

## REVIEW ARTICLE

Edward W. Campion, M.D., *Editor*Interventional Approaches  
to Gallbladder Disease

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**C**HOLECYSTECTOMY IS A WELL-ESTABLISHED AND FREQUENTLY PERFORMED procedure.<sup>1</sup> The criteria for diagnosing acute cholecystitis and for grading its severity are shown in Table 1.<sup>2</sup> The demand for safer and less-invasive interventions continues to promote innovations in the management of gallbladder disease. Whether the approach to the management of gallbladder disease is surgical, endoscopic (as in the fairly recent introduction of natural orifice transluminal endoscopic surgery [NOTES]), or percutaneous, the most important considerations in selecting an approach are the patient's overall medical condition and the local and systemic consequences of the disease (Tables 1 and 2).

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## SURGICAL APPROACHES TO CHOLECYSTECTOMY

## LAPAROSCOPIC APPROACH

Laparoscopic cholecystectomy, which was introduced in 1985,<sup>3</sup> has markedly reduced the need for open cholecystectomy<sup>4</sup> and its attendant complications.<sup>5</sup> The procedure has become the standard treatment for symptomatic cholelithiasis and mild-to-moderate acute cholecystitis. Recent data favor early laparoscopic cholecystectomy over medical management with delayed laparoscopic cholecystectomy.<sup>6</sup> In one randomized trial involving patients with uncomplicated acute cholecystitis, laparoscopic cholecystectomy, when performed within 24 hours after the onset of cholecystitis, significantly reduced morbidity, length of hospital stay, and costs without increasing the need for conversion to open surgery.<sup>7</sup>

Patients who undergo laparoscopic cholecystectomy generally have few adverse effects, but bile-duct injury occurs more frequently during this procedure than during open cholecystectomy and may have dire consequences.<sup>8,9</sup> Dissection may be more technically demanding when there is marked inflammation, which can distort local anatomy and increase the risk of bile-duct injury. The prevention of bile-duct injuries requires a mind-set that puts safety first,<sup>10</sup> which means maintaining a low threshold for conversion to open cholecystectomy when there is a lack of progress with dissection, avoiding dissection when the anatomy is poorly defined, and being willing to abandon total cholecystectomy in favor of subtotal cholecystectomy<sup>11</sup> or cholecystostomy. Open cholecystectomy remains an alternative to laparoscopic cholecystectomy, but laparoscopy is usually attempted first, assuming that the patient is a candidate for general anesthesia and has no contraindications to safe laparoscopic peritoneal access or carbon dioxide insufflation.

Ongoing efforts to minimize surgical trauma to the abdominal wall have led to the use of smaller and fewer laparoscopic ports (Fig. 1). In single-incision laparoscopic cholecystectomy, one large, transumbilical, multi-instrument port is used instead of four incisions, leaving only a periumbilical scar. Theoretical but unproven

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**Table 1. Guidelines for the Diagnosis and Determination of Severity of Acute Cholecystitis.\*****Diagnostic Criteria**

## Local signs of inflammation

- Murphy's sign
- Mass, pain, or tenderness in right upper quadrant

## Systemic signs of inflammation

- Fever
- Elevated levels of C-reactive protein
- Leukocytosis

## Findings on imaging characteristic of acute cholecystitis

- Gallbladder-wall thickness  $\geq 5$  mm, pericholecystic fluid, or direct tenderness when probe is pushed against gallbladder (i.e., ultrasonographic Murphy's sign)

**Diagnosis**

## Suspected

- Positivity for one item in local signs of inflammation and one item in systemic signs of inflammation

## Definitive

- Positivity for one item in local signs of inflammation, one item in systemic signs of inflammation, and findings on imaging characteristic of acute cholecystitis

**Disease severity**

## Grade I (mild)

- Acute cholecystitis in otherwise healthy patient with mild local inflammatory changes and without organ dysfunction
- Criteria for grade II or III not met

## Grade II (moderate) — any one of the following characteristics

- Leukocytosis ( $>18,000$  cells per  $\text{mm}^3$ )
- Palpable, tender mass in right upper quadrant
- Symptom duration  $>72$  hr
- Marked local inflammation (gangrenous or emphysematous cholecystitis, pericholecystic or hepatic abscess, biliary peritonitis)

## Grade III (severe) — organ dysfunction in any one of the following systems

## Cardiovascular

- Hypotension requiring administration of  $\geq 5 \mu\text{g}/\text{kg}/\text{min}$  of dopamine or any dose of norepinephrine

## Neurologic

- Decreased level of consciousness

## Respiratory

- $\text{PaO}_2:\text{FiO}_2 < 300$

## Renal

- Oliguria
- Creatinine  $>2.0$  mg/dl ( $>177 \mu\text{mol}/\text{liter}$ )

## Hepatic

- International normalized ratio  $>1.5$

## Hematologic

- Platelet count  $<100,000/\text{mm}^3$

\*  $\text{PaO}_2$  denotes partial pressure of arterial oxygen, and  $\text{FiO}_2$  the fraction of inspired oxygen.

advantages include improved cosmesis and reductions in postoperative pain, recovery time, and wound-related adverse events.<sup>12-14</sup> However, postoperative hernias are significantly more common after laparoscopic cholecystectomy than after open cholecystectomy,<sup>15</sup> and the likelihood of bile-duct

**Table 2. Advantages and Disadvantages of Interventional Approaches to Symptomatic Gallbladder Disease.\***

Approach	Advantages	Disadvantages
Laparoscopic cholecystectomy	Is associated with minimal or no visible scarring	Is technically difficult in patients with severe cholecystitis or prior abdominal surgery; is associated with increased incidence of bile-duct injury
NOTES	Is associated with minimal or no visible scarring	Is limited in terms of availability of procedure; transvaginal approach is restricted to women
Percutaneous cholecystostomy	Is widely available and can be performed at bedside	Is associated with frequent adverse events and tube dislodgement; is a poor long-term solution; diminishes quality of life while drainage catheter is in situ
Peroral endoscopic transpapillary drainage	Does not require external catheters, can be performed in patients with ascites or coagulopathy, allows for simultaneous treatment of bile-duct stones	Is technically difficult and is not widely available
Peroral endoscopic transmural drainage	May allow placement of stent with large diameter and permits endoscopic extraction of gallstones	Is not widely available; may interfere with subsequent surgeries

\* NOTES denotes natural orifice transluminal endoscopic surgery.

injury is increased because visualization, dissection, and intraoperative cholangiography are more challenging with laparoscopic cholecystectomy.<sup>16</sup>

Another less invasive technique, mini-laparoscopy, involves the use of access ports and instruments with a small diameter (2 to 5 mm). The cosmetic results are better than with standard laparoscopic cholecystectomy, but randomized trials have not shown other advantages.

Single-incision laparoscopic and mini-laparoscopic cholecystectomy have failed to gain widespread acceptance because the techniques are more challenging to learn, and the procedures prolong operative time and increase costs.<sup>17</sup> Similarly, robotic-assisted laparoscopic cholecystectomy, which has technological appeal, has not been widely adopted for these reasons, in addition to the lack of proof of clinical benefit, limited access to the technology, and dramatically increased costs.<sup>18</sup>

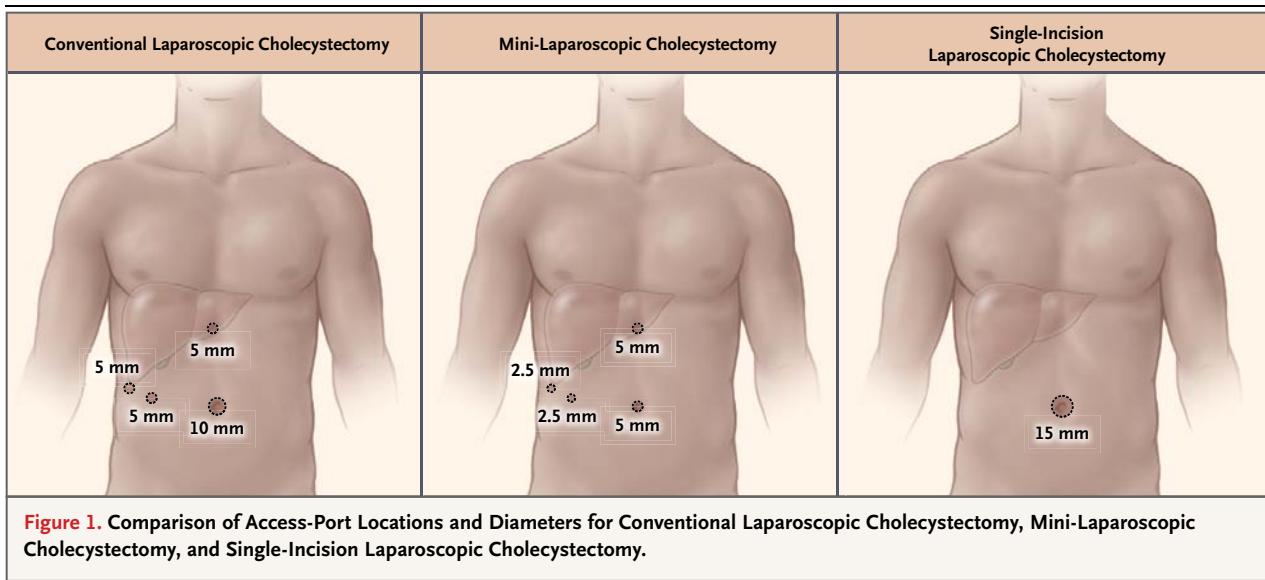
#### NOTES

NOTES is a technique in which surgery is performed through a naturally existing orifice and does not leave a cutaneous scar (Fig. 2). NOTES cholecystectomy was first performed in 2007.<sup>3</sup> It is typically performed by means of transgastric or transvaginal access with the use of flexible or rigid endoscopes, alone or in combination with limited laparoscopic access (which is known as hybrid NOTES).<sup>19,20</sup> A major advantage of NOTES

over laparoscopic approaches is the fact that removal of the resected gallbladder does not require an incision in the abdominal wall, which can be a source of postoperative pain and complications in wound healing. The procedure has been performed only a few thousand times, most often through the transvaginal route in patients without acute cholecystitis.<sup>19</sup> Outcomes have been similar to those achieved with laparoscopic cholecystectomy, although it is associated with a better aesthetic outcome, a shorter recovery time, and less pain.<sup>21,22</sup> Overall sexual function does not appear to be adversely affected,<sup>23</sup> and there have been no reports of the development of fistulae or fertility problems after transvaginal cholecystectomy. NOTES requires special equipment and is technically very difficult. Consequently, adoption of this technique has been limited to a few select medical centers.

#### PERCUTANEOUS CHOLECYSTOSTOMY

Percutaneous cholecystostomy, which was introduced in 1980,<sup>24</sup> is a technique that involves puncture of the gallbladder during ultrasonographic or computed tomographic guidance, followed by wire-guided placement of a pigtail catheter.<sup>25</sup> This approach effectively resolves acute cholecystitis in approximately 90% of patients. It is particularly useful for patients who cannot safely undergo laparoscopic cholecystectomy owing to contrain-



dications to anesthesia, severe cholecystitis, late presentation (>72 hours after symptom onset), or the lack of improvement after several days of medical therapy (Table 1).<sup>26-28</sup> External drainage allows time for resolution of both the systemic illness and local inflammation; resolution of local inflammation also reduces the probability that conversion to open cholecystectomy will be needed at subsequent surgery.<sup>29</sup>

Adverse events occur in up to one quarter of patients. Inadvertent dislodgement of the catheter within the first few weeks after initial insertion may result in peritonitis. Cholecystostomy tubes are uncomfortable and have a negative effect on quality of life.<sup>30</sup> Elective removal of the catheter can be considered once the tract is mature (a process that usually requires 3 to 6 weeks) and cholecystitis has resolved,<sup>31</sup> particularly if the cystic duct is patent, few gallbladder stones remain, and there are no bile-duct stones.<sup>32,33</sup> Extraction of gallbladder stones through the mature percutaneous tract<sup>34,35</sup> can facilitate the removal of the cholecystostomy tube and may obviate the need for surgery.

The use of percutaneous cholecystostomy in the Medicare population increased from 0.3% to 2.9% of all gallbladder procedures performed from 1994 to 2009.<sup>36</sup> Although results of controlled trials comparing the effectiveness of surgical and percutaneous management of cholecystitis have not been published, a large randomized study of laparoscopic cholecystectomy and percutaneous

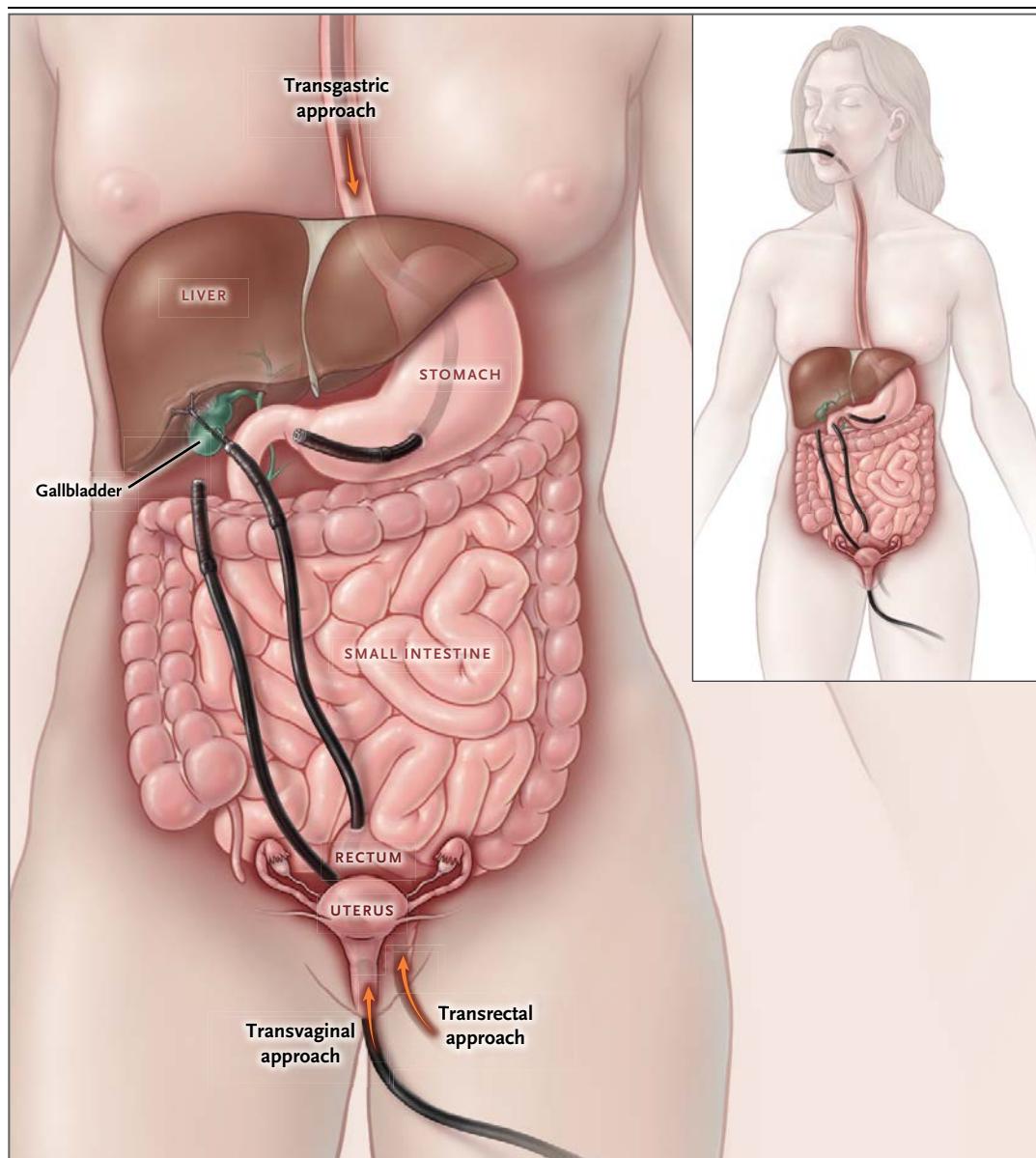
cholecystostomy in severely ill patients with acute calculous cholecystitis is ongoing.<sup>37</sup>

#### PERORAL ENDOSCOPIC GALLBLADDER DRAINAGE

Endoscopic drainage of the gallbladder can be established through the transpapillary route (i.e., through the papilla of Vater, guided by endoscopic retrograde cholangiography [ERCP]) or through the transmural route (i.e., directly into the adjacent gastrointestinal tract, guided by endoscopic ultrasonography [EUS]).<sup>38</sup> Although these procedures are conceptually similar to percutaneous cholecystostomy, they differ in the technical aspects of tube design, the tube diameter, and the capacity to apply suction. Endoscopic procedures may be a plausible alternative when percutaneous drainage is contraindicated, such as in patients with ascites and coagulopathy.<sup>25</sup>

#### TRANSPAPILLARY DRAINAGE

Transpapillary drainage of the gallbladder, which was first reported more than 25 years ago,<sup>39</sup> follows the standard procedure for cannulation of the bile duct with the use of ERCP. A guidewire is advanced through the cystic duct and into the gallbladder. One end of a pigtail stent is deployed within the gallbladder (Fig. 3), and the other end is either brought out through a nasobiliary catheter that exits through the nose or left to drain

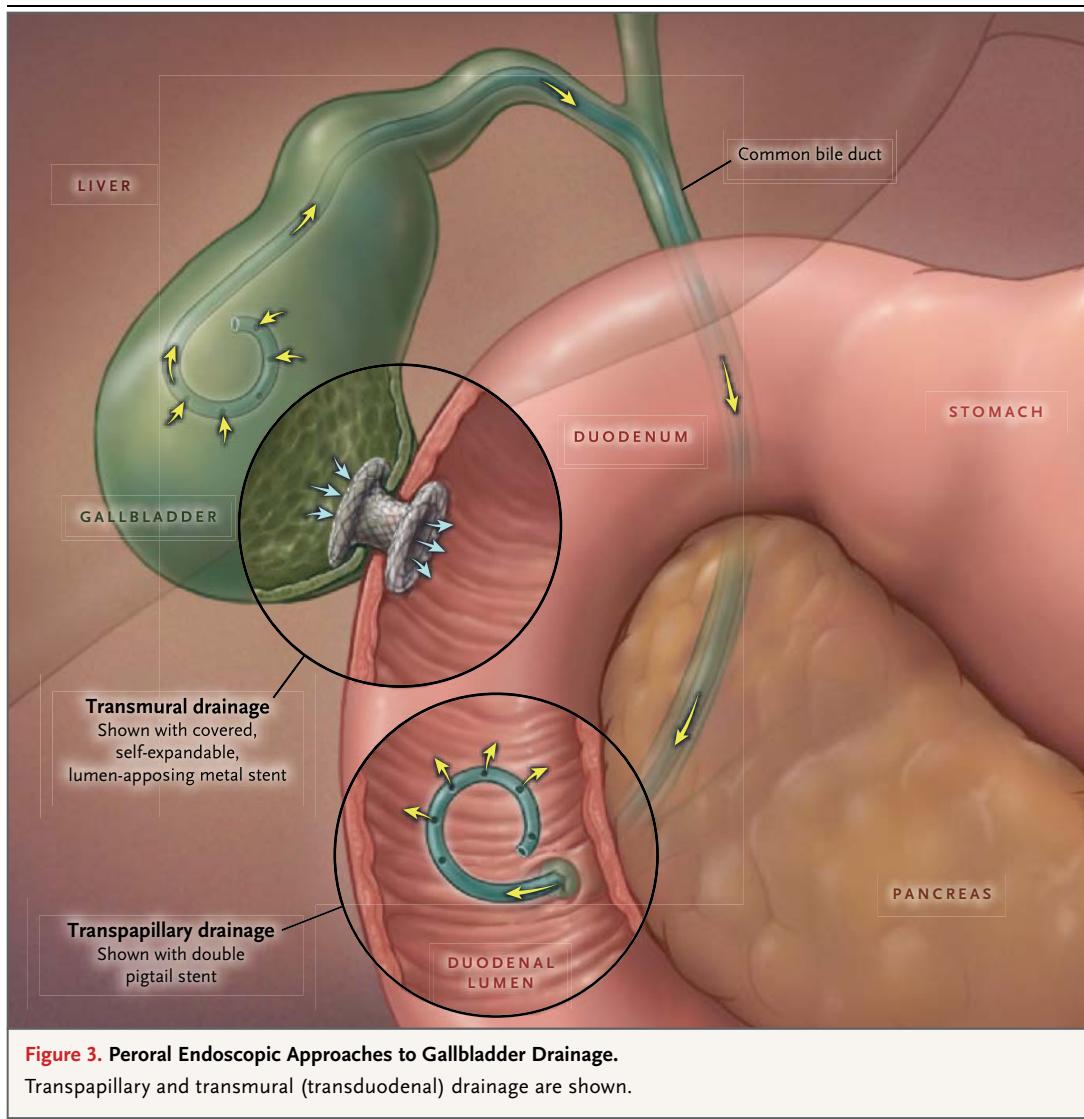


**Figure 2.** Sites of Entry for Cholecystectomy with Natural Orifice Transluminal Endoscopic Surgery (NOTES).

Transgastric, transvaginal, and transrectal approaches are shown.

internally within the duodenum (double pigtail stent). When the procedure is technically successful, transpapillary drainage provides effective treatment in more than 90% of patients with acute cholecystitis. Like percutaneous cholecystostomy, transpapillary drainage can provide definitive therapy for acute acalculous cholecystitis,<sup>40</sup> although a subsequent endoscopic procedure may be required to remove the stent once the cholecystitis

has resolved. Transpapillary drainage can also be used to facilitate removal of a percutaneous cholecystostomy tube<sup>41</sup> and is helpful in patients with symptomatic cholelithiasis who are not good candidates for percutaneous therapy<sup>42</sup> or surgery,<sup>43</sup> particularly those with advanced liver disease, ascites, or coagulopathy.<sup>44</sup> The risk of bleeding is low provided that an endoscopic sphincterotomy is not performed.



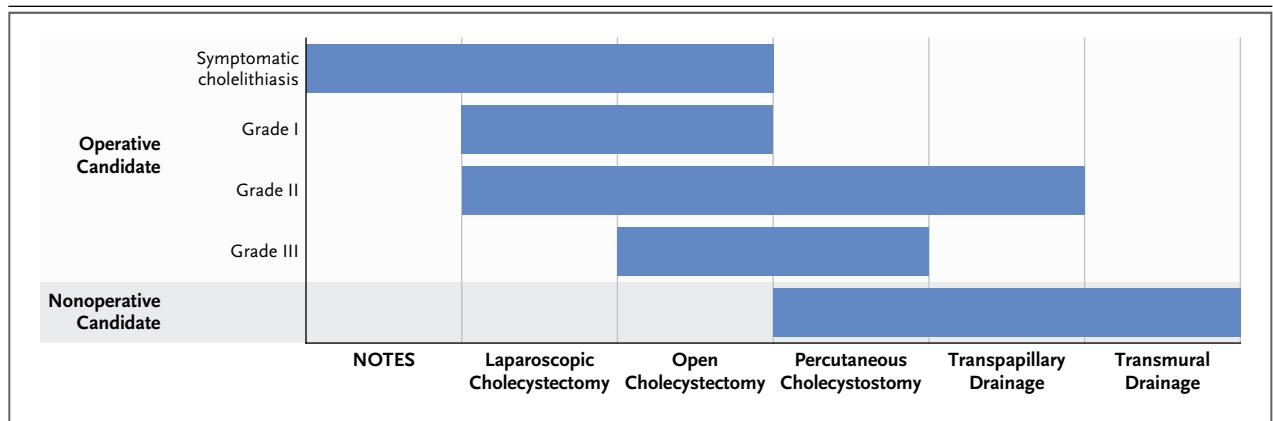
The use of transpapillary drainage of the gallbladder is limited by the technical difficulty of advancing a guidewire from a retrograde position through the cystic duct, which is often long, narrow, and tortuous and is sometimes occluded by an impacted gallstone. In addition, the cystic duct can accommodate only small-caliber plastic stents (5 to 7 French), which are prone to occlusion with biofilm. It is not known whether stent occlusion limits the long-term efficacy of the procedure, since bile can often flow around the stent.<sup>45</sup>

#### TRANSMURAL DRAINAGE

The most recent alternative to percutaneous cholecystostomy is transmural EUS-guided gallblad-

der drainage, which was described in 2007.<sup>46</sup> The gallbladder is usually closely apposed to the gastrointestinal tract and is conspicuous on endosonography. The use of Doppler imaging allows the endoscopist to avoid vessels while introducing the needle into the gallbladder. A guidewire is then positioned within the gallbladder, which allows for the deployment of transnasal drainage catheters or internal stents (Fig. 3).

Although assessments of EUS-guided gallbladder drainage have been limited to small studies conducted at expert centers, the procedure has been effective in the treatment of more than 95% of high-risk surgical patients who have acute cholecystitis. In a recent review of 155 patients



**Figure 4. Procedures for the Treatment of Symptomatic Gallbladder Disease, Stratified According to Patient Operative Status and Disease Severity.**

Grades I, II, and III denote mild, moderate, and severe gallbladder disease, respectively. NOTES denotes natural orifice transluminal endoscopic surgery.

with acute cholecystitis who were treated with EUS-guided drainage, technical and clinical success were reported in 97% and 99%, respectively.<sup>30</sup> It remains unclear whether these stents are appropriate for the treatment of the full spectrum of acute and chronic inflammatory gallbladder diseases. Transmural gallbladder drainage is feasible in patients with advanced liver disease and ascites.<sup>30,47</sup>

When endoscopic transmural drainage was used as a bridge to subsequent laparoscopic cholecystectomy in a prospective randomized trial involving patients with acute calculous cholecystitis who did not have a response to medical treatment, it was found to be as effective as percutaneous cholecystostomy.<sup>33</sup> Postprocedural pain was significantly lower among patients treated with the endoscopic approach.

Long-term data regarding the use of endoscopic transmural drainage as definitive therapy are limited. In one retrospective study involving 63 patients with acute calculous cholecystitis for whom surgery was considered unsuitable, transmural placement of a 10-mm self-expandable metal stent was highly successful, with late adverse events noted in only 6% of patients.<sup>48</sup> Long-term outcomes were evaluated in 56 patients, and 54 of these patients (96.4%) had no recurrence of acute cholecystitis during a median follow-up period of 275 days; the median duration of stent patency was 190 days. In a prospective long-term evaluation of 30 high-risk surgical patients with

acute cholecystitis, the use of lumen-apposing stents as definitive therapy was technically successful in 90% of the patients and clinically successful in 96% of the patients. Recurrent cholecystitis occurred in 7% of the patients owing to stent occlusion.<sup>49</sup>

Adverse events include perforation, bleeding, and intraperitoneal bile leakage, which can occur if access to the guidewire is lost during the procedure. Delayed leakage after successful stent placement appears less likely since the introduction of self-expandable, covered, lumen-apposing metal stents (although these stents are not yet approved by the Food and Drug Administration for use in gallbladder drainage). These stents, which measure 10 mm and 15 mm in diameter, allow endoscopic access to the gallbladder for the purposes of decompression and stone removal.<sup>50</sup>

The development of endoscopic transmural access to the gallbladder introduces new questions, such as whether the stent can be easily removed, as well as whether the stent should be removed and, if so, when it should be removed. The question of whether adherence of the gallbladder to the stomach or duodenum will interfere with subsequent cholecystectomy or other intraabdominal surgeries must also be addressed.

## CONCLUSIONS

The decision as to whether cholecystectomy or gallbladder drainage is more appropriate for a

patient with symptomatic gallbladder disease should be based on the severity of the acute illness,<sup>51</sup> the patient's overall health, and the locally available expertise and technology (Table 2 and Fig. 4, and Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). There have been few comparative trials of the various approaches. Limited data on recently developed endoscopic methods for gallbladder drainage suggest that these procedures may be useful alternatives to percutaneous cholecystostomy and are associated with fewer adverse effects. Controlled trials will be required

to assess both the short-term and long-term outcomes of these emerging endoscopic interventions.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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