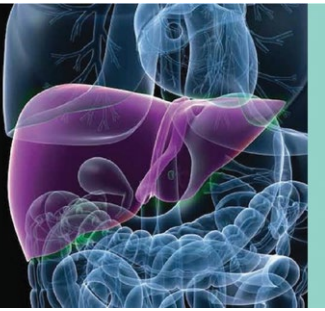


# Endoscopic Sedation of the Patient With Cirrhosis

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Choosing an appropriate sedative in the setting of endoscopy in patients with cirrhosis is challenging for many reasons. Providers must take into account the severity of liver disease, underlying causative factor, medication metabolism and interactions, baseline hemodynamics, and history of opioid, benzodiazepine, or alcohol dependence. A reduction in hepatic blood flow, increased portosystemic shunting, and decreased function and number of hepatocytes have all been implicated in impaired drug metabolism.<sup>1</sup> Evidence of decompensated liver disease, such as the presence of edema, ascites, hepatic encephalopathy, and hepatorenal syndrome, further influence pharmacokinetics of most medications used for sedation.<sup>2</sup> Endoscopy in patients with cirrhosis is usually well tolerated, and several prospective controlled trials have confirmed acceptable safety profiles in upper and lower endoscopy as well as endoscopic retrograde cholangiopancreatography (ERCP).<sup>3-8</sup> However, controversy exists regarding which is safer—MAC or moderate sedation—and recent data from

a retrospective study at our institution suggest that moderate sedation may be safer than MAC.<sup>9</sup>

## MEDICATIONS USED IN SEDATION FOR ENDOSCOPY

A multitude of medications and approaches can be used in the context of sedation for endoscopy (Table 1). For example, some patients can be effectively sedated with only minimal sedation (also known as anxiolysis). This degree of sedation is highly desirable in patients who may have severe underlying medical disease and in whom other forms of sedation may be dangerous. Moderate sedation (also conscious sedation) for endoscopy typically uses a combination of an opioid and a benzodiazepine to achieve appropriate sedation. It is commonly used across a variety of different procedures and is generally considered to be highly safe and effective. It is often used in practice where rapid onset and clearing of sedative effects is desired.

Abbreviations: ASA, American Society of Anesthesiologists; ERCP, endoscopic retrograde cholangiopancreatography; GETA, general (endotracheal) anesthesia; MAC, monitored anesthesia care.

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**TABLE 1. LEVELS OF SEDATION**

	Responsiveness	Airway	Spontaneous Ventilation	Cardiovascular Function
Minimal sedation (anxiolysis)	Normal response to verbal stimulation	Unaffected	Unaffected	Unaffected
Moderate sedation	Purposeful response to verbal or tactile stimulation	No intervention required	Adequate	Usually maintained
Deep sedation	Purposeful response after repeated or painful stimulation	Intervention may be required	May be inadequate	Usually maintained
General anesthesia	Unarousable even with painful stimulus	Intervention often required	Frequently inadequate	May be impaired

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Deep sedation typically involves use of propofol as well as similar medications used in moderate sedation (i.e., a combination of opioid and benzodiazepine). However, because of the potential for loss of airway and ventilatory function, special training and credentialing is typically required for physicians using this level of sedation. General anesthesia requires endotracheal intubation and may be desirable in situations where it is vital to protect the patient’s airway, a prolonged procedure time is anticipated, or increased patient stillness or cooperation is required for a procedure.

Sedation in endoscopy uses a variety of different types of drugs with different characteristics (Table 2). Opiates are primarily metabolized via CYP450 (CYP2D6 and CYP3A4) and glucuronidation in hepatocytes and are therefore affected by both liver injury and disease.<sup>10,11</sup> Fentanyl is most commonly used because it has a faster onset of action, is rapidly cleared, and causes nausea less often than meperidine.<sup>12</sup> The starting dose of fentanyl is 50 to 100 µg, and doses are repeated every 3 to 5 minutes until adequate sedation is achieved. Meperidine is commonly used for moderate sedation, although its use has been more limited because of the superior characteristics of fentanyl. The active metabolite of meperidine, normeperidine, is toxic and can result in tremors, delirium, and seizures; thus, we recommend that meperidine be avoided in patients with cirrhosis.<sup>13</sup> Benzodiazepines such as midazolam have been demonstrated to have a prolonged half-life in patients with

cirrhosis,<sup>14</sup> and thus the respiratory depressive and hemodynamic effects of benzodiazepines may be prolonged.<sup>10</sup> It is also possible that benzodiazepines may trigger hepatic encephalopathy.<sup>7</sup> It is therefore recommended that they be used with caution in patients with cirrhosis (Table 2). The starting dose of midazolam should be 1 to 2 mg, and adequate time between repeat dosing is recommended (3-5 minutes) until adequate sedation is achieved. It is important to note that, although there are no dosage adjustments in the package labels for midazolam and fentanyl, clinicians should exercise caution because the dose needed for sedation may be significantly lower and the dosing interval needed to maintain sedation may be significantly longer than that required for patients without cirrhosis.

Propofol is used with monitored anesthesia care (MAC) sedation; this medication is a hypnotic agent that can be used to provide moderate or deep sedation during endoscopic procedures.<sup>4</sup> It does not need dose adjustment in cirrhosis, and when compared with midazolam, has a faster onset of action, shorter effect, and faster recovery of motor and cognitive functions (Table 2). Pharmacokinetics and protein binding of propofol do not appear to be markedly affected by cirrhosis.<sup>15-18</sup> Recovery times are significantly longer, and patients with cirrhosis have a larger volume of distribution than patients without cirrhosis, but no differences in protein binding, clearance, or terminal elimination half-life have been reported.<sup>15,19,20</sup>

**TABLE 2. COMPARISON OF MEDICATIONS**

Drug	Onset of Action (minutes)	Peak Effect (minutes)	Duration of Effect (minutes)	Dosing/Initial Dose	Maximum Dose	Significant Adverse Effects
Fentanyl	1-2	3-5	30-60	25-100 µg	400 µg	Respiratory depression, vomiting, transient hypotension
Midazolam	1-2	3-4	15-80	1-2 mg	10 mg	Respiratory depression, disinhibition
Propofol	<1	1-2	4-8	10-40 µg	400 µg	Respiratory depression, cardiovascular instability
Ketamine	<1	1	10-15	0.5 mg/kg	Titrate to effect	Emergence reaction, laryngospasm

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General (endotracheal) anesthesia (GETA) has been used in some patients with cirrhosis, often in those in whom airway protection is important. The decision to use GETA most often depends on local practice patterns and the resources available at the time of the procedure. In our practice, GETA may be used to protect the airway in patients with gastrointestinal hemorrhage or other diseases that place the patient at high risk for aspiration. Again, this varies greatly depending on local practice patterns. GETA often uses combinations of many different agents, a discussion of which is beyond the scope of this review. Notably, the inhalation anesthetics (sevoflurane, desflurane, and isoflurane) are infrequently used in endoscopy. These agents undergo minimal hepatic metabolism and are considered safe for use in GETA.<sup>21</sup> Desflurane is thought to be the ideal volatile agent because it is the least metabolized and provides the quickest emergence while also relatively preserving hepatic blood flow and cardiac output.<sup>22</sup> The flurane family of drugs reduces mean arterial pressure and cardiac output and, consequentially, reduces hepatic blood flow. Halothane, no longer available in the United States, has been associated with hepatotoxicity and should not be used in patients with cirrhosis.<sup>23</sup>

Ketamine has also been used for endoscopic sedation. It produces dissociative anesthesia and has a combination of sedative, amnestic, and analgesic effects without suppressing the reticular activating system. Laryngeal reflexes remain intact, and cardiorespiratory function is not depressed.<sup>24,25</sup> It has the benefit of increasing blood pressure and cardiac output, the exact mechanism of which is currently not entirely understood. Furthermore, cardiac function, breathing, and airway reflexes typically remain functionally intact in contrast with many of the side effects of benzodiazepines and opioids. These properties, coupled with the rapid onset and short duration of action, make ketamine an ideal sedative agent for short procedures, especially in hemodynamically unstable patients such as those with cirrhosis, who typically have a lower baseline blood pressure,

and in those suffering from acute gastrointestinal hemorrhage. Ketamine is metabolized and excreted in the liver, where it undergoes *N*-demethylation by the P450 system to norketamine, which retains a fraction of the potency of the parent compound, followed by hydroxylation, glucuronidation, and renal elimination. No hepatic dosing is required.<sup>26</sup> (Table 2) Finally, ketamine has been demonstrated to have little influence on arterial or portal blood flow in experimental models.<sup>26,27</sup> Ketamine may be a beneficial agent in patients with hypotension, such as patients with cirrhosis in general, as well as those who are actively bleeding, because it has the benefit of increasing blood pressure. It may also benefit patients who are opioid or benzodiazepine tolerant and have a history of requiring high doses of standard moderate sedation medications.

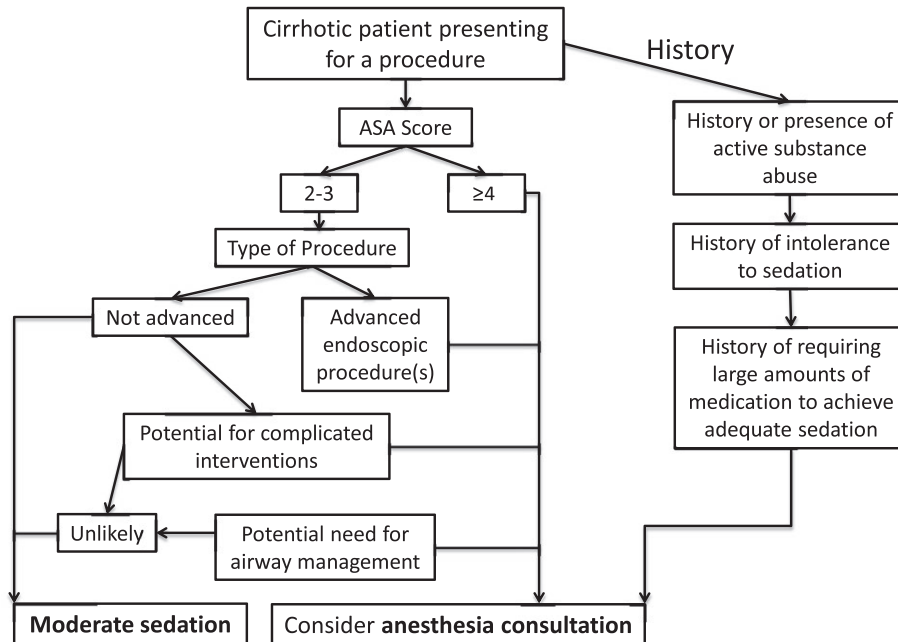
## WHEN TO ENGAGE ANESTHESIOLOGY CONSULTATION

The engagement of anesthesia professionals in endoscopy has now become common in practice. In general, anesthesia professionals are considered to be important for sedation of patients with severe comorbid disease (especially those with cardiopulmonary disease, morbid obesity, or neurological or neuromuscular disorders), usually with American Society of Anesthesiologists (ASA) classification 4 or 5 (Table 3). There are also several other situations in which involvement of an anesthesiologist would be considered appropriate, including patients with a history of alcohol or substance abuse who may be difficult to sedate with standard moderate sedation or patients who are uncooperative or delirious. In addition, anesthesiology consultation is typically required when propofol or other general anesthetic agents are used. Also, certain procedures that are likely better performed with the assistance of an anesthesiologist include ERCP, endoscopic ultrasound (EUS), and complex therapeutic procedures.<sup>12,28</sup> (Fig. 1)

**TABLE 3. ASA CLASSIFICATION**

Class	Description
I	Patient is normal and healthy.
II	Patient has mild systemic disease that does not limit activities (e.g., controlled hypertension or controlled diabetes without systemic sequelae).
III	Patient has moderate or severe systemic disease that does not limit the activities (e.g., stable angina or diabetes with systemic sequelae).
IV	Patient has severe systemic disease that is a constant threat to life (e.g., severe congestive heart failure, end-stage renal failure).
V	Patient is morbid and at a substantial risk for death within 24 hours (with or without a procedure).
E	Emergency status: In addition to indicating the underlying ASA status (1-5), any patient undergoing an emergency procedure is indicated by suffix "E."

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**FIG 1** When to consider engaging anesthesiology for assistance in sedation.

## INTRAPROCEDURAL MONITORING

For moderate sedation, physiological parameters, such as blood pressure, heart rate, respiratory rate, and oxygen saturation, should be frequently assessed.<sup>29</sup> Currently, the American Gastroenterological Association recommends continuous ECG monitoring for patients with a history of significant cardiovascular disease or arrhythmia.<sup>30</sup> Hypoxemia from depressed respiratory function is the main risk factor for adverse respiratory events during sedation, and some experts advocate the use of capnography monitoring. However, there is insufficient evidence to support the possibility that its routine use improves patient safety.<sup>31</sup> Current ASA guidelines recommend standard monitoring consisting of pulse oximetry, arterial blood pressure, and heart rate every 5 minutes and do not differentiate the monitoring of patients with cirrhosis when compared with those without cirrhosis, although the decision to increase the frequency or intensity of monitoring should be tailored to the specific clinical setting.<sup>32</sup>

## CONCLUSIONS

Endoscopy in patients with cirrhosis is safe and should not be withheld. Recent data from a retrospective cohort

study at our institution indicate that moderate sedation may be safer than MAC sedation and that the complication rate for patients with cirrhosis is similar to that of the general population.<sup>9</sup> As such, the majority of endoscopic procedures can be completed safely with midazolam- and fentanyl-based moderate sedation, and use of anesthesiology should be reserved for those patients with ASA classification 4 to 5 or those undergoing advanced endoscopic procedures such as ERCP or EUS.

## CORRESPONDENCE

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