



SPECIAL ARTICLE

Management of acute calculous cholecystitis in high risk surgical patients

Manejo de la colecistitis aguda litiásica en pacientes con alto riesgo quirúrgico

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Due to population ageing in Western countries, as well as an increased incidence of diseases related to gallstone disease, growing numbers of patients of advanced age are requiring hospitalisation for this reason.^{1,2}

In the elderly population, the prevalence of diseases caused by gallstones ranges from 14%–23%, and may be as high as 80% in individuals over 90 years of age.³ Furthermore, this population has higher morbidity compared to younger individuals, meaning that the treatment considered to be of choice in younger people is questionable in these patients. Beyond that, it must be taken into account that treatment objectives centred on these patients' quality of life and independence have been recommended for decades.⁴ On this point, the therapeutic management of acute calculous cholecystitis (ACC) reflects the dilemma that arises from choosing a more invasive treatment or a more conservative one in this group of patients who are older and have more morbidity and more fragility.²

The objective of this article was to conduct an up-to-date, in-depth review of the management of acute

cholecystitis in patients ineligible for surgery, focused on ultrasound-guided endoscopic treatment as a new treatment option, as well as to analyse outcomes reported with strictly conservative management.

In ACC, several treatment options are available: conservative management; percutaneous cholecystostomy (PC); endoscopic transpapillary drainage (ETD) or endoscopic ultrasound-guided transmural cholecystenterostomy (EUS-CE); and surgical treatment through laparoscopic cholecystectomy (LC) or open cholecystectomy. The one widely considered a first-line treatment and recommended as such is LC.^{5–7} It is recommended that the treatment modality be selected based on ACC severity as well as the characteristics of the patient and of the underlying disease.⁵ In mild, moderate and severe ACC, early LC is recommended if the surgical risk is deemed acceptable. If it is not, LC should be delayed until medical treatment has taken effect and the patient's general condition has improved; the option of gallbladder drainage as a bridge to surgery should be weighed in moderate or severe ACC.⁵ In addition, the clinical practice guidelines open up the option of avoiding surgery in cases of severe ACC with anticipated high technical difficulty and high-risk patients.^{5,8} However, outcomes of early LC in elderly patients are worse; a recent meta-analysis found a

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morbidity rate of 24% with a mortality rate of 3.5% in this population.^{2,9}

PC is a simple, noninvasive drainage method that is widely available in our setting; furthermore, it is highly effective in acute disease. It is associated with rates of technical success of approximately 82%–99% and clinical success of approximately 60%–85%, but it is also associated with a rate of adverse effects that can be as high as 51% with a mortality rate of 10%.^{10,11} LC has proven superior to PC in managing patients with ACC and high surgical risk as it reduces numbers of adverse effects, usage of healthcare resources and costs.¹²

Endoscopic drainage, on the other hand, can be performed by means of two different techniques, ETD or EUS-CE. The latter offers rates of technical success (OR 5.22; 95% CI 2.03–13.44; $p = 0.0006$; $I^2 = 20\%$) and clinical success (OR 4.16; 95% CI 2.00–8.66; $p = 0.0001$; $I^2 = 19\%$) that are both superior to ETD, with no differences with regard to adverse effects (1.30; 95% CI 0.77–2.22; $p = 0.33$, $I^2 = 0\%$).¹³ Therefore, today, the endoscopic technique considered of choice for gallbladder drainage is EUS-CE, although it requires an experienced endoscopist.

Comparison of outcomes of these three non-surgical minimally invasive techniques to treat ACC confirmed that EUS-CE and PC offer higher rates of technical and clinical success, EUS-CE is associated with a lower risk of recurrence of ACC, PC has a higher risk of need for further intervention and unplanned readmissions, and ETD carries a lower risk of mortality.¹⁴

Outcomes of EUS-CE and PC have been compared in numerous studies, most of them retrospective. A meta-analysis published in 2019 that included five studies – one randomised clinical trial and four retrospective studies – compared outcomes in 206 patients treated by EUS-CE and 289 patients treated by PC.¹⁵ No significant differences were found between the two procedures with respect to technical success (OR 0.43; 95% CI 0.12–1.58; $P = 0.21$; $I^2 = 0\%$) or clinical success (OR 1.07; 95% CI 0.36–3.16; $P = 0.90$; $I^2 = 44\%$).¹⁵ However, EUS-CE was associated with fewer adverse effects (OR 0.43, 95% CI 0.18–1.00; $P = 0.05$; $I^2 = 66\%$); a shorter hospital stay, with a standardised mean difference of -2.53 (95% CI (-4.28) – (-0.78) ; $P = 0.005$; $I^2 = 98\%$); and lower needs for further intervention (OR 0.16; 95% CI 0.04–0.042; $P < 0.001$; $I^2 = 32\%$) and unplanned readmissions (OR 0.16, 95% CI 0.05–0.53; $P = 0.003$; $I^2 = 79\%$).

Subsequently, a multicentre randomised clinical trial was published that compared outcomes of EUS-CE and PC in high surgical risk patients with moderate or severe ACC.¹⁶ The EUS-CE group included 39 patients and the PC group included 40; follow-up was completed after a year in all patients. Analysis of the results confirmed that the rate of adverse effects at 30 days and one year in the group that underwent EUS-CE was significantly lower: 12.8% versus 47.5% ($p = 0.010$) and 25.6% versus 77.5% ($p < 0.001$), respectively. However, the rate of further intervention in the first month of follow-up (2.6% versus 30%, $p = 0.001$), the number of unplanned readmissions (15.4% versus 50%, $p = 0.002$) and the rate of ACC recurrence (2.6% versus 20%, $p = 0.029$) were also significantly better in the EUS-CE group, with PC being the factor predictive of ACC recurrence (OR 5.63, 95% CI 1.20–53.90, $p = 0.027$). There were no differences with respect to technical success (97.4% versus 100%, $p = 0.494$),

clinical success (92.3% versus 92.5%, $p = 1$) or mortality rate in the first month (7.7% versus 10%, $p = 1$).

Following the publication of this randomised clinical trial, a new meta-analysis was recently published that compared EUS-CE to PC in patients diagnosed with ACC at high surgical risk that included a total of 722 patients between the two groups from eight studies.¹¹ Technical success was significantly better with PC (98.9% versus 96.1%; OR 0.32; 95% CI 0.13–0.83; $P = 0.02$; $I^2 = 0\%$); there were no significant differences with respect to clinical success (93.4% versus 96%; OR 1.47; 95% CI 0.75–2.90; $P = 0.26$; $I^2 = 9\%$), adverse effects (OR 0.63; 95% CI 0.30–1.33; $P = 0.22$; $I^2 = 72\%$) or recurrence of cholecystitis (OR 0.54; 95% CI 0.27–1.06; $P = 0.41$; $I^2 = 26\%$). Numbers of further interventions and readmissions were significantly higher in the PC group ([OR 0.15; 95% CI 0.07–0.32; $P < 0.00001$; $I^2 = 7\%$] and [OR 0.24; 95% CI 0.08–0.67; $P = 7$; $I^2 = 80\%$], respectively). A subanalysis including only studies that used lumen-apposing stents to perform EUS-CE revealed that adverse effects and recurrence of cholecystitis were also significantly lower with EUS-CE (OR 0.35 95% CI 0.13–0.93; $P = 0.03$; $I^2 = 81\%$ and OR 0.27; 95% CI 0.10–0.71; $P = 0.008$; $I^2 = 0\%$, respectively).

Given these data, it can be said that the currently available evidence shows better outcomes for EUS-CE in managing patients with ACC at high surgical risk, and therefore should be considered the definitive approach for gallbladder drainage in these patients.¹⁷

In recent years, intrahospital management of this group of patients with ACC at high surgical risk has changed; now, it is common for them to be admitted to medical departments such as gastroenterology, internal medicine or geriatrics, where there may be a stronger trend towards noninvasive medical management.¹⁸ This conservative treatment includes nothing by mouth, fluid therapy, analgesia and antibiotics. Treatment with antibiotic therapy should be indicated in cases of ACC with complications and in fragile or immunocompromised patients, and it would only have the effect of preventing sepsis or bacteraemia caused by ACC.^{2,19} There is uncertainty as to the distribution of the antibiotic beyond the gallbladder wall, without reaching an effective concentration inside the gallbladder or surrounding inflammatory component.¹⁹ This emphasises the need to combine drainage with treatment, which would surely decrease the development of antibiotic resistance.¹⁹

In acute ACC, this conservative management yields good outcomes and also avoids the risk of surgery.^{18,20} This was demonstrated in a systemic review that analysed 14 prospective studies, 10 of which were randomised clinical trials comparing initial conservative management to invasive treatment, with 1315 patients analysed in total.²⁰ The weighted rate of clinical success of initial conservative management was 86%, with complete resolution of symptoms and no need for any invasive manoeuvres. The weighted death rate in the conservative management group was 0.5%; the highest mortality rate reported in any study was 17%. In the mild ACC subgroup, the clinical success of conservative management was 96% and there were no deaths.

However, conservative treatment does not lead to definitive resolution; it only resolves the acute infectious and inflammatory process. In keeping the gallbladder in situ, there is a risk of recurrence of ACC as well as other condi-

tions stemming from gallstones. Studies that have evaluated this matter have shown that rates of recurrence of ACC and other biliopancreatic conditions requiring repeat admissions of these patients are high — according to most studies, 30%–40% or even higher. In an observational study that included 47,500 patients over the age of 80 diagnosed with ACC, 89.7% (42,620) received definitive conservative treatment, with emergency cholecystectomy performed in just 3539 (7.5%) and PC in 1341 (2.8%).²¹ Thirty-day mortality in the conservative treatment group was 9.9% versus 11.6% in the surgical treatment group and 13.4% in the group treated with PC ($p < 0.001$). At three months, the mortality rates in the conservative group and the surgical group were equal (16.1% versus 15.6%, $p > 0.05$), with higher mortality persisting in the PC group (22.5%, $p > 0.001$). Finally, mortality after one year of follow-up was significantly lower in the surgical group versus the conservative group and the percutaneous group (20.8% versus 27.1% versus 35%, respectively, $p < 0.001$), with PC being a factor associated with higher mortality after a year (OR 1.46; 95% CI 1.29–1.64; $p < 0.001$). However, in addition to that, the rate of ACC recurrence in the conservatively treated group was 37.7%; this, added to the appearance of other biliopancreatic events related to gallstones, resulted in a rate of readmissions of 55.2% for the entire series. Although this study's methodology was lacking as it was a retrospective study, the number of patients included gave us quite a clear sense of outcomes of conservative treatment for ACC.

The above-mentioned systematic review also evaluated outcomes in long-term conservative management by analysing 10 studies: two randomised clinical trials and eight retrospective observational studies with a follow-up of one to 14 years.²⁰ Analysis of the 526 patients included revealed a rate of recurrence of gallbladder disease of 19.7%, although some studies considered only ACC recurrence, with a range of 3%–47%. Recurrence was most common in the two years after the initial episode of ACC.

In recent years, further studies have been published reporting outcomes of definitive conservative treatment. A retrospective study that included patients with ACC at high surgical risk compared outcomes of PC during the initial episode of ACC (97 patients) versus definitive conservative treatment (104 patients).²² There were no differences with regard to adverse effects or mortality between the two groups during initial admission. After a median follow-up of 1.6 years, 38.6% of patients were readmitted for biliopancreatic conditions related to gallstones, with a rate of ACC recurrence of 25.3%. No significant differences were found in readmissions for biliopancreatic disease between the PC and conservative management group (37.1% versus 32.7%). After stating that more than one out of every three patients were readmitted for conditions related to gallstones and more than one out of every four were readmitted for ACC recurrence, the authors recommended reconsidering surgical treatment in these patients as the only curative treatment. Special mention must be made of an idea put forward by the authors in their article: that, to their surprise, making the assumption that this group of elderly patients with high comorbidity will die before being readmitted for biliopancreatic disease related to gallstones, as suggested by other authors,^{20,23} is incorrect in an excessive percentage of cases. They believed that, at least in their department,

there was a trend towards overtreating patients using this strategy, and recommended rethinking it, adding that PC should not be routinely used in managing these patients.²²

In our country, the situation is similar, as demonstrated in a study that reported recurrence of biliopancreatic conditions in 38.2% of patients treated conservatively or with PC, the latter being a risk factor for greater recurrence.²⁴

Another recently published study compared conservative management to invasive management, which includes surgery, endoscopic drainage and percutaneous drainage, although it evaluated only outcomes during initial admission with a follow-up of just six months.¹⁸ That study showed a trend towards a higher rate of intrahospital mortality with conservative management (4.9% versus 2.6%), with a significantly lower incidence of cutaneous fistula (0.3% versus 2.3%) and a shorter hospital stay (7 versus 7.9) in this group. The authors recommended always considering conservative management during initial admission for ACC, but, as mentioned above, these data refer to initial conservative management, even as a bridge to delayed LC, not definitive conservative management. In a significant percentage (39.3%) of patients initially included in the conservative treatment group, delayed LC was subsequently performed.

Thus these studies reveal that although conservative treatment is tempting in this group of patients, and even effective in the acute process of ACC, it should not be considered a valid definitive treatment in view of the high rate of patients requiring subsequent readmissions and further intervention.¹⁹ Not performing definitive treatment increases the mortality rate higher than expected based on comorbidities in these patients.¹

In addition, most retrospective studies that have evaluated outcomes of conservative treatment have not performed real clinical follow-up of patients with assessment of quality of life; presence of pain not requiring assessment in an accident and emergency department; intake of a normal diet; occurrence of febrile episodes that were self-limiting, managed in primary care or managed by the patient; patient transfer to another healthcare area, etc. In general, they have only assessed whether or not patients were readmitted, without doing any real follow-up of clinical course; therefore, the recurrence rate could be underestimated and the quality of life that these patients could be thought to have been given through avoidance of invasive examinations could be overestimated.

It is tempting, once acute signs and symptoms of cholecystitis resolve, to propose not performing any further treatment manoeuvres with the hope that ACC will not recur prior to the patient's death due to other reasons. However, the studies published show that this usually does not happen. Rates of recurrence and readmission for ACC and other biliopancreatic conditions exceed 50%, adding greater morbidity, greater mortality and also higher costs to the management of these patients.^{1,2,12,19}

At present, endoscopic treatment is available that has not been compared to definitive conservative treatment but has proven superior to PC.^{15,16} In addition, while there are still no high-quality studies comparing EUS-CE to LC, a recent retrospective comparative study found no differences with respect to technical success (100% versus 100%), clinical success (93.3% versus 100%), hospital stay (6.8 versus 5.5), adverse effects after 30 days (13.3% versus 13.3%) or

mortality (6.7% versus 0%) between the two techniques.²⁵ Recurrence of biliary conditions (10% versus 10%), further intervention (13.3% versus 10%) and unplanned readmissions (10% versus 10%) in the first year of follow-up were also not significantly different.

These results, together with those of available prior studies, corroborated EUS-CE as a suitable technique not only as a treatment for acute episodes of ACC, but also as a definitive middle- to long-term treatment, as it prevents recurrence of subsequent biliopancreatic events with all that this entails for elderly patients with comorbidities. Based on this, at hospitals with experience in therapeutic endoscopic ultrasound, the trend in treatment for ACC in patients at high surgical risk should be towards a better indication for PC and for definitive conservative treatment, which are the treatments associated with the worst middle- and long-term outcomes.

The choice of treatment offered to this group of patients should therefore be personalised. According to the data currently available in the literature, early LC remains the treatment of choice for ACC. In patients with high surgical risk considered ineligible for LC, the most advisable treatment seems to be endoscopic treatment through EUS-CE. At centres with sufficient experience in therapeutic endoscopic ultrasound, this treatment should be offered to patients who are going to be able to perceive the improvement in quality of life that this treatment may bring them. In our opinion, definitive conservative treatment should be reserved for patients who are not going to perceive this improvement in quality of life, due to either their baseline situation or their prognosis of limited short-term survival.

Ultimately, according to the data currently available in the literature, EUS-CE offers definitive palliative treatment for ACC in patients ineligible for surgical treatment. It is associated with a lower rate of adverse effects, lower recurrence of cholecystitis, lower numbers of further interventions and fewer unplanned readmissions than PC. Although there are no comparative studies, the observational studies available have yielded worse middle- to long-term results with conservative management. Therefore, if a poor short-term prognosis cannot be anticipated, then it seems reasonable to perform EUS-CE in these patients.

Conflicts of interest

Juan J. Vila is a consultant for Boston Scientific and has given talks for Cook Endoscopy and Olympus. All other authors declare that they have no conflicts of interest.

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