizations along with repeated discomfort. Those managed with PC might be subjected to repeated episodes of cholecystitis if there are technical issues with the tube (impacted stone, kinking of tube, displacement of tube, etc.) or if the tube is removed without definitive management [13]. There is literature evidence that only 40 % of patients who are managed with PC are ultimately offered interval cholecystectomy, essentially committing a large percentage of patients to lifelong PC along with its challenges for them and their families [14]. Further, interval cholecystectomy after NOM for acute cholecystitis (regardless of presence of PC), when it is offered, can prove more difficult due to fibrosis and scarring, which predisposes the patient to further complications [13]. Given existing

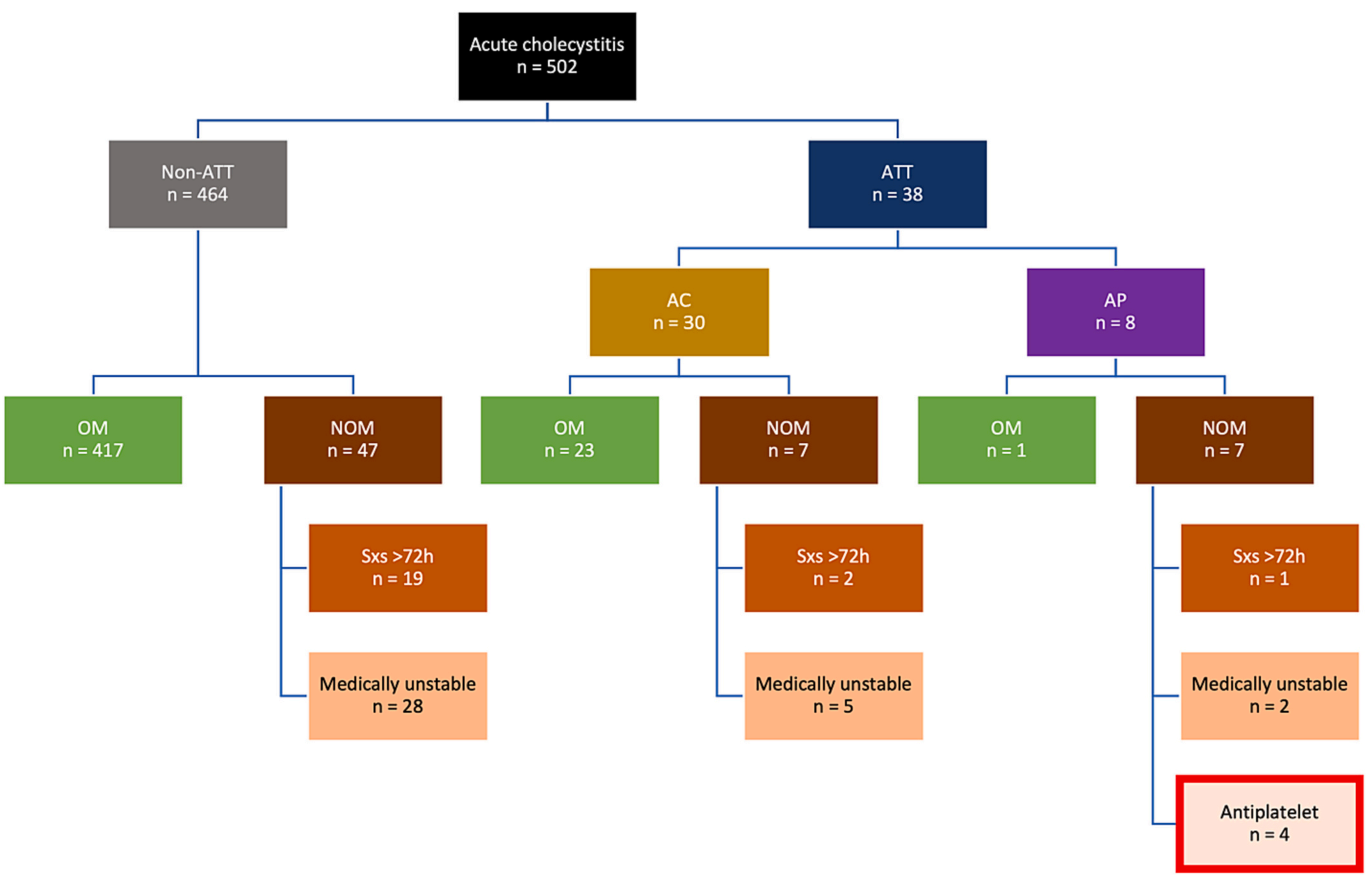

Fig. 1. Management of acute cholecystitis in presence or absence of antithrombotic therapy.
This figure outlines the management of patients with acute cholecystitis. Patients are divided based on whether they are on antithrombotic therapy (ATT) or not (Non-ATT). The ATT group is further divided into those on anticoagulation (AC) and those on antiplatelets (AP). In each of the groups, the number of patients managed operatively (OM) vs nonoperatively (NOM) are outlined. For the patients who received NOM, the specific reasons for that clinical decision is illustrated. “Sxs” = symptoms.

evidence that LC can be safely performed in patients on ATT, and considering the consequences of delaying OM outlined above, a strong argument can be made that we should move to change the management practices for these patients.

There are several limitations to our study. First, this is a retrospective study, and is therefore subject to the well described methodological limitations of such type of study. Second, our sample size is relatively small, particularly for the ATT groups. Third, this is a single-center study, so the findings cannot necessarily be generalized to the population as a whole nor can it be taken to represent national practice patterns; our center serves a more rural population which again could affect generalizability. Finally, despite our initial analysis with small numbers, it remains possible that ATT is a confounder in that it represents a patient population that is more comorbid or aged, which would make these patients less likely to tolerate an operation – irrespective of their ATT status. In fact, the baseline characteristics of the two patient groups (Table 1) shows that the ATT group is more aged and has a higher ASA status, so it is possible that the differences between groups noted in this study are not attributable to ATT therapy. Though with respect to ASA, it is possible that the indication for ATT alone in the ATT group is responsible for higher ASA scores. We acknowledge that the two groups of patients are different in their baseline characteristics, still we seek to understand whether these differences are enough to account for the vast difference in management approach. While this study is small and cannot answer definitively whether there was harm from delayed operative management in the ATT group, numerous studies have demonstrated inferior quality of life in patients with delayed operative management [15]. Further study with a larger study population could address some of these limitations.

Despite existing evidence on the safety of undergoing LC while on ATT, it appears that our internal practice does not reflect this information. This leads us to question whether our own experience is reflective of practices at other academic surgical programs. Towards this end, we plan to examine this question from two directions: 1) a retrospective review of a national dataset to identify if these patterns of management of acute cholecystitis and concurrent ATT therapy are pervasive, and 2) a more detailed study that involves a collaborative regional multi-institutional review of practice patterns. We hope that by expanding the assessment of how these patients at the time-sensitive intersection between potentially conflicting treatment guidelines are managed we would be able to better characterize just how much of a clinical dilemma this issue represents. If it is found to be pervasive, then we hope this information can be used to refine future iterations of therapeutic recommendations for acute cholecystitis.

Conclusions

Our single center experience shows that patients who are on ATT are less likely to undergo surgery for acute cholecystitis during initial hospitalization compared with patients not on ATT. Further, those on AC are more likely to undergo OM as compared to those on AP, with the ostensible rationale being concern of bleeding complications if surgery is pursued prior to the washout period of AP agents. Given that there is evidence that deferring surgery in patients with acute cholecystitis leads to increased morbidity due to repeated episodes of disease and/or need for long-term management of PC, and that early OM is safe in patients on ATT, delaying or deferring OM due to concerns for bleeding may not be an optimal approach. We believe that a review of our experience, as limited as it may be, can help shed light on this potential dilemma that, given the aging population, is almost certainly to become more common. We believe that this issue will need to be directly addressed as the management guidelines for acute cholecystitis continue to evolve.

Ethical approval statement

This study was reviewed and approved by the University of Vermont's institutional review board.

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None.

CRediT authorship contribution statement

Solomon Feuerwerker: Conceptualization, methodology, formal analysis, investigation, writing (original draft and editing). **Ruja Kambli:** Investigation, visualization. **Diana Grinberg:** Investigation. **Ajai Malhotra:** Methodology, writing – review and editing. **Gary An:** Conceptualization, methodology, supervision, and writing – review and editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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