We all feel the squeeze. We've got a long list of ever-more-complicated patients, and not only do we strive to do what's right for our patients, but we also face pressures from hospital administrators looking to keep bed turnover up and resource use to the minimum with the barest margin for error. You need quick, digestible tips to boost your confidence that you're doing right by your patients and your sponsoring institution.

Gut Shots:

a Hospitalist's Quick-Hit Digestive Disease Pearls

Preston Seaberg, MD, FACP

That's what our session's about today: giving you updates in diagnosis and management of hospitalized adults with common digestive disorders linked to high rates of readmission and high potential to make a difference, all backed by scientific studies published over the past few years. I'm your facilitator, Preston Seaberg, a practicing internist clinician-educator in West Virginia.

Educational Objectives

- Select appropriate diagnostic tests for common inpatient gastrointestinal syndromes
- Recall appropriate management of common inpatient gastrointestinal syndromes
- Apply findings of clinical research involving pharmacotherapy for digestive disorders encountered in the

Our main focus will be the management of hospitalized adults with gastrointestinal and hepatobiliary diseases, but we'll touch a bit on some decision-making about appropriate use of consultative diagnostic testing, all framed by interactive clinical questions we'll try to answer using the best available evidence.

Disclosures

- Non-Declaration Statement: I have no relevant relationships with ineligible companies to disclose within the past 24 months. (Note: ineligible companies are defined as those whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.)

A brief aside: I have no conflicts of interest to disclose, so let's get started!

Digestive Disease-related Visits in US Adults

	Emergency Department Principal Diagnoses*	**Hospital Principal Diagnoses**	**Readmission Rate of Diagnoses**
#1	Noninfectious gastroenteritis or colitis	GI bleeding (upper > lower ~ unspecified)	Liver disease (~31%)
#2	Constipation	Cholelithiasis, cholecystitis	C. difficile infection (~23%)
#3	GI bleed (upper > lower ~ unspecified)	Acute pancreatitis	Functional or motility disorders (~20%)
#4	Cholelithiasis, cholecystitis	Liver disease ~ intestinal obstruction	Inflammatory bowel disease (~19%)
#5	Nonbleeding gastritis, duodenitis, or peptic ulcers	Diverticulitis	GI bleeding (upper > lower) (~17%)

Peery et al (2021)

We see all kinds of digestive diseases in the hospital. What we see depends on our patient population and what service lines the hospital and its affiliated clinics or providers offer. Still, there's predictability to which digestive disease syndromes land patients in the hospital (or back in the hospital). In 2021, Dr. Peery and colleagues queried several national databases to gather information about the burden of digestive disease in the United States.

In the Emergency Department, the most common principal diagnoses related to digestive diseases in adults were abdominal pain, followed by nausea and vomiting. Together, they were nearly as common as all other digestive diseases or their symptoms *combined*. BUT because of their lack of specificity, I excluded these from the list.

Among more specific diagnoses, here are the most common digestive disease-related principal diagnoses for adults in the Emergency Department and patients admitted to the hospital. Note that liver disease here is an umbrella term encompassing a range of illnesses and symptoms. Alcoholic liver disease was the most common etiology.

Among the digestive conditions linked to more than 10,000 readmissions in the US in 2018, here are those with the highest readmission *rates*. Given the differences in

number of cases of these principal diagnoses in the index hospital stay, though, the greatest *number* of readmissions are from GI bleeding, followed by liver disease, followed by acute pancreatitis. On the other hand, cholelithiasis and cholecystitis are associated with some of the lowest *rates* of readmission among digestive diseases, though their commonness means they were still number 5 in *number* of readmissions in this study.

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Peery et al (2021)

But let's cut through the noise and focus on a handful of high-yield topics that most commonly lead to hospital admission and re-admission. The emphasis will be practice points to help provide excellent care to your patients while keeping costs low. After all, the focus on both quality boosts and cost savings is the main reason hospitalist physicians and advanced practice providers are in demand.

A patient with upper GI bleeding from a high-risk gastric ulcer, now treated successfully with endoscopic therapy, is alert and without vomiting or dysphagia. Considering efficacy, safety, and cost, which of the following is the most appropriate initial treatment to prevent rebleeding?

A. IV bolus → continuous infusion of IV PPI
B. IV bolus → intermittent doses of IV PPI
C. IV bolus → intermittent doses of oral PPI
D. Oral bolus → intermittent doses of oral PPI

Here's our first question.

Acid Suppression in Nonvariceal Upper GI Bleed

Placebo	1.21 (0.91 ,1.63) - (-)	**0.70 (0.57, 0.86)** **96.4% (0.00)**		**0.37 (0.24, 0.55)** **57.8% (0.07)**
	H2RA	**0.35 (0.23, 0.53)** **31.0% (0.19)**	**0.39 (0.21, 0.73)** **0.0%(0.54)**	0.31 (0.09, 1.03) - (-)
	H2RA no better than placebo	High-dose PPI (i.v.)	1.00 (0.73, 1.39) 0.0% (0.60)	0.92 (0.54, 1.58) 0.0% (0.94)
		High-dose IV PPI beats H2RA and placebo	PPI (i.v.)	1.10 (0.47, 2.59) - (-)
			IV PPI beats H2RA, equals high-dose IV PPI	PPI (p.o.)
				PO PPI beats placebo, equals IV PPI

Jiang, Chen and GAO (2016)

Here's information to help answer our question. In 2016, Jiang, Chen, and Gao performed systematic review of medications for nonvariceal upper GI bleeding. They performed a net-work meta-analysis (for treatments not directly compared) and pair-wise meta-analysis (for treatments directly compared) of RCTs in adults with endoscopically confirmed GI hemorrhage. This table depicts column treatments compared with row treatments, one versus another.

Here are the punchlines for this table. The investigators found that for preventing rebleeding, H2-receptor antagonists like famotidine and ranitidine were no better than placebo. As for high-dose IV PPI, standard-dose IV PPI, and oral PPI, all were associated with reduction in rebleeding when compared with either placebo or H2-receptor antagonists, and there was no clear winner among them.

That said, the American College of Gastroenterology cites a *different* meta-analysis when it recommends that for ulcers treated endoscopically, high-dose PPI should be used initially. High-dose PPI means twice daily. The optimal oral dosing strategy is unknown, but evidence supports the use of 40 mg of PPI twice to four times daily. For ulcers requiring endoscopic treatment, guidelines recommend a high-dose regimen for 72 hours after endoscopic treatment, then a twice-daily regimen for the first two weeks after endoscopy.

Here's a bonus secret: although it's common practice to administer PPIs to those with suspected upper GI bleeding even before endoscopy is performed, there's not enough evidence to make a recommendation as to whether PPIs should be administered before or after endoscopy. It's probably minimally harmful to administer PPIs up front, and doing so may be associated with reduced need for endoscopic treatment of an identified culprit lesion, so it's sensible to administer PPIs as soon as an acute nonvariceal upper GI bleed is suspected.

Oral PPIs for acute, nonvariceal upper GI bleeding

Jiang, Chen and GAO (2016)

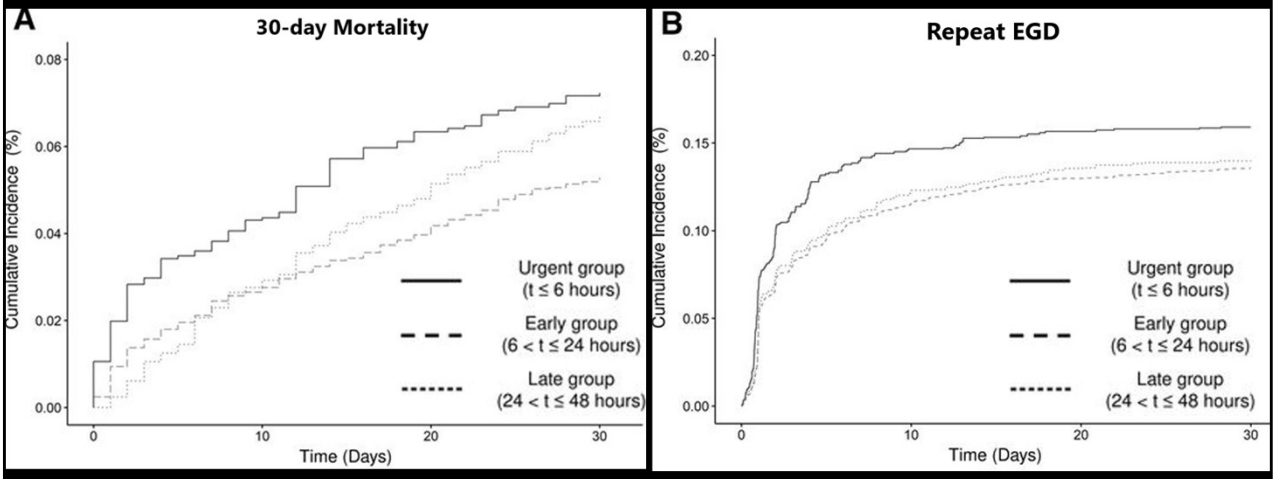
...assuming the patient can take them.

Relevant guidelines: Laine et al (2021)

For patients with acute gastrointestinal bleeding, which of the following rows is true regarding early (<6-24 hours after presentation) endoscopy compared with routine (>24 hours after presentation) endoscopy?

	Acute Upper GI Bleeding	**Acute Lower GI Bleeding**
A.	No benefit to early endoscopy	No benefit to early endoscopy
B.	Possible benefit to early endoscopy	No benefit to early endoscopy
C.	No benefit to early endoscopy	Possible benefit to early endoscopy
D.	Possible benefit to early endoscopy	Possible benefit to early endoscopy

Endoscopy Timing in Acute Upper GI Bleeding



Guo et al (2020)

In 2020, a pair of papers were published in hopes of shedding light on optimal timing of endoscopy for acute GI bleeding.

Guo and colleagues examined data from all public hospitals in Hong Kong for their retrospective cohort study. They compared outcomes of three cohorts with acute upper GI bleeding: those with urgent endoscopy within 6 hours of presentation, those with early endoscopy from 6 to 24 hours after presentation, and those with late endoscopy from 24 to 48 hours after presentation.

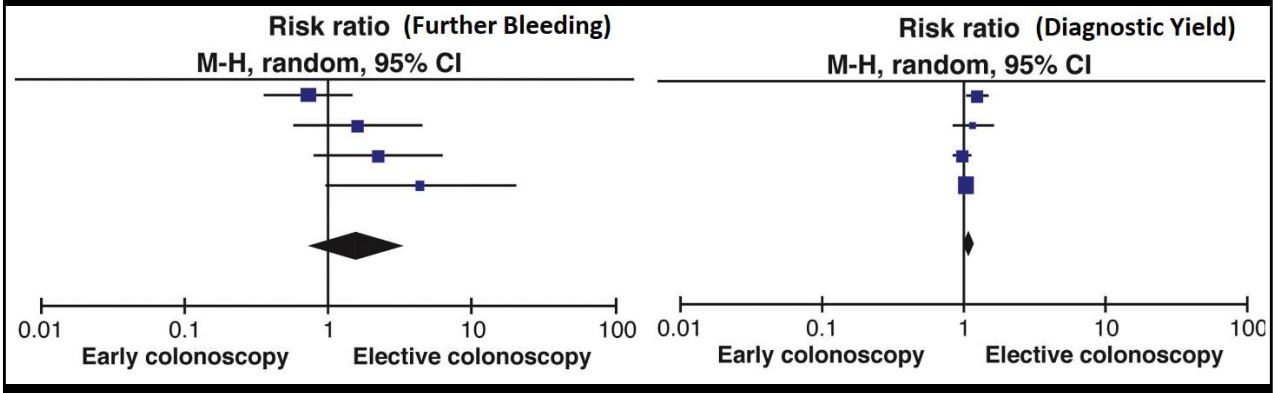
For all measured outcomes, the group with the worst outcome was the urgent group who received endoscopy within 6 hours of presentation. With respect to mortality, early versus late upper endoscopy was associated with better patient outcomes. This figure shows cumulative incidence of 30-day mortality for each cohort. The urgent endoscopy group is depicted as the solid line; the early group, as the more coarsely dashed line; and the late group, as the more finely dashed line. You can see the mortality rate was highest in the urgent endoscopy group and lowest in the early endoscopy group.

Early versus late upper endoscopy was also associated with lower rates of repeat endoscopy. This figure uses the same conventions. The scale makes it difficult to

appreciate, but the differences between groups were actually larger than the between-group differences in mortality. Again, the investigators found that those in the urgent endoscopy group had the worst outcomes, and those in the early endoscopy group had the best outcomes.

The authors concluded that in those with acute upper GI bleeding, early endoscopy was associated with better outcomes than was late endoscopy. The caveat is that even though the authors tried to account for factors that may lead to a specific timing of endoscopy, this was a cohort study and not a randomized, controlled trial. Although the authors tried to match group members based on prognostic factors, you can imagine those receiving urgent endoscopy may have had more severe disease than those patients who could wait for endoscopy, and maybe those who received late endoscopy had their endoscopies delayed because the patients were on the borderline of being too sick for early endoscopy and needed more stabilization first, or maybe they were in hospitals with less endoscopy provider availability.

Endoscopy Timing in Acute Lower GI Bleeding



Tsay et al (2020)

Let's turn our attention to acute lower GI bleeding. Dr. Tsay and colleagues performed a systematic review and meta-analysis of randomized, controlled trials comparing outcomes of patients with acute lower GI bleed treated with either early colonoscopy within 24 hours of presentation, or elective colonoscopy more than 24 hours after presentation. With respect to risk of further bleeding and ability to find a source of bleeding, there was no significant difference between the two groups. In these figures, the four blue squares represent the results of individual trials, and the black diamonds are the pooled results of all individual trials combined. They're constructed such that if one approach were associated with different outcomes than the other approach, the bottom diamonds would be entirely on one side of the central line of unity. Since we see the diamonds on both sides of the line of unity, that means it's possible that either approach is better than the other. Put another way, there's no clear winner between the two approaches for acute lower GI bleeding: early colonoscopy within 24 hours, or elective colonoscopy 24-48 hours of presentation are both viable options.

Acute upper GI bleeding: endoscopy after stabilization but within 24 hours

Guo et al (2020)

…colonoscopy for acute lower GI bleeding can wait longer.

Tsay et al (2020)

A 76-year-old man is hospitalized for severe colonic diverticular hemorrhage, confirmed endoscopically to have stopped. The patient takes aspirin for secondary prevention after myocardial infarction two years ago. He is intolerant to clopidogrel. Which of the following is the most appropriate recommendation?

A. Resume aspirin the day of endoscopic confirmation of hemostasis

B. Resume aspirin 72 hours after endoscopic confirmation of hemostasis

C. Resume aspirin 7 days after endoscopic confirmation of hemostasis

D. Resume aspirin 14 days after endoscopic confirmation of hemostasis

Resuming Anti-platelet or –coagulant Drugs after Major GI Bleeds

Strong indication(s)?
Patient preference?
Interaction(s)?
Forthcoming procedure?

2° prevention stroke/ischemia
High-risk thromboembolism
High-risk atrial fibrillation
Mechanical valve
Ventricular assist device

Tomaselli et al (2020)

Of course, resumption of antiplatelet or anticoagulant drugs after major GI bleeding is associated with a higher risk of GI bleeding than not resuming those drugs. But when given for good reasons, those drugs generally tend to have a greater likelihood of benefit in reducing ischemic or thromboembolic events than they have in increasing bleeding events. On the whole, when appropriately prescribed, anti-platelet and anticoagulant drugs are likely associated with lower risk of mortality. (Sostres et al, 2019)

That said, a few important questions should be answered before resuming a medication linked to risk of major GI bleeding.

Now, for our question, I had to add the intolerance to clopidogrel because a reasonable option could be discontinuing aspirin and starting clopidogrel, a choice that may be associated with more protection from ischemic events and similar or lower risk of bleeding, as seen in the HOST-EXAM study. (Kang et al, 2022)

Resuming Anti-platelet or –coagulant Drugs after Major GI Bleeds

Medication	When to Resume
Aspirin	**Day 0 (Weak evidence)**
Warfarin	**Day 7-14? (Retrospective evidence)**
$P2Y_{12}$ Inhibitor	? (Individualize)
Direct Oral Anticoagulant	? (Individualize)

Abraham et al (2022)
Kido and Scalese (2017)

If the decision is made to resume an anti-platelet or anticoagulant medication, the timing can get tricky. The strongest data are found in studies of aspirin or warfarin use, and believe me when I say strong is a relative term.

Aspirin's probably safe to resume as soon as hemostasis is confirmed, and that's if it's even held at all!

Warfarin's probably best resumed about a week after hemostasis is confirmed. Delays are linked to risk of ischemic and thromboembolic events.

For $P2Y_{12}$ inhibitors like clopidogrel, ticagrelor, or prasugrel, and for direct oral anticoagulants like apixaban, rivaroxaban, and dabigatran, we don't have a lot of evidence to guide timing of resumption after major GI bleeding. Some extrapolations have been made based on data from warfarin use, and otherwise available data are retrospective, heterogeneous, and hard to draw conclusions from. These decisions are highly individualized and frought with uncertainty. Consider working with consultants and the patient to create a safe plan for resumption and monitoring.

After major GI bleeding, offer resumption of anticoagulant or – platelet drug in those with strong indication(s) and mitigated bleeding risk

Kido and Scalese (2017)

…aspirin immediately, warfarin in 1-2 weeks, and the others on individualized basis.

Abraham et al (2022)

A 52-year-old woman is in the Emergency Department for non-severe, acute, gallstone-associated pancreatitis without bile duct obstruction. Blood pressure, hematocrit, plasma lactate, serum creatinine, and serum electrolytes are normal. Which of the following is most appropriate?

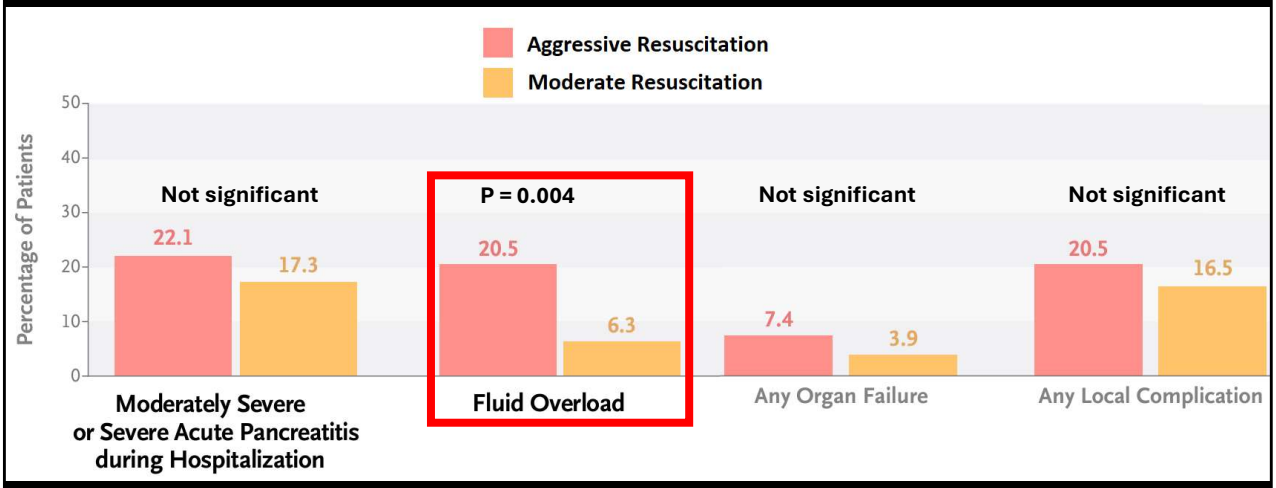
A. IV normal saline, 20 $\frac{cc}{kg}$ bolus followed by 3 $\frac{cc/kg}{hr}$

B. IV normal saline, 10 $\frac{cc}{kg}$ bolus followed by 1.5 $\frac{cc/kg}{hr}$

C. IV lactated Ringer's solution, 20 $\frac{cc}{kg}$ bolus followed by 3 $\frac{cc/kg}{hr}$

C. IV lactated Ringer's solution, 10 $\frac{cc}{kg}$ bolus followed by 1.5 $\frac{cc/kg}{hr}$

Moderate Fluids in Acute Pancreatitis*



de Madaria et al (2022)

Investigators in 18 centers across four countries performed an open-label, randomized, controlled trial comparing efficacy and safety of aggressive versus moderate fluid resuscitation in carefully selected patients with acute pancreatitis. The median age was 56-57 years. About half of patients were women, and gallstones accounted for the majority of causes of acute pancreatitis in the sample. In general, the group had a low number of comorbid conditions.

And, wow, this had a ton of exclusion criteria!

A. Uncontrolled arterial hypertension (systolic blood pressure >180 and/or diastolic blood pressure >100 mmHg)
B. New York Heart Association class II heart failure or worse, or ejection fraction <50% in the last echocardiography, or clinical signs or symptoms of volume overload including peripheral edema or lung crackles
C. Decompensated cirrhosis (Child's class B or C)
D. Baseline kidney failure (basal glomerular filtration rate <60 mL/min per 1.73 m2)
E. Shock or respiratory failure according to the revised Atlanta classification at recruitment (non-fluid-responding systolic blood pressure <90 mmHg, PaO2/FIO2 ≤300)
F. Time from pain onset to arrival to emergency room >24 h, or time from

confirmation of pancreatitis to randomization >8 h

G. Severe comorbidity associated with an estimated life expectancy <1 year
H. Confirmed chronic pancreatitis [in case of recurrent alcoholic pancreatitis a recent (<6 months) computed tomography (CT) scan/magnetic resonance imaging (MRI) or endoscopic ultrasound is needed to rule out chronic pancreatitis]

Anyway, they didn't find any advantage to aggressive fluid resuscitation in their study population, and they did find harm in terms of fluid overload. In some cases it was mild, like just detecting inspiratory crackles when auscultating the lung fields. But in other cases, it required a change in treatment. In short: moderate IV fluid resuscitation won the day over aggressive IV fluid resuscitation.

In non-severe acute pancreatitis, moderate IV fluid resuscitation over aggressive IV fluid resuscitation

de Madaria et al (2022)

...and consider using lactated Ringer solution over normal saline.

Tenner et al (2024)

A 50-year-old woman is in the Emergency Department on Friday for non-severe, gallstone-associated acute pancreatitis. She is alert. Elective cholecystectomy is tentatively scheduled for Tuesday. Which of the following is most appropriate?

A. Order low-fat diet now

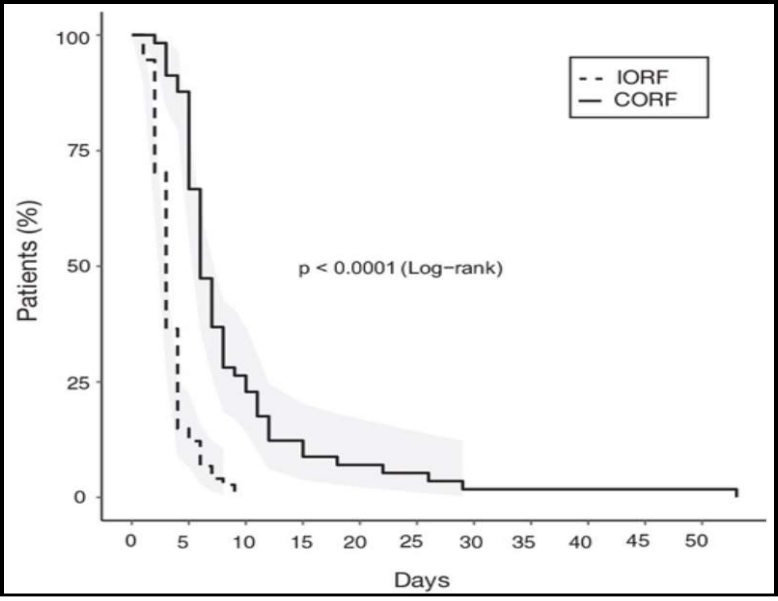
B. Order low-fat diet after 24-48 hours of bowel rest

C. Order clear liquid diet now, and advance as tolerated

D. Order clear liquid diet after 24-48 hours of bowel rest, and advance as tolerated

E. Order clear liquid diet after 24-48 hours of bowel rest, and advance after abdominal pain resolves

Immediate vs Conventional Oral Feeds in Non-severe Acute Pancreatitis



Ramírez-Maldonado et al (2021)

In a study in four hospitals in Spain, enrolled patients with non-severe acute pancreatitis were randomized to either receive either immediate low-fat diet or to conventional oral refeeding. In the conventional oral refeeding group, a period of fasting was followed by initiation of a clear liquid diet, with advancement to a low-fat diet after improvement in specific clinical parameters. The primary endpoint was length of hospital stay.

On average, patients were in their late 60s, overweight, had mild systemic disease at baseline (ASA class 2) and had a biliary cause of pancreatitis. About half were women. The immediate oral refeeding group was older than the conventional oral refeeding group.

I'll highlight two results. The first is the primary outcome: hospital length of stay. It's presented pictorially here. The immediate oral refeeding group is represented by the dashed line, and the conventional oral refeeding group is depicted as the solid line. The average hospital length of stay in the immediate oral refeeding group was more than **five days shorter** than that of the conventional oral refeeding group! Of course, the immediate oral refeeding group had, on average, a two-day head start on nutrition compared with the conventional feeding group.

Immediate vs Conventional Oral Feeds in Non-severe Acute Pancreatitis

Outcomes	IORF Group n = 71	CORF Group n = 60	*P* value
Length of hospital stay, days, mean (SD)	3.4 (1.7)	8.8 (7.9)	<0.001
Days from admission to refeeding, days, mean (SD)	0	2.8 (1.7)	<0.001
Days from refeeding to discharge, days, mean (SD)	3.4 (1.7)	5.4 (4.8)	<0.001
Need for opioids or analgesia infusion	0	5 (8.3)	<0.001
Intolerance diet n (%)	1 (1.4)	13 (21.6)	<0.001
Progression of acute pancreatitis, n (%)	0	6 (10.0)	<0.006
★ Complications, n (%)	3 (4.2)	11 (18.3)	<0.009

Ramírez-Maldonado et al (2021)

The other impressive result is shown here, with the rate of disease-related complications lower in the immediate oral refeeding group as compared with the conventional oral refeeding group. A possible caveat: the authors wrote that "eleven CORF patients **presented with** [organ failure], peripancreatic [fluid] collection, and infected pancreatic necrosis" (emphasis mine). The verbiage makes it seem as though these complications were known on presentation, in which case the baseline prognosis of the conventional oral refeeding group may have been worse than that of the immediate oral refeeding group. Still, for none of the secondary outcomes was there an associated benefit to the conventional oral refeeding strategy.

In non-severe acute pancreatitis without reason to be nil per os, immediate oral refeeding with low-fat, solid diet

Ramírez-Maldonado et al (2021)

…it's as safe as (+ linked to shorter lengths of stay than) starting with a liquid diet.

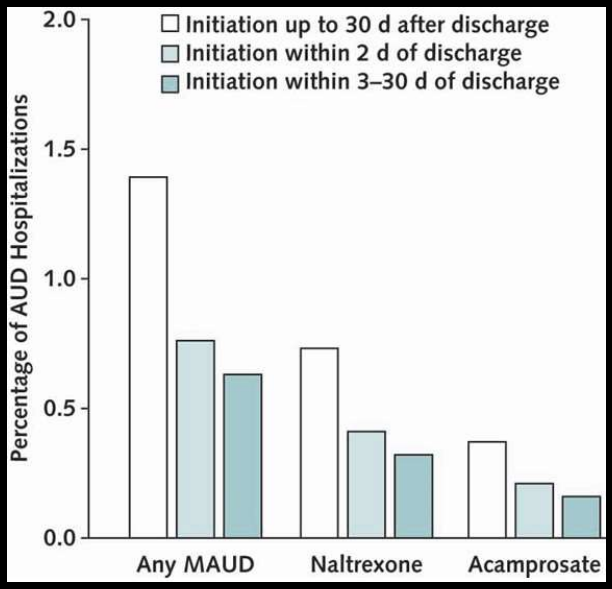
Tenner et al (2024)

A 55-year-old woman with alcohol use disorder is hospitalized for acute cholecystitis, since treated. Serum transaminase levels are mildly elevated. She does not have cirrhosis and does not take opioids. She is interested in medications for alcohol use disorder (MAUD). She sees her primary care provider in two weeks. Which of the following is most appropriate?

A. Prescribe naltrexone at discharge
B. Prescribe acamprosate at discharge
C. Prescribe disulfiram at discharge
D. Recommend she discuss MAUD with her primary care provider

I had to be very careful in building this question. Medications for alcohol use disorder have several reasons to promote skittishness among hospitalists considering initiation of them at the time of discharge. Evidence is gradually accumulating to weaken the arguments against starting them in the hospital or at the time of discharge. Let's talk about that.

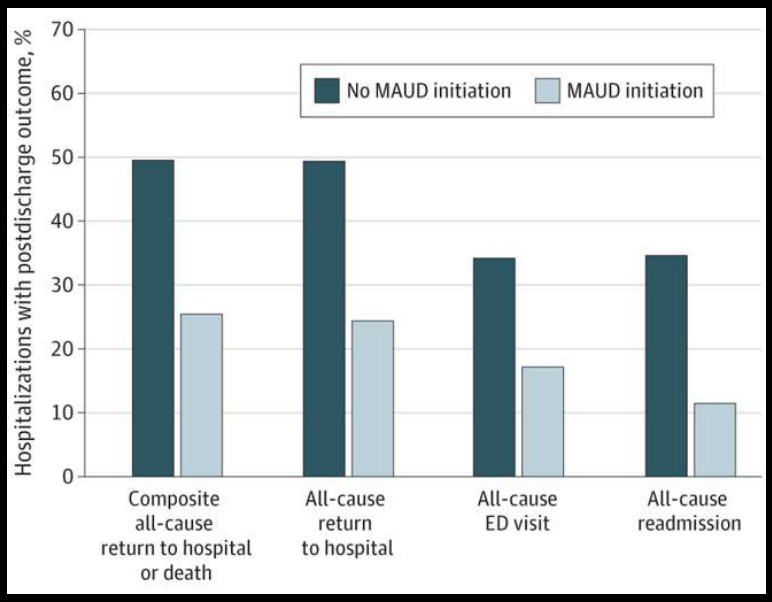
MAUD at Discharge: Uncommon



Bernstein et al (2023)

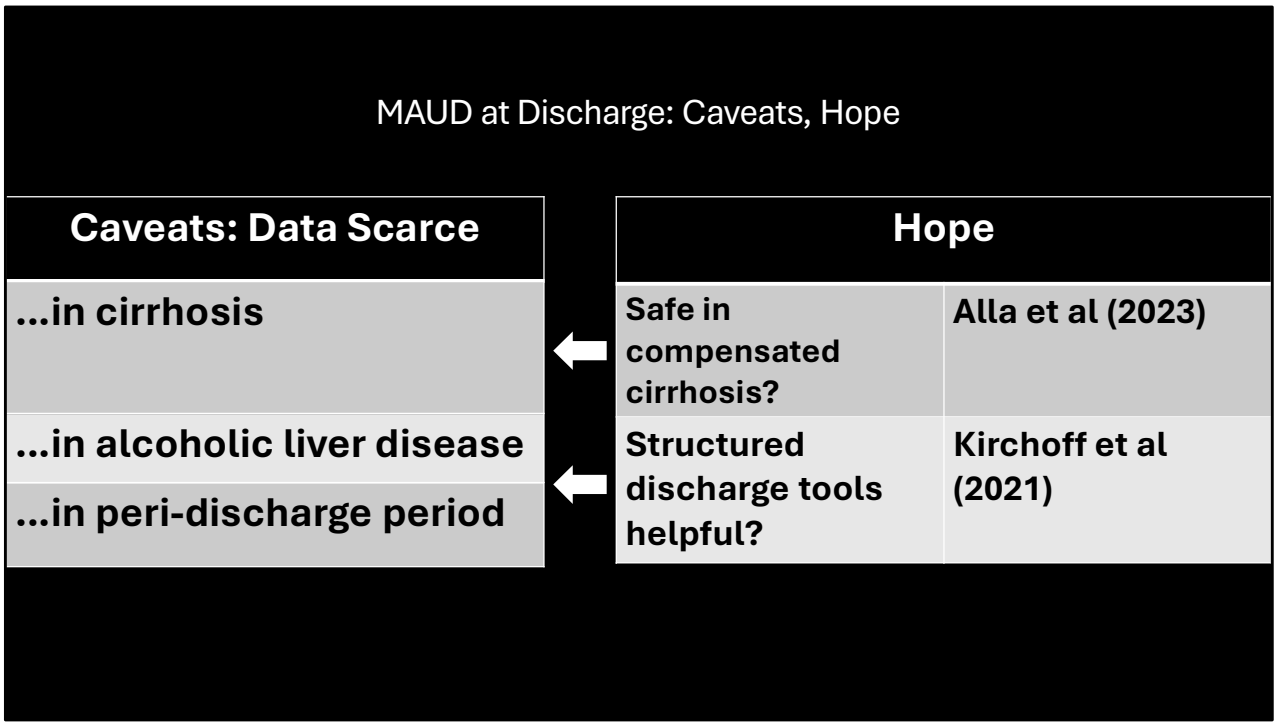
In a national sample of traditional Medicare beneficiaries hospitalized for alcohol use disorder from 2015-2017, excluding those with *recent* MAUD prescription or contraindications to naltrexone and acamprosate, only 1.3% of the time were MAUD were prescribed within 30 days of discharge. That means it's not just hospital medicine providers being skittish, but outpatient providers, too (and I'm sure reliable follow-up isn't always possible, and the nature of the disease itself leads to resistance to treatment initiation). Naltrexone and acamprosate have proven efficacy in reducing rates of harmful drinking but are under-prescribed.

MAUD at Discharge: Helpful



Bernstein et al (2024)

Dr. Bernstein and her colleagues then turned their attention to whether prescription of MAUD at the time of discharge from an alcohol-related hospitalization was associated with a reduction in repeat visits to the Emergency Department or hospital ward. Compared with those not prescribed MAUD at discharge, those prescribed MAUD at discharge had a lower rate of readmission or ED re-visits, with a relative risk difference of 42% and an absolute risk difference of 18%. That's amazing! Hospital administrators everywhere are probably salivating over these numbers.



BUT, Dr. Bernstein's exciting findings about readmission rates come with a caveat: those with liver disease (of any kind) were excluded. Naltrexone—and disulfiram for that matter—undergo hepatic metabolism and have been associated (if uncommonly) with liver injury. Previously, the FDA included a "black box" warning about the use of naltrexone in acute hepatitis or liver failure based primarily on studies of the drug administered at supratherapeutic doses. The warning has since been removed, but liver-related concerns persist, and consequently, naltrexone isn't well studied in those with cirrhosis or with alcoholic liver disease such as acute alcoholic hepatitis.

Fortunately, some investigators have given us cause for hope.

At last year's meeting of the European Association for the Study of the Liver, Alla and colleagues presented exciting, randomized, controlled trial-level data on naltrexone use and alcohol abstinence in patients with cirrhosis. We'll be on the lookout for a full publication of the trial data to understand just how excited we should be.

In a systematic review of studies on naltrexone initiation in the inpatient setting, Kirchoff and colleagues at the Mayo Clinic found little available literature, but the two pre-post studies they *did* find on the subject found that structured discharge plans increase the rate of prescribing, and some patients even had some degree of alcoholic

liver disease. Following implementation of the discharge planning tools, the two institutions noted that rates of revisits—perhaps when adjusting for certain prognostic factors—seemed to be lower in patients starting or even simply counseled on naltrexone use for alcohol use disorder.

In those with alcohol-related hospitalizations, discuss existence of medications for alcohol use disorder

…and consider prescribing naltrexone (if no opioid use or severe liver disease) or acamprosate (if no chronic kidney disease) at the time of discharge.

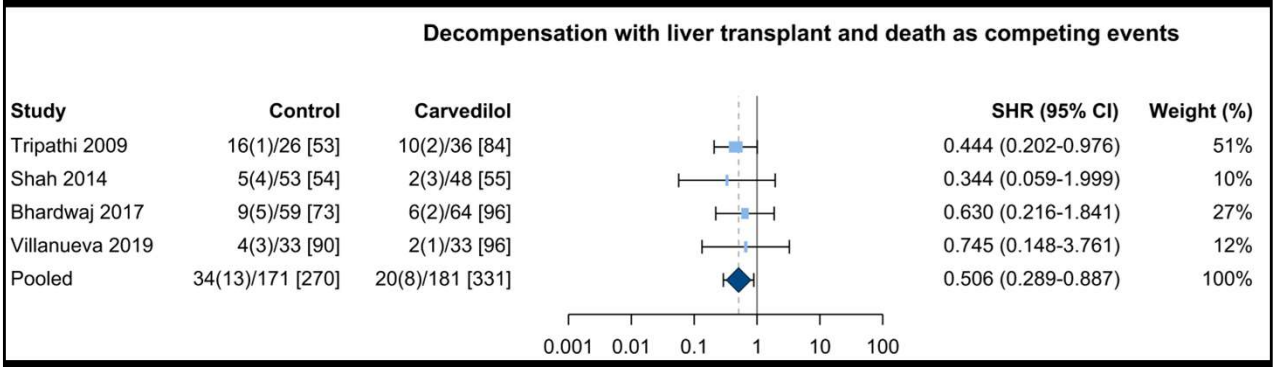
Bernstein et al (2024)

Although guidelines from the American Association for the Study of Liver Diseases remain mum on the subject due to scarcity of data in those with alcoholic liver disease, evidence—largely from small prospective or larger retrospective studies—seems to be building that the use criteria for naltrexone may be broader than originally thought.

A 60-year-old man is hospitalized with newly diagnosed alcoholic cirrhosis, ascites and nonbleeding esophageal varices. Blood pressure is 100/60 mm Hg, and heart rate is 70/min. He has no asthma. In addition to avoiding hepatotoxic drugs and substances and discussing endoscopic variceal ligation, which of the following is most appropriate to reduce the risk of further events related to clinically significant portal hypertension?

A. Nadolol, started at low dose
B. Propranolol, started at low dose
C. Carvedilol, started at low dose
D. Atenolol, started at low dose

Carvedilol for Portal Hypertension



Villanueva et al (2022)

We've seen that nonselective beta-blockers are helpful in those with cirrhosis. While historically they've been prescribed to help reduce the risk of variceal hemorrhage, they may have other beneficial effects. Certainly they can reduce hepatic venous-portal gradient through decreasing cardiac output and increasing splanchnic vasoconstriction (thereby decreasing splanchnic blood flow). There's evidence carvedilol does a better job of it than propranolol or nadolol, the two nonselective beta-blockers with widest past use for this indication. And because carvedilol relies on the liver for metabolism, in those with cirrhosis, it's given at low doses and can be dosed once daily, which is convenient (Kaplan et al, 2023).

To see how these hemodynamic changes translate to clinical outcomes, Villanueva and colleagues performed a systematic review and competing-risk meta-analysis of four trials of carvedilol versus either endoscopic variceal ligation or placebo for those with clinically significant portal hypertension. The outcomes of interest were decompensation or death. Competing risks—events that prevent a patient from experiencing an outcome of interest—were liver transplant and/or death.

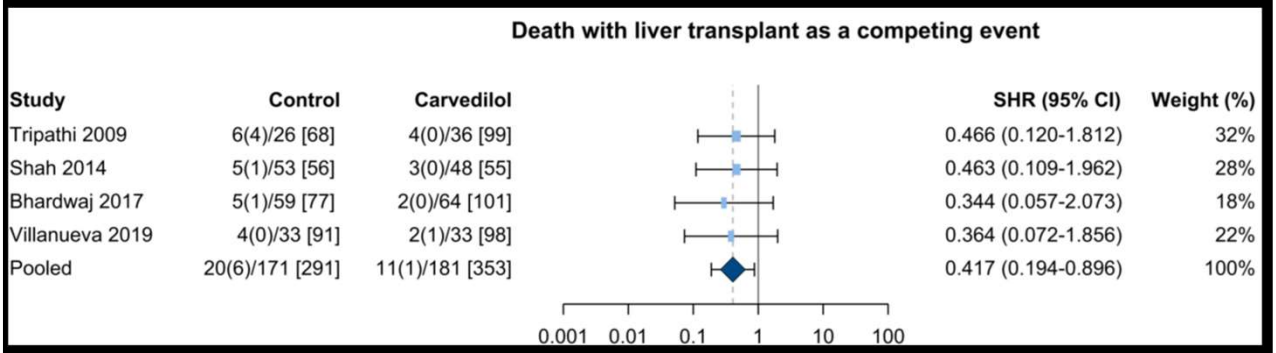
By the way, the American Association for the Study of Liver Diseases has a helpful classification system to justify its terminology. In those with cirrhosis, clinically significant portal hypertension is defined as the presence of a clinical

decompensation event such as ascites, variceal hemorrhage, or hepatic encephalopathy, or the identification of gastroesophageal varices on endoscopy or cross-sectional imaging.

This Forest plot is constructed similarly to the ones we saw earlier, this time comparing carvedilol versus control treatment in terms of risk of cirrhosis decompensation event. Control treatments here were either no active treatment or endoscopic variceal ligation. Individual trial results are shown as the small, light blue shapes with confidence bars extending to either side. The pooled results are shown as the larger blue diamond. A blue diamond with confidence bars that all sit squarely on one side of the line of unity without crossing it means there was a significant difference between groups. Villanueva and colleagues found that in those with clinically significant portal hypertension, at least when data were pooled, carvedilol use was associated with reduced risk of decompensation. The reduced risk of decompensation was mainly driven by reduced risk of ascites. These are exciting results, but there's a catch…

Patient with decompensated cirrhosis like the patient in our question stem were excluded. This is simply a high-risk population to study. What to do for them?

Carvedilol for Portal Hypertension



Villanueva et al (2022)

The authors also found that carvedilol use was associated with lower mortality rates than control treatments.

Patient with decompensated cirrhosis like the patient in our question stem were excluded. This is simply a high-risk population to study. What to do for them?

Carvedilol in Decompensated Cirrhosis

	Compensated Cirrhosis	**Decompensated Cirrhosis**
Starting dose	6.25 mg daily	**3.125 mg daily**
Titration (3 days)	6.25 mg twice daily	**3.125 mg twice daily**
Target	12.5 mg once daily or split	**6.25 mg once daily or split**
Stop if systolic BP < 90 mm Hg		

Kaplan et al (2023)

The AASLD does comment on the use of carvedilol in those with decompensated cirrhosis, referencing several studies indicating safety of nonselective beta-blockers in those with cirrhosis and ascites…as long as the beta-blockers are used in a safe manner!

The first thing to know is that if the systolic blood pressure is < 90 mm Hg, any nonselective beta-blocker should be stopped, and if stopped, should only be re-trialed at a lower dose.

The second thing to know about carvedilol, specifically, is how to dose it in those with cirrhosis.

Carvedilol depends on the liver for its metabolism, and it's typically given at lower does and often just once a day in those with cirrhosis. In this patient population, the starting dose is 6.25 mg once daily for those with compensated cirrhosis and adequate blood pressure. For those with decompensated cirrhosis but adequate blood pressure, consider starting at a lower dose of 3.125 mg once daily. If it's well tolerated, after three days, the dose can be doubled to 6.25 mg (or 3.125 mg) twice daily. The target maintenance dose is a total of 6.25-12.5 mg daily, either as a single dose or divided into two doses.

In those with clinically significant portal hypertension and systolic blood pressure > 90 mm Hg, consider initiating carvedilol to reduce risk of decompensation events

…with lower doses in those who’ve already had a decompensation event.

Kaplan et al (2023)

A 68-year-old woman treated for C. difficile infection is hospitalized two months later for severe, non-fulminant C. difficile infection. She takes immunosuppression after kidney transplant and has stage 3B chronic kidney disease of the renal allograft. She does not have heart failure. Which of the following initial management strategies is recommended by the Infectious Diseases Society of America?

A. Oral vancomycin and intravenous metronidazole
B. Oral vancomycin
C. Oral fidaxomycin
D. Oral fidaxomycin and intravenous bezlotoxumab

Fidaxomicin, Bezlotoxumab

Fidaxomicin is a macrolide antibiotic that received FDA approval for the treatment of CDI in 2011. Bezlotoxumab is a monoclonal antibody that binds to a domain of C. difficile toxin B and received FDA approval in 2016 for prevention of recurrent CDI in those at high risk of recurrence despite treatment with standard-of-care antibiotics.

Despite caring for patients who were good candidates for these treatments, I personally haven't prescribed them often, and that's true of most hospitalists in most places. I'm betting you all know the reason...

...yep, it's money.

Fidaxomicin costs thousands of dollars for a single treatment course, and bezlotoxumab costs thousands of dollars for a single dose. Insurance carriers, hospitals, and patients all balk at the up-front price of these things. So why do these feature so heavily in the IDSA's 2021 focused guideline update for the management of C. diff infection in adults?

Fidaxomycin vs Vancomycin for First C. diff

				Anticipated Absolute Effects	
Outcomes (Follow-up)	**No. of Participants (Studies)**	**Certainty of the Evidence (GRADE)**	**Relative Effect, RR (95% CI)**	**Risk With Vancomycin**	**Risk Difference With Fidaxomicin (95% CI)**
Sustained response of CDI (follow-up: 4 weeks after EOT)	1673 (4 RCTs) [14,–,17]	⊕⊕⊕◯ Moderate[a,b]	1.16 (1.09 to 1.24)	631 per 1000	101 more per 1000 (57 more to 151 more)

Johnson et al (2021)

In truth, the IDSA acknowledged the financial constraints surrounding the use of both fidaxomicin and bezlotoxumab. Where there was evidence of potential patient benefit of the direct effects of the drug, the IDSA tended to weight that more heavily than financial constraints, at the same time arguing that the direct costs are at least partly offset by reduction in risk of readmissions and their attendant costs. Indeed, when weighing patient benefit and financial concerns, the authors wrote that resource use was of limited importance when they decided their recommendations.

Let's first look at fidaxomicin. The IDSA give a recommendation for its preferential use in the treatment of initial and recurrent CDI, though they write that its use depends on available resources.

By pooling data from available studies, lead author Johnson and colleagues estimated that for every 1000 people treated with fidaxomicin for first occurrence of C. difficile infection, a sustained treatment response would be achieved in about 101 more patients than if those same patients were treated with vancomycin.

Fidaxomycin vs Vancomycin for Recurrent C. diff

				Anticipated Absolute Effects	
Outcomes (Follow-up)	**No. of Participants (Studies)**	**Certainty of the Evidence (GRADE)**	**Relative Effect, RR (95% CI)**	**Risk With Vancomycin**	**Risk Difference With Fidaxomicin (95% CI)**
Sustained response of CDI (follow-up: 30 days after EOT)	253 (3 RCTs) [14,–,16]	⊕⊕◯◯ Low[a,b]	1.27 (1.05 to 1.54)	558 per 1000	151 more per 1000 (from 34 more to 269 more)

Johnson et al (2021)

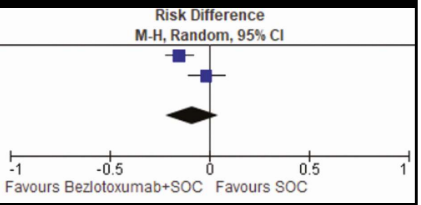
The investigators also estimated that in those with recurrent CDI, treatment of 1000 patients with fidaxomicin would be associated with about 151 more sustained treatment responses than would be expected among 1000 patients treated with vancomycin. Notably, the evidence supporting this finding was weaker than the evidence supporting fidaxomicin use in first C. difficile infection.

Bezlotoxumab for C. diff Infection (CDI)

First CDI

Study or Subgroup	Bezlotoxumab with SOC Events	Total	SOC Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Initial episode with ≥ 1 risk factor	41	278	76	255	52.5%	-0.15 [-0.22, -0.08]
Initial episode no risk factor	28	146	30	145	47.5%	-0.02 [-0.11, 0.08]
Total (95% CI)		**424**		**400**	**100.0%**	**-0.09 [-0.22, 0.05]**
Total events	69		106			

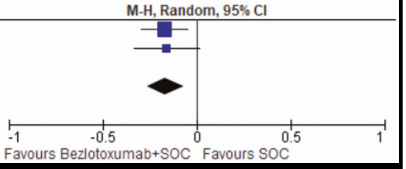
Heterogeneity: Tau² = 0.01; Chi² = 5.30, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 1.27 (P = 0.20)



Recurrent CDI

Study or Subgroup	Bezlotoxumab with SOC Events	Total	SOC Events	Total	Weight	Risk Difference M-H, Random, 95% CI
1 episode of CDI in the past 6 months	31	114	48	109	65.9%	-0.17 [-0.29, -0.04]
≥2 episodes of CDI in the past 6 months	23	56	41	72	34.1%	-0.16 [-0.33, 0.01]
Total (95% CI)		**170**		**181**	**100.0%**	**-0.17 [-0.27, -0.06]**
Total events	54		89			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 3.22 (P = 0.001)



Johnson et al (2021)

Let's take a look at bezlotoxumab, too. Again, bezlotoxumab is a monoclonal antibody that binds to a domain of C. difficile toxin B and has FDA approval for prevention of C. difficile infection recurrence in those at risk of it.

With the caveat that this is all subgroup analysis performed by the guideline authors—put another way, the studies weren't necessarily designed to answer the question of which specific patients benefit most from bezlotoxumab—the IDSA guideline authors led by Dr. Johnson found some signals to help focus bezlotoxumab use.

We have another Forest plot here. The patient population is those with initial C. difficile infection, and the outcome of interest is C. difficile infection recurrence for those treated with standard-of-care antibiotics plus bezlotoxumab, or standard-of-care antibiotics alone. The individual studies are depicted as small blue squares, and the pooled data is represented by the larger black diamond. If a square and its confidence bars both lie on one side of the line of unity, there's a significant treatment effect. Similarly for the diamond.

We see that for patients with initial CDI, there were signs that bezlotoxumab use reduced risk of recurrent CDI in those who had at least one risk factor for recurrence, like age > 65 years, immunosuppressed state, and severe CDI on presentation. Those

without such risk factors didn't get much additional benefit from bezlotoxumab, and the pooled results including all patients showed no significant treatment effect.

In those who experience a recurrence of CDI within 6 months, adding bezlotoxumab to the treatment regimen during that recurrence seemed to be linked to lower rates of C. difficile infection recurrence.

In short, patients at high risk of recurrence stand to benefit most from the addition of bezlotoxumab to the treatment regimen, while patients at average risk of CDI recurrence probably get little to no benefit if bezlotoxumab is added to their treatment regimen.

A relative contraindication to bezlotoxumab use is a diagnosis of congestive heart failure. Use it only after thorough discussion with the patient.

To make things more challenging, in the studies analyzed by the guideline authors, bezlotoxumab was uncommonly used with fidaxomicin. Combining bezlotoxumab with vancomycin was more common.

In those with C. difficile at high risk of recurrence, consider using fidaxomicin, with additional bezlotoxumab for those at the highest risk of recurrence.

Johnson et al (2021)

…just be aware of the financial burden. Your hospital may have a policy for appropriate use of these medications.

Take-home Points

- GI bleeding
  - Oral over IV PPIs for UGIB
  - Early endoscopy for UGIB, routine for LGIB
  - Resume aspirin early if good indication
- Nonsevere acute pancreatitis
  - Moderate IV fluids + immediate oral refeeding
- Liver disease
  - Discuss, ?prescribe MAUD in those with AUD
  - Carvedilol for portal hypertension if SBP > 90 mm Hg
- C. diff + recurrence risk
  - Fidaxomicin +/- bezlotoxumab, finances depending

References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Thank you!