We're very lucky today to have our very own Dr. Christopher DiMaio for his Grand Rounds on Severe Acute and Necrotizing Pancreatitis. Dr. DiMaio obtained his medical degree from SUNY at Buffalo School of Medicine. He completed his internal-medicine residency training at Thomas Jefferson University, where he also served as chief resident. Dr. DiMaio went on to complete a gastroenterology fellowship at Columbia University, and then an advanced-endoscopy fellowship at Harvard Medical School, which is a combined program with MGH and Brigham.

He currently serves as an associate professor of Medicine here at Mount Sinai. Dr. DiMaio's research interests are in patients with pancreatic cysts and pancreatic cancers, with a particular interest in using novel endoscopic techniques to diagnose and treat these lesions.

As now system director of interventional endoscopy, Dr. DiMaio's clinical interests are in advanced diagnostic and therapeutic endoscopic procedures. And we're very lucky to have him for this talk today. It should be fantastic. So please join me in giving a warm welcome to Dr. Christopher DiMaio.

CHRISTOPHER DIMAIO: Thank you so much. And to clarify, it's Mount Sinai system, not like the solar system. [INAUDIBLE] But soon to-- OK, all right, because I don't I don't have enough on my plate already.

I'd really like to thank the department of medicine for the invitation. It's a real honor and privilege to speak to you guys today and talking about something that I think is an underrated problem in internal medicine, certainly in gastroenterology. And I hope to shed some light on why pancreatitis in general should be considered a medical emergency because even though most patients do fine, there is a small subset of patients who can turn south very quickly. And we, as internal medicine and gastroenterologists on the frontlines of this, have a major opportunity to prevent severe morbidity and mortality.

Just some disclosures-- so my objectives today are to discuss the evidence-based interventions in the management of acute pancreatitis and describe minimally invasive endoscopic techniques for drainage and debridement of pancreatic-fluid collections.

So acute pancreatitis is one of the most-common GI problems we're going to face. As of 2012, it's the third-most-common GI disease. It's actually the most common disease at the time of hospital discharge, with just over a quarter of a million admissions per year and accounting for close to $3 billion health-care dollars per year.

The traditional approach to pancreatitis for the past century has consisted of this-- impression-- acute pancreatitis, plan-- NPO, IV fluids, pain control. And for most patients, this was fine, a bit rudimentary, but this was fine.

But what we know-- oops, sorry-- but specifically, when we look at severe pancreatitis, this is far and away lacking in specificity. In particular, traditionally, there's not been any specific criteria on how to diagnose someone with severe pancreatitis. There have been very lax recommendations regarding how much fluid resuscitation and what type of fluid one should get.

Nutrition, traditionally, has been to keep these patients NOP and to give them TPN if they are going to be NPO for a prolonged period of time. Typically, antibiotics were always given prophylactically. And then as far as the timing and type of interventions, surgical drainage was always the mantra. And it was always wait a minimum of four to six weeks, again, for a patient like this.

Over the past decade or so, there's been an explosion in pancreatitis research. Pancreatitis research has actually been far behind other areas of gastroenterology, but there's been an explosion in interest in pancreatitis and pancreatic disease in general. And with these new research studies, there's been a better understanding in the natural history of acute pancreatitis, as well as the development of evidence-based guidelines on how to best manage these patients. And these are just some of the guidelines that are currently in use today, one of which, the bottom one, was just published in *Gastroenterology,* which is the flagship journal for our field.

And again, looking at what the last slide showed, as far as the very general and non-specific recommendations, these evidence-based guidelines now provide a very nice framework and a very nice roadmap for how we should manage these patients. In particular, there are specific criteria on how to make a diagnosis of acute pancreatitis. One would think it's very straightforward. It always isn't-- not always is.

Fluid resuscitation-- there's now specific criteria in terms of type of fluid, the rate of infusion, and what our goal should be. Antibiotics-- there is no longer a need for prophylaxis antibiotics. In fact, most patients with pancreatitis. Should not be getting prophylactic antibiotics. Nutrition should be early, as opposed to NPO, and it should be enteral, as opposed to parenteral.

And then there are a whole host of data showing evidence-based outcomes with improvements in timing of cholecystectomy for patients who have gallstone pancreatitis, the appropriate use of ERCP for patients with suspected biliary pancreatitis, and, of course, as we'll focus on today, the appropriate management of pancreatic-fluid collections.

So I think, for all of us who manage patients, who get consults, who admit patients with acute pancreatitis, we always know-- I think all of us get frustrated because there seems to be no consistency in how these patients are managed. I know from a GI perspective, we'll often get a consultation after the patient's been sitting in the emergency room for 40 or 72 hours. Not to pick on ER, but 48 or 72 hours, getting IV fluids, normal saline at 100 species per hour-- the patient, by the time we come see them, they look horrible, they're in a lot of pain, they're hungry, and they're just not getting good care.

So we had an interest in looking at the quality of care of patients with pancreatitis at Mount Sinai Hospital. And specifically, we wanted to see if we can identify gaps in knowledge as a first step in improving evidence-based care.

So this was actually done by a former resident, Calley Levine and Sanchit Gupta, who were residents here-- graduated a few years ago. And what we did is we audited two year's worth of patients who had acute pancreatitis-- were admitted here with acute pancreatitis. And then we went back and applied all of these evidence-based criteria to their hospitalization to see how well we did at Mount Sinai in terms of managing these patients.

As part of this, we also wanted to assess knowledge gaps. So we came up with a 10-question pre-test that we administer to internal-medicine residents, surgical residents, ER, critical care, and gastroenterology Fellows, as well as the faculty. Now, we didn't get great responses, but I decided to pull the internal-medicine house staff results to just show you where things were. So these are the 10 learning objectives we tested. Let's see how we did.

So you can see that internal-medicine house staff residents here are really good at making a diagnosis, sort of OK at choosing which IV fluids to give, and knowing when to do an ERCP, and when to feed these patients. But universally, we're all pretty lousy at predicting the severity of someone's course, when to use radiology, which tests to get, the timing of those tests, how to assess fluid resuscitation, when to use antibiotics, and then dismally, how to use endoscopic and surgical interventions, or when to employ ICU care-- so clearly, a major opportunity for us.

Globally, when we looked at the clinical performance-- and this is all Mount Sinai providers-- we see that specific parameters, such as receiving the appropriate amount of IV fluids, at least six liters in a 24-hour period-- only 8% of the patients we audited received that. About 2/3 had appropriate use of cross-sectional imaging, and about half had inappropriate use of IV antibiotics.

And then for gallstone pancreatitis, we now know that patients who undergo a cholecystectomy during their index admission have far better outcomes. Again, in our population, only 16% of patients with gallstone pancreatitis underwent appropriate timing of their cholecystectomy-- so a major, major opportunity for us to improve.

But why is this important? Why do we care? We know that the majority of patients with acute pancreatitis have a mild course, it's self-limited, and they're out of the hospital in a few days. We also know that about 10% of patients will develop necrosis, and the mortality related to pancreatic necrosis can be as high as-- some studies say 39%.

We know that mortality is related to the severity of their pancreatitis. And severity, while it used to be defined by how long you were in the hospital, we now know that severity is defined by the persistence of organ failure. And we'll talk about that specifically.

So when we talk about the early treatment of acute pancreatitis, I look at it as three main areas-- their presentation. It's important that we make a prompt diagnosis so that we can initiate treatment, and most importantly, identify patients who are at increased risk for morbidity and death. That first 12 to 24 hours, our goal should be to identify the etiology. This is something you would think is common sense, but again, in our population, in our study, less than half of patients had an etiology identified by the time of discharge. So we want to find an etiology, we want to treat reversible causes, we want to use this time to optimize their medical management, and again, prevent and reduce the risk of organ failure.

And then in that day one and day two-- 24 to 48 hours-- we want to be able to recognize and manage local and systemic complications, again, with the goal of minimizing morbidity and preventing death. We want to be proactive with these patients, not reactive. And these are the areas I'll focus on for this talk.

So as I mentioned, when we talked about severity of pancreatitis, traditionally, this was defined by length of stay in the hospital or the development of local complications, such as fluid collections. This has all been turned on its ear because now, again, with some of these newer research studies, we've been able to stratify patients and stratify them according to mortality.

So mild acute pancreatitis is defined as those patients who do not have any organ failure and have no local or systemic complications. And for the purposes of this, organ failure consists of respiratory, renal, or cardiac dysfunction. Moderately severe acute pancreatitis involves transient organ failure-- so usually resolving within 48 hours-- with or without the presence of local or systemic complications-- so again, pancreatic-fluid collections being the main one. And then severe acute pancreatitis is defined by persistent organ failure of one or multiple organs for more than 48 hours.

And you can see the associations with mortality, depending on the severity. And again, this is all based on presence and persistence of organ failure.

So how can we tell if somebody-- or how can we predict if somebody with acute pancreatitis is going to turn south? How do we know if they're going to crash? There are some very easy predictor scores that we can use.

So traditionally, we use things like Ransom's criteria or the APACHE score. Those are very impractical. Ransom's criteria requires collecting data for 48 hours. APACHE score-- I'm sure there's an app for it, but as you know, it's like 30 different variables. It's not very user friendly. These are not very practical.

But there are some very easy things that we can do, immediately on assessment of the patient, that may help predict a patient's mortality related to acute pancreatitis. One of them is the BISAP score, which stands for "Bedside Index for Severity and Acute Pancreatitis." And this consists of five variables-- a BUN greater than 25, the presence of impaired mental status, presence of SIRS, age greater than 60, or presence of a pleural effusion.

Each of these gets you one point. If your BISAP is 0, 1, or 2, your in-hospital mortality related to your pancreatitis is very low. But once you start getting at three points or higher, you see that you have an exponential rise in hospital-mortality rate related to pancreatitis.

So one can imagine, when you're assessing a patient on the floor or in the emergency room, you can do this quick BISAP score and say, boy, my patient has three or four points. I think we need to get them to an intensive care unit or a step-down, again, to be more proactive as opposed to reactive.

Even more simple predictors of mortality are two basic labs that we check on every patient. One is hematocrit. And this is a very simple but elegant study by Peter who is a forefather of pancreatitis research in the pancreatitis world.

And he noticed something as a junior attending when he was rounding on the floors. They noted that patients who had a hematocrit of higher than 47% on admission or those pancreatitis patients that whose hematocrit did not drop within 24 hours were more likely to have necrotizing pancreatitis.

Looking at this another way-- this is a large retrospective-- cohort study of 5,000 patients-- pancreatitis patients that were nonsurvivors had a much worsening trend of their BUN over 48 hours compared to survivors. And if you looked at the trend of their BUN, for every five-point increase in there BUN, their odds ratio of death went up by 2.2-- for every five-point increase.

So again, these are two very simple things we can use, BUN and hematocrit-- to assess the volume status of our patients and predict whether or not they may have a bad outcome from their pancreatitis. And again, this all points to intravascular volume. And if you're going to take anything away from this talk, it's that fluids are the first, second, and third-line treatment for any patient with acute pancreatitis-- the one thing we can do to impact their outcomes.

So why are fluid so important? Well, we know these patients have vomiting, they can't have PO intake, there's a lot of insensible losses. At the cellular level, there's increased vascular permeability, pancreatic edema, third spacing of fluid, all of which leads to intravascular-volume depletion, again reflected by their hematocrit and BUN. All this hypovolemia will lead to hypoperfusion of the pancreatic microvasculature.

And we know them the pancreas is a very finicky organ. It doesn't like to be messed with. We learn this very early on in our training. So once you hypoperfuse that microvascular, it just sets off this whole chain of events. You get cell death, you get release of pancreatic enzymes, this sets off SIRS, this sets off the vicious cycle which can lead to pancreatic necrosis and peripancreatic necrosis. Again, at a cellular level, these patients have increased intestinal permeability, higher risk for bacterial translocation, and infected necrosis. So again, fluids, fluids, fluids-- very important.

We now have emerging data on how best to administer IV fluids, and it comes down to two things-- early aggressive fluid resuscitation, and possibly the choice of fluids that we use. So this is one very nice study. And this is a very big area in the field of pancreatitis research is fluid administration. So this is one study. It's retrospective, but I think it hammers home the point.

They took patients with cute pancreatitis, and they stratify them by how much fluid they got in 72 hours. Those patients who got more than one third of their fluid volume, of that three-day fluid volume in the first 24 hours were called the "early-aggressive-fluid-resuscitation group." Those who received less than one third of that three-day fluid bolus were considered the "late-fluid-resuscitation group."

And again, not surprising, these outcomes, based on what I just presented to you-- those patients who received early aggressive fluid resuscitation had significantly lower rates of SIRS at all time points, had half the rate of organ failure, less than half the rate of need for ICU, and a significantly decreased length of stay. And these were all statistically significant factors.

As far as the type of IV fluids, there is a lot of interest in this. And one study looked at lactated ringers versus normal saline. This was prospective randomized control.

And one of the outcomes of this study was that when they looked at patients who received lactated ringers versus normal saline, those patients that that received lactated ringers-- 84% of them had a reduction in SIRS at the 24-hour time point compared to normal saline. And these were all patients that were matched as far as the severity of their pancreatitis.

The theory is that-- and you guys probably can explain this better than me. You're closer to it than I am. But the theory is that normal saline can induce a low-grade metabolic acidosis. And that metabolic acidosis may impact intracellular calcium metabolism in the acinar cells, which may lead to further activation of pancreatic enzymes.

Lactated ringers, on the other hand, is more pH neutral, more pH balanced, and it seems, at that cellular level, you may not see that activation, or increased activation. And that is one of the theories behind why lactated ringers may lead to reduction in SIRS. And again, SIRS is really a surrogate for long-term outcomes and mortality.

So as far as evidence-based approach to IV-fluid recommendations, these are some expert guidelines and expert opinion papers. The recommendations are that patients should receive aggressive fluid hydration, at least 250 cc's an hour, which equates to about a minimum of 6 liters of fluid over a 24-hour period. It may be higher. If your patient is able to tolerate higher fluid rates, they should get that. Bolus is maybe needed, particularly if they are hypotensive or have other indicators of intramuscular-volume depletion.

The key with all this is its most beneficial in the first 12 to 24 hours. By the time that patient, who's been sitting in the ED for 36, 48 hours-- we may have missed that window. We still need to hydrate them and replete them, but as far as the impact, it's really those first to 12 and 24 hours.

None of the guidelines have come out and outright endorsed lactated ringers as the fluid of choice, but I think all of us anecdotally use that. I know in unit, when we were doing ERCP, we used lactated ringers predominantly for these patients as a way of minimizing their risk of post-ERCP pancreatitis. So that is where the trend is. It hasn't been officially endorsed yet.

These patients need to be monitored closely-- again, any patient with pancreatitis because you just don't know which one is going to go south. This isn't the kind of patient that you round on at 10:00 in the morning and then not see them again until 10:00 AM the next day. They need to be reassessed frequently, and they need to have labs monitored closely.

And again, our goal is really, to improve their intravascular-volume status. And we can monitor that in two very easy ways-- their serum BUN and hematocrit, or if they have a Foley catheter, you can consider monitoring their urine output, and this is one recommended target, as far as urine output.

The hallmark of severe pancreatitis and necrotizing pancreatitis is often the development of pancreatic-fluid collections. Now, this is a relatively rare event. About 20% of patients with acute pancreatitis will develop a PFC. The vast majority of these are clinically insignificant, and most of them-- at least 80%-- will resolve spontaneously. But as I will go through over the next several set of slides, these can be a significant problem for these patients and a major cause of morbidity and mortality.

Just one word-- traditionally, all fluid collections with the pancreas are known as "pseudocysts." That's what we just call them. And as I'm going to show you in the next slide, that no longer holds true.

So in 2019, all pancreatic-fluid collections are classified according to what's called the "Atlanta classification." This was an expert international-consensus paper that was published in 2013. And they describe acute pancreatitis being divided into two different types. There's interstitial pancreatitis, where you have inflammation and edema of the pancreatic parenchyma. And then there's necrotizing pancreatitis, where you have necrosis of the pancreatic parenchyma and/or peripancreatic tissues.

Fluid collections associated with each of these two entities is defined by their age. So for example, patients with interstitial pancreatitis can develop acute peripancreatic-fluid collections. And these are less than four weeks old, they tend to be very amorphous and disorganized. These are very rarely clinically insignificant, and the vast majority of these will just dry up. Nothing really needs to be done about these.

A subset of these patients, though, particularly if they have a very large amount of acute peripancreatic fluid, over time, in typically, four weeks or greater, they will organize into what we call a "pseudocyst." And this is an organized collection of fluid, very little, if not any, debris.

Necrotizing pancreatitis, similarly, can develop acute necrotic collections-- again, amorphous, unorganized of both parenchyma and peripancreatic tissue. These are much less likely to resolve on their own. They may over time, but more commonly, after three or four weeks, these collections will organize into what we now called "WON," or "Walled-Off-Necrosis.

There are major sequelae of pancreatic-fluid collections. So in the acute and early phase, these can cause mass effect, leading to abdominal pain and early satiety, gastric-outlet obstruction, and biliary obstruction, and in rare cases, if they're large, it can lead to abdominal compartment syndrome, which is a surgical emergency. The most serious complications-- and usually, these occur after the second or third week-- are infection and sepsis, persistence of SIRS, and they can help precipitate multi-organ failure, and ultimately, lead to the patient's demise.

For patients with stable or chronic fluid collections, these can result in fistula. These can fistulize to the small bowel, they can fistulize to the colon, the skin, to the plural. They can cause recurrent acute pancreatitis, they can be associated with thrombosis of major vessels, and then, I think, again, often underrated intracystic hemorrhage due to pseudoaneurysm development. And we'll talk a little bit about these as we go on.

We'll start with pseudocysts. Traditionally, patients with symptomatic pseudocysts underwent surgical drainage by a procedure called a "surgical-cyst gastrostomy." And this can often be done laparoscopically. Surgeons will go in, they'll go to the lesser sac and posterior wall of the stomach, and they'll just create a fistulous tract between the fluid collection and the stomach so that all that fluid content drains into the stomach.

The whole idea of waiting for weeks was based on surgical data in that you needed at least four weeks for the wall of these pseudocyst to be mature enough to suture to them. In 2019, we no longer do surgical-cyst gastrostomies, except in extremely rare circumstances. Now, in large, pancreatic pseudocysts are drained endoscopically, and the main modality by which we drain them is a technique using endoscopic ultrasound. So what is endoscopic ultrasound?

Endoscopic ultrasound is a type of video endoscope that has a small ultrasound probe on the tip. When we insert it into the stomach or the small intestine, we can do an intraluminal ultrasound and see all of the structures adjacent to the GI lumen. So obviously, the pancreas is immediately posterior to the stomach, so we obviously get a great view.

The other advantage of endoscopic ultrasound, as you see in the upper-right-hand corner, is that this allows us to guide a needle directly into our target under real-time imaging. So in the lower picture, you see us doing a needle biopsy of a pancreatic mass. But we can now use that needle to access these collections and use it as a conduit to create that fistula that surgeons typically will do.

So let's see if this-- so this is a fluid-- I don't know why my mouse isn't working. Here we go.

So this is a fluid collection on endoscopic ultrasound. And what you're going to see in a second is us using a needle to access that collection. So there, we've punctured, under real time, the fluid collection. And now, we're inside the stomach, and what we're doing is using endoscopic accessories to create a fistulous tract between the stomach and the pancreatic collection. And this never gets old-- every time I watch this video.

So you can see it's very dramatic. You get immediate relief, immediate drainage of this collection. We've created a fistulous tract. And we can maintain that fistula by placing some stents in there.

And these patients do incredibly well. These collections collapse within days. They will close down around those stents, and we simply pull those stents out in a couple of weeks. And the vast majority of these patients do well without need for further intervention.

How safe is this? How effective is this? Well, this is a landmark paper published a few years ago in *Gastroenterology,* which was a randomized controlled trial comparing this endoscopic-drainage approach versus the traditional surgical drainage of pseudocysts.

And what you see is that in terms of outcomes-- sorry. I'm having trouble with my mouse here. In terms of outcomes, there was no difference in recurrence, treatment success or failure, and adverse events, or need for re-intervention between the endoscopic group and the surgical group. But there was a major benefit in that patients who underwent the endoscopic drainage had a much lower hospital stay and significantly lower costs.

So the conclusion of this paper-- again, I think this was a landmark study-- was that surgical drainage of pancreatic pseudocysts is not superior to endoscopic drainage and that the endoscopic approach is associated with shorter length of stay, lower cost, and better quality of life. And this has now become the standard of care.

Moving on to necrotizing pancreatitis-- as we said, necrosis occurs in up to 10% of cases of acute pancreatitis, and there is a significant mortality associated with this. Sterile necrosis can be associated with mortality of up to 10%. If infection sets in, that mortality can be as high as 30%.

And these patients typically die for one of two reasons. Early on in their course, it's usually due to multi-organ failure. And again, this is just the precipitation of SIRS and single or multi-organ failure that they just never recover from.

If they survive those first two or three weeks, the major cause of mortality in these patients is one of two things-- infection leading to sepsis, which again, can precipitate organ failure; or they can bleed due to pseudoaneurysm development and rupture of the pseudoaneurysm.

And this is a little bit of a different animal than a simple fluid collection. These patients can develop these large, walled-off solid collections, which you just simply can't stick a needle in or put one simple drain in and expect it to drain. And similar to pseudocysts, these can cause all types of similar consequences-- pain, infection, luminal obstruction, thrombosis of vessels, pseudoaneurysm, and bleeding. But unlike pseudocysts, walled-off necrosis is more associated with clinical deterioration, SIRS, ongoing organ failure, and death.

And because there's associated necrosis, a significant number of these patients will develop endocrine dysfunction, which is now known as "type 3c diabetes," exocrine insufficiency, and long-term sequelae if they survive-- that being recurrent, acute pancreatitis, chronic pain and chronic pancreatitis, and something called the "disconnected pancreatic-duct syndrome," which we'll talk about at the end.

So as the title of my talk implies, the pendulum has now shifted in how we approach these patients. Traditionally, patients with necrotizing pancreatitis would get TPN, all of them would get antibiotics, and surgical drainage would be the mainstay of their treatment. But as I'm going to go over in the next few set of slides, all of this has now changed.

So when to suspect infected necrosis-- well certainly, if patients have ongoing fevers, certainly if they have bacteremia and worsening leukocytosis. I think that's a pretty easy way to detect these patients with infected necrosis.

The more subtle ones are those that have clinical deterioration without any obvious infectious symptoms, or those that are called "persistent unwellness." And that's an official term used in the guidelines-- persistent unwellness-- these patients who are sort of stately crappy. They just don't seem to get better, they can't get out of a step-down or an ICU, but there is not one thing you can necessarily localize their etiology to. And this is what we're talking about-- again, pancreatic infection.

A true diagnosis of infected necrosis is when there's gas in the collection. And this is a collection that was never instrumented. It spontaneously developed gas in, presumably, a patient that was clinically unwell or deteriorating.

The old-school method of diagnosing infected necrosis was to do CT-guided fine-needle aspirates and send for gram stain and culture. That has really gone the way of the dinosaur because we a significant number of these patients will have false negatives as far as their FNA. But I think more importantly, we know that these collections, if they're sterile, we don't want to risk contaminating them, even if it's done under sterile technique.

So CT-guided FNA is really done very, very rarely, and really, the only indication, I think, in this day and age is if a patient has persistent bacteremia and we need help speciating their organism and determining sensitivities for antibiotic selection.

Treatment is really two things-- broad-spectrum IV antibiotics. Ideally, you want something that penetrates the pancreas well-- ideally, a carbapenem, like meropenem. You can also use quinolones, you can use piperacillin tazobactam, anaerobic coverage-- but something that's broad spectrum that has good penetration to the pancreas. And then ultimately, these patients need drainage and debridement.

The question always comes up when these patients hit the emergency room or hit the ICU-- they may be an organ failure, they may be in SIRS-- do we just give them antibiotics? And again, traditionally, the answer was typically yes.

We now have multiple very well-designed prospective randomized trials-- placebo-controlled trials, looking at the role of prophylactic antibiotics. And interestingly, prophylactic antibiotics had zero impact on these patients developing infected necrosis, whether they get systemic complications, whether they die, or whether they need surgical interventions. In fact, giving prophylactic antibiotics only precipitates bad things in patients without infection. They often get drug-resistant bacteria that develop if they do get infections, or they get other consequences like, C. diff.

There's been at least one very interesting study in which shows that probiotics actually increase mortality. And this is postulated to be due to the increased risk of bacterial translocation. We don't want to flood the small bowel with more bacteria. This actually increases the risk of infected necrosis.

And the other thing that always comes up-- the only other concept that always comes up in these patients is if we're giving them these broad-spectrum antibiotics, these big gun antibiotics, should we routinely administer antifungals? And again, there's no data to support that. The role for antifungals is only if they do develop a fungal infection.

How about nutrition? Again, traditionally, we are always taught NPO and TPN for patients with pancreatitis. That has really been thrown out the window. For pay all patients with pancreatitis, we now know that they get major benefit from early initiation of feeding. In fact, if your patient is hungry, let them eat.

Multiple randomized controlled trials-- I don't have time to go through the specifics in the data-- but multiple randomized controlled trials show that patients with hepatitis who are given immediate feeds, compared to on-demand or delayed feeds, actually have a shorter length of stay. And the fear is always oh, my, goodness, I'm going to precipitate their pain. I'm going to make their pancreatitis worse. Again, these randomized trials do not show that. These patients have no difference in their pain relapse or worsening condition.

The other thing that always comes up is oh, we should start them on clear liquids or a low-fat diet. Again, randomized control trials-- good science-- shows that no one diet is superior and that there is no difference in outcomes, whether you start your patient on a full diet, a soft-food diet, or clears. Again, these patients get out of the hospital sooner, and you don't have a deal deleterious effect on their outcome.

For patients who are more ill-- the severe-pancreatitis patients, the patients in the ICU, the necrotizing-pancreatitis patients-- it's even more critical to get food in them or get nutrition in them quickly. And this is something that should be prioritized within their first 24 to 72 hours. These patients are in a catabolic state, they have a compromised gut, they have decreased motility, they're at increased risk for bacteria overgrowth because of this decreased motility, they have increased permeability and increase for bacterial translocation. So if you give them enteral nutrition, this will maintain their gut integrity and, in theory, decrease their risk for infected necrosis.

And sure enough, again, we have good data to support feeding these patients enterally. These are two highly quoted randomized controlled trials-- patients with severe pancreatitis who were randomized to getting enteral nutrition by a feeding tube versus TPN. And both of these studies show quite dramatically the same outcome.

Enteral nutrition was associated with significantly fewer infected necrosis, significantly lower rate of multi-organ failure. And look at the death rate. It's unbelievable. In the similar study, organ failure, multi-organ failure-- significantly lower, less need for surgery, less incidence of infected necrosis, and again, a significant reduction in mortality when these patients receive enteral nutrition.

This usually leads to the next discussion of well, how do we feed these patients? If they're intubated or they're vomiting and they can't tolerate a PO diet on their own, should we put a nasojejunal tube in, or can we drop an NG tube? Again, multiple randomized controlled trials-- that NG-tube feeds are non-inferior to NJ-tube feeds. And again, this relates to their outcomes in terms of pain and infection.

I think for most of us, an NG tube is much easier to place. NJ tube typically involves bringing these patients down to the endoscopy unit. We can often do it at the bedside, but we typically like to do this with fluoroscopy. If they're too sick to move down to endoscopy, again, place an NG tube. The only time I wouldn't consider an NG tube is if the patient has high aspiration risk-- say from gastroparesis, an ileus or gastroduodenal obstruction.

So back to the final aspect of these patients with infected necrosis-- it comes down to drainage and debridement. All these patients should start with conservative therapy, but oftentimes, they're going to need some type of drainage procedure. The traditional approach to this has been the open-surgical necrosectomy.

Has anyone encountered this here in the past few years? Last time I saw this was when I was a medical student. These patients undergo these long these huge laparotomies. They typically have to do hand debridement of all of the debris. They usually leave the wounds open, and pack them, and bring them back to the OR every other day.

And these are what these patients often look like. They live in the surgical ICU, they have all these tubes and drains coming from them, and not surprisingly, these patients have a horrible outcome. If you look at quoted rates of mortality related to this-- up to 50%. These patients have a high rate of incisional hernias, a high rate of external fistula. So even though you may control the infection, you're trading one problem for the other.

Over the past decade, there has been a major shift towards using minimally invasive approaches to dealing with walled-off necrosis. This includes percutaneous drainage, this includes a minimally invasive surgical procedure, known as "video-assisted retroperitoneal debridement, and then, of course-- I wouldn't be standing up here-- endoscopic debridement. And oftentimes, we're using all of these in combination.

So percutaneous drainage and debridement is just what it sounds like. You have a retroperitoneal collection. Interventional radiology can place a drain through the skin directly into that collection. And this gives you the advantage of doing irrigation, drainage, and you can upsize these drains to, actually, quite large, where actual bits of debris can be aspirated out.

There is a downside to this. Whereas many patients-- up to a third of patients-- their infected necrosis can be treated solely with percutaneous drainage, there is a significantly high rate of external fistula related to this.

One step beyond percutaneous drainage is what's known as the "VARD," or "Video-Assisted Retroperitoneal Debridement." So in this procedure, these patients typically will have a percutaneous drain in place. And after that tract has matured over the course of a couple of days or a week, surgeons can use that track as a conduit to place rigid endoscopes and rigid grasping forceps to again, manually debride these collections. They can replace the drain and go back in every few days-- obviously, much less taxing for the patient, but again, still leaves you with the problem of a percutaneous drain and potential for external fistula.

External fistula is not a problem to be undermined because this is a major cause of long-term morbidity for these patients. And they can be very difficult to deal with and oftentimes may require surgical intervention. So how can we minimize or eliminate the risk of external drainage? Well, we can do it all internally. And that's where the concept of direct endoscopic necrosectomy comes in.

So similar to how I showed you we drain pancreatic pseudocysts, we can use the same endoscopic techniques to create a fistulous tract between the stomach and the pancreatic collection. And we can use that tract as a conduit to go in and use endoscopic techniques to directly debride the collection. So remember this picture because I'm going to show you the outcome with this patient.

So the way we do this is with a new stent, which you may see in many of our reports-- something called a "Lumen-Apposing Metal Stent," or abbreviated as "LAMS." And what this is a short dumbbell-shaped covered metal stent that, when placed, it brings the two walls-- the stomach wall and the cavity wall-- together and helps fuse them together and create a fistula.

This is deployed by an EUS-guided needle-like device. And it's actually quite ingenious. It has this little electrocautery-enhanced tip. So basically, this is a hot tip. We can apply energy. It basically goes right through the stomach wall or right through the intestine wall into the cavity. And then it's a one-step deployment directly into the cavity.

So let's see if we get this to work. So this is the patient that I showed you. Here, we're entering the fluid cavity. We're deploying the first internal flange of that lumen-apposing metal stent.

And now we've deployed the internal flange, and you see immediate drainage of debris and fluid. We can dilate this up and then insert our camera directly through this conduit into the cavity, and you see all this solid debris.

And what we'll do is we'll typically bring these patients back every two or three days, and we will use manual necrosectomy techniques. We'll use snares, baskets, basically, anything you can think of to just pick apart this infected necrosis. We'll pull it out into the stomach. Sometimes we'll pull it out and put it in a little basin. And if you're lucky, you can really get big pieces of this debris. And when you're done, you have a nice empty cavity with beautiful, healthy, pink granulation tissue, which will just close down and resolve on its own.

So early studies looking at this technique really, were proof of principle. They showed safety of the technique, they showed feasibility of the technique. But again, there's been this explosion in really high-quality data, and we now have prospective randomized controlled trials looking at the efficacy of these endoscopic interventions.

In the Netherlands, there is this group called the "Dutch Pancreatitis Group." It is a consortium of multiple academic hospitals in the Netherlands. I really don't know what goes on in the Netherlands that there's all this pancreatitis, but they actually have a pancreatitis hotline. So if you're at one of these outlier hospitals and your patient is sick, you call like 1-800-pancreatitis, and you get shifted to one of these academic centers.

And they've really been at the forefront of doing these large prospective studies. And these are the three landmark studies that they've published over the past decade. The first was the PANTER trial, which was a multi-center randomized controlled trial of 88 patients, where they compared using primary open-surgical necrosectomy versus what they called a "minimally invasive step-up approach," meaning you started with a percutaneous drain or endoscopic drainage, and then moved on to the video-assisted retroperitoneal debridement if needed.

The primary endpoint was a composite of major adverse events for death. And what do we see? We see that the step-up approach has significantly lower rates of reaching that composite major endpoint or death, significantly lower rates of multi-organ failure-- no difference in the death rate, but significantly lower rates of these patients developing endocrine or exocrine insufficiency. And interestingly, about a third of patients were successfully treated with percutaneous drainage alone. Now, they didn't really report fistula outcomes, which is sort of a major downside of this study.

They went on and did a second study called the "PENGUIN trial," which was a much smaller study, but they looked at ways of debriding, either surgically or using endoscopic. And again, not surprising-- similar outcomes. The endoscopic approach had very significant decreased rates of having major adverse events or death. None of the patients in the endoscopic group developed multi-organ failure. Small numbers comparing death. But now they reported fistula rates, and you see significantly lower rates of fistulas.

And then the hallmark study was the recently published TENSION trial, where they compared the endoscopic approach versus the surgical step-up approach, keeping open surgical necrosectomy to me as the last resort as opposed to the first resort. So 98 patients, same primary endpoint.

And interestingly, the surgical step-up approach and the endoscopic step-up approach had no significant difference in terms of the major adverse events or death, new-onset multi-organ failure. But there was significantly lower rates of fistula and significantly lower rates of days in the hospital.

So what have we learned from these studies? So these studies have shown that in patients with infected and symptomatic walled-off necrosis, improved outcomes are seen with a minimally invasive approach compared to open surgery. Improved outcomes are seen with endoscopic necrosis over a minimally invasive surgical approach.

Either way you go, a step-up approach is favored, meaning less invasive to more invasive, and that when you compare endoscopic step-up to surgical step-up, they're more or less equivalent, but the endoscopic step-up has significant advantages in terms of fewer external fistulas and lower length of stay.

And here is this at work. So this is a patient, actually, who is in the hospital right now. We have a number of these patients in the hospital right now. This is a patient who is in the hospital with necrotizing pancreatitis. She actually came to us from another institution after about two weeks of gallstone pancreatitis.

Now, her collection was pretty immature. It was only about two weeks. And we said, let's just treat this conservatively. She was febrile.

We said, let's just treat this conservatively. Let's give her antibiotics. She was able to eat. And let's just monitor her.

Well, despite starting broad-spectrum antibiotics, within about 48 hours, her fevers persisted through antibiotics, she came bacteremic, and her white count was going up. So we repeated imaging, and sure enough, she now has a pocket of foci of gas in there, which is diagnostic for infected necrosis.

We were a little hesitant at first. We said, this is only about three weeks old, but compared to the two-week scan, we see that there's a little bit more of an organized wall here. So we offered her endoscopic debridement, or endoscopic drainage as the front-line approach.

So here you see this big bulge into the posterior wall of the stomach. Here is the collection. We're going to access it with our lumen-apposing metal stent. In this case, we placed a large 20-millimeter-diameter lumen-apposing metal stent. And here's what the cavity looked like just full of pus, full of debris.

And this was done on Thursday. By Friday, she looked like a million bucks. And quite frankly, she probably could have gone home over the weekend. We decided to just keep her and monitor her. And we repeated a scan yesterday to assess whether or not she needs any actual debridement, and the collection's almost gone. She just has a small amount left, and we're hopefully going to discharge her in the next day or so.

Not all patients with walled-off necrosis are the same. I've been showing you cases where patients have sort of a centrally located collection. But as we know, some of these collections can extend far down into the retroperitoneum, down into the paracolic gutters. We're just not going to be able to reach these effectively by placing a superior endoscopic drain. So these patients often need a multi-modality approach.

So this was one of our patients who has-- I don't know my my mouse isn't working here. Whoops, sorry.

So these patients have both percutaneous on either side and endoscopic drains in the middle. So they get a multi-modality approach. And similar to VARD, we can actually use those percutaneous drains as a conduit to do what's called "sinus-tract endoscopy."

So here's a typical example-- patient with a very complicated collection extending down to the pelvis. We can get initial access through the stomach or through the small bowel. We can then place a percutaneous drain into their pelvic collection. We can remove that drain, place a wire, dilate up that tract, and place our endoscope through the tract, and again, do direct endoscopic necrosectomy through that sinus tract, and then replace a big drain to allow access going forward.

So this is all very relevant. Actually, in this month's issue, the March issue of*Gastroenterology,* there are two major randomized control trials looking at comparing minimally invasive surgical approaches to endoscopic approaches. The first is a single-center US study of 66 patients, similar primary endpoints. And these are just the best results I think we're going to see.

Endoscopic step-up had significantly lower primary endpoints-- so major adverse events or death during a six-month follow-up. No difference in death rate, but look at that-- zero external fistula. Decrease in major complications and significantly lower costs.

The quality of life at short-term follow-up was significantly higher for the endoscopy group. But again, I can't give you any better data to show that endoscopy should be the primary modality for these patients.

The other study published is actually a follow-up to the initial PANTHER trial, where they compare the open necrosectomy versus the step-up approach. And they looked at the long-term outcome of these patients, and it's actually quite scary when you look at it-- oop-- I'm sorry-- actually quite scary when you look at the data.

The long-term death rate in the open necrosectomy group was 73% compared to 44% in the step-up group. Endoscopic step-up or minimally invasive step-up-- less incisional hernias, much less exocrine insufficiency, much less endocrine insufficiency, and really, no difference in the need for additional drainage or additional surgery when doing either of these treatments-- but again, clear benefits to doing a minimally invasive approach.

So just closing in the last few slides with an algorithm-- so in patients who have acute pancreatitis, we should be suspecting severe or necrotizing pancreatitis if they have clinical deterioration with fever or sepsis; if they have persistent, ongoing organ failure; or if they develop luminal or signs of biliary obstruction. The work-up should proceed with a contrast-enhanced CT or MRCP.

Typically, you're going to need to wait 48 or 72 hours for necrosis or fluid collections to develop, but once you've diagnosed a patient with one of these fluid collections, you have to stratify them into sterile or infected. If it's sterile, we're going to do conservative treatment-- supportive care, no antibiotics, no drainage-- immediately, unless they have a compartment syndrome or other major complications.

If they mature their collection and it's still symptomatic, endoscopic drainage should be first line. If it's an infected collection, again, we're going to do conservative measures. We're going to treat them actively with broad-spectrum antibiotics and best supportive care. And if we can, we're going to try to delay any kind of drainage procedure for three to four weeks.

If they do need a drainage procedure because of ongoing organ failure or failure to control the infection, we're going to approach this with a step-up approach. Here, we typically will do an endoscopic-drainage approach unless we cannot reach the collection, in which case we would do a percutaneous drainage. In some cases in these complicated collections, we need to do both. And if they're not improving after that, then we will go into to do necrosectomy, primarily with direct endoscopic necrosectomy, and then doing that step-up approach as needed.

You should be aware of other sequelae of pancreatic necrosis. I keep harping on pancreatic fistula. These can be both internal or external. And these can be very difficult to manage. Typically, these patients undergo an ERCP and rerouting of their pancreatic secretions with a pancreatic-duct stent.

I mentioned that not an insignificant number of these patients will develop pancreatic dysfunction. You can see from these two meta-analysis, about a quarter of patients will develop excrete insufficiency and need to be on lifelong pancreatic enzyme-replacement therapy. And up to almost half of patients will develop some type of endocrine dysfunction, whether it's pre diabetes or full-blown diabetes. And about 15% from this meta-analysis will need insulin.

We do see splanchnic-vein thrombosis. In fact, the patient that I just showed you the drainage procedure on does have a splenic-vein thrombosis. This is not uncommon. It can occur in up to 20% of patients. But it rarely causes long-term sequelae. These patients rarely develop portal hypertension, or varices, or anything of that nature.

And you really have to weigh the risk of anticoagulation. We know these patients are at increased risk of developing pseudoaneurysms and bleeding. And in my opinion, the risk of anticoagulation far outweighs any benefit they're going to get. You're basically treating a radiological finding. You're not really impacting their outcome by treating a splenci-vein thrombosis, as an example.

Pseudoaneurysms are a major cause of death in these patients, and, I think, an underrecognized and underappreciated development. This is a very toxic inflammatory environment. There's pancreatic enzymes in this fluid, there's ongoing inflammatory mediators, and that's all going to create erosion of any kind of artery coursing through these pancreatic collections.

And they can develop a pseudoaneurysm, which can very easily rupture. And this can be at the splenic artery or the other arteries you see listed there. Once this happens, if it's unrecognized, you basically will die. And you have to catch this early.

And the way these patients typically present is with acute worsening of their abdominal pain, a drop in their hematocrit, and a rapid expansion of their known collection or presence of blood in the collection. These need to be treated as a true emergency. These patients need a stat CT angiogram. And while they're on their way to CT, you need to call IR, because really, the only way to save these people is with an emergent immobilization.

The other complicated long-term sequelae of pancreatic necrosis is this entity called the "disconnected-duct" or "disconnected-tail syndrome." And this is due to a complete disruption of the pancreatic duct, usually in the central part of the pancreas.

This is typically seen with necrotizing pancreatitis, but can be seen in chronic-pancreatitis or in traumatic-pancreatitis cases. And basically, what this refers to is you have this orphaned pancreatic tail, where it's not draining into anything. The duct that it used to drain into is gone, so that functional pancreatic tail just constantly secretes pancreatic fluid. And this results in either recurrent collections. These can result in fistulas, pancreatic ascites, pleural effusions, and recurrent acute pancreatitis.

By and large, when this is discovered, if the patient is a good surgical candidate, they should undergo a surgical procedure. I don't have time to get into some of the other innovative endoscopic measures we can use to control this, but the important point here is to recognize it when your patient may be at risk for it.

So in closing, what is the road ahead for acute pancreatitis here? I foresee a number of improvements we can make in the recognition and management of these patients. I think early recognition is key. And just like we have a STOP-sepsis program, I think we should have a stop-pancreatitis program that maybe gets triggered whenever there's an elevated lipase, or a radiologist types in "pancreatitis" in their read, or if an ICD-10 code is put in the chart. I think that should trigger an automatic GI consult so we can evaluate these patients.

I think we can do better as far as having e-tools in Epic, as far as order sets for IV fluid, recommendations as far as fluid types, fluid rates, and how often and what kinds of labs we should be checking.

We have developed the clinical-care pathway, looking at all phases of pancreatitis, whether it's the early phase-- that first 24 to 48 hours-- or in patients with severe and necrotizing pancreatitis. So efforts are underway as far as implementing these, and that will involve these other two steps that I mentioned previously.

One thing that I didn't mention but I think you have already picked up on is that these are sick patients, and they need a multi-disciplinary approach. We can't do this by ourselves. We need other stakeholders-- surgery, IR. We need critical-care medicine, infectious disease, nutrition, endocrine. It's really a whole host of other stakeholders that are involved in successful management of these patients.

And ideally, I think a lot of centers are starting to develop these dedicated teams for severe necrotizing pancreatitis. The University of Minnesota, where Dr. Marty Freeman is, who is the senior author on many of these studies that I've shown you today-- they actually see so much necrotizing pancreatitis they actually have their own service dedicated to it, and they usually have double-digit number of patients on it. And the interventional endoscopists and the surgeons around together every day on these patients. So that is something to be considered.

And then again, I think just education of all of the stakeholders-- you'll notice that in any of our procedure reports, whenever we have one of these patients that we do a necrosectomy on, the last line and our recommendation is, if patient develops signs or symptoms of bleeding, get a CT angio and call IR and GI immediately.

We need to be aware of, what are the possible adverse events that these patients can develop? It amazes me still that when patients are in the hospital, sometimes an ID wants to stop their meropenem, and then they get a fever two days later, and everyone's like, well, why are they getting a fever? It's because they have a pocket of dead pancreas and pus in their abdomen. That's why. We can't stop antibiotics on these patients. So I think we have to all do a better job of understanding the natural history and outcomes.

So to summarize, acute pancreatitis can be associated with severe morbidity and mortality. Prompt recognition and triage is the key, and I gave you some very easy tools that you can use.

Evidence-based management-- the paradigm has shifted from the old ways. We want to do aggressive hydration and lactated ringers, enteral nutritional support, appropriate use of antibiotics, pancreatic-fluid collections. We need to understand the indications for drainage. Just because you have a collection does not mean it needs to be drained, but we want to know the most appropriate way on how to manage these patients-- and then again, understanding the sequelae of necrosis.

And then I'll leave you with this. Everyone in this room-- we'll waive the registration fee for our third-annual live endoscopy course. This is coming up in one month, where we have about 15 expert talks on various complex GI disorders.

And the most important and most fun part of the day is that we'll actually be doing live endoscopic procedures and transmitting them via satellite feed into the Hess auditorium. So if you're interested, shoot me an email, and we'll waive the registration fee. And we hope to see you there. So thank you very much.