MARTIN FREEMAN: Well, thanks very much for the invitation. And I appreciate the opportunity to speak with all of you, and the support from Boston Scientific to make this possible.

So we're going to talk about necrotizing pancreatitis, focus on latest terminology, management modalities, outcomes and complications. Acute pancreatitis is the most common gastrointestinal cause for inpatient admissions now in the United States, over a quarter of a million admissions, resulting in $2.5 billion annually, just in the US.

You can see that at the University of Minnesota we have a very large experience with acute pancreatitis. This is their quarterly admissions. And compared to all these other major academic transplant centers, we're actually the highest in the country. So we have a service that's dedicated just to taking care of these patients, with four faculty who specialize in pancreas disease.

So some background. It's very important to understand the lingo and terminology of acute pancreatitis, because it has changed. 85% to 90% of pancreatitis is interstitial, and the remaining 10% to 15% is necrotizing. It's very important to differentiate the two.

Organ failure is very rare in interstitial pancreatitis. And it's quite common, about half of patients with necrotizing pancreatitis. Mortality is much higher in necrotizing pancreatitis. Without organ failure, it's very low. With single organ failure, up 3%. But with multi-organ failure, it's up to 50%, traditionally. We're going to show you that that has been modulated quite a bit with current intervention strategies and supportive care.

Probably the single most important thing now to understand severe acute pancreatitis, is to review the classifications of acute pancreatitis from the 2012 revision of the Atlanta criteria. This is-- an international panel of experts worked on this for a number of years. And it's actually very simple. It's not like memorizing porphyrias, or even segments of the liver.

There's four kinds of collections now in acute pancreatitis. And think of it this way. In the first four weeks it's either an acute peripancreatic collection in interstitial pancreatitis, or it's an acute necrotic collection if it's necrotizing. After four weeks-- and this is an arbitrary number-- acute peripancreatic fluid collections evolve into pancreatic pseudocysts, which mind you, are extra-pancreatic. And they're rather rare after severe acute pancreatitis.

In necrotizing pancreatitis, the acute necrotic collections evolve to walled-off necrosis. And so there's really only four collections that you need to know. Terms like phlegmon, infected pseudocyst, hemorrhagic pancreatitis, are all obsolete. And we'll cover that more later.

A pseudocyst, just to differentiate, has a well-defined wall, homogeneous fluid density, no solid component. But most importantly, it's extra-pancreatic So when you see something in the pancreas, part of the pancreas is gone, even if it's liquefied, that's walled-off necrosis, not a pseudocyst.

And they're really very rare. We now have 300 necrotizing pancreatitis patients in our database in the last six years at the university, and a grand total of 25 pseudocysts. So it's more than 10 to one. Granted, we have something of a referral bias. But you will find that the majority of collections after pancreatitis are actually post-necrotic.

Now walled-off necrosis has a well-defined wall, heterogeneous, mixed density, solid component usually. And they can be intra or extra-pancreatic. And we'll cover that here. What happens with pancreatic necrosis, the pancreas itself becomes devitalized. There's a lack of IV contrast enhancement.

But in extra-pancreatic necrosis, such as this patient, who has a perfectly preserved pancreas with perfusion, has massive extra-pancreatic necrosis here, involving mesenteric fat. And notice this is an obese patient. That's quite typical.

So the term walled-off pancreatic necrosis is also obsolete, because walled-off necrosis can equally involve pancreatic tissues, extra-pancreatic tissues, or both. Extra-pancreatic necrosis typically dissects down the left retroperitoneal space into the left pelvis. Or it can extend anteriorly into the peritoneal cavity. It's very important to keep those in mind.

I just want to also show that there's been some very important consensus meetings recently. I had the privilege of leading a group of international experts, mostly surgeons, radiologists, and GI specialists. And this was the first consensus that really emphasized the role of minimally invasive management.

I think the single best paper for you all to refer to, that really covers diagnosis, management, interventions for pancreatitis, is this IAP/APA evidence based guidelines. It was published in 2013 in *Pancreatology,* and it's absolutely spot-on and it's evidence based.

Indications for intervention. When do you need to intervene? And this is true whether it's percutaneous, surgical, or endoscopic. They're all the same. And this is per two international consensuses. Suspected or documented infected necrosis with deterioration-- and that's important, because just because somebody has infected necrosis, if they're rock stable and it's premature to intervene because of the evolution of the collection-- they don't need urgent intervention. But they do probably eventually need it.

Ongoing organ failure several weeks after the onset of acute pancreatitis, that's a more controversial but important indication. And then in sterile necrosis, once it's walled-off, typically, four to eight weeks. But it can be sooner if they have gastric outlet, intestinal or biliary obstruction, if they have persistent symptoms. And this is quite common. They just don't feel well, they can't eat, they have pain or disconnected pancreatic duct.

Now what's key in all of this is that multidisciplinary management is critical. You cannot do this with just primary care and GI. You need to have sophisticated surgery, diagnostic interventional radiology, and critical care. If you try to do it solo, it's a little like this guy probably taking on a bit too much by himself. It takes more than one or two.

Timing of intervention should be delayed, wherever possible, until at least after four weeks. But if a patient is deteriorating and infected, you have to pull the trigger sooner. And it's not a good idea to allow somebody to deteriorate too far. We do know that early interventions are associated with poor outcomes.

Now traditionally, surgery, was the management. By any route, percutaneous catheter drainage and endoscopic are your other options. They've evolved a lot in the last 10 years at a dramatic pace.

The gold standard was open necrosectomy, but had very high complication rate. Mortality with fistula, diabetes, pancreatic insufficiency, and hernias. And you can see here a very large incision necrosectomy. One of the problems being this patient has been on a trach for a month with multiple debridements, has an open abdomen. We'll never put that abdomen back to the normal state.

So the ways of doing this minimally invasively, which we'll just touch on as the details will be the subject of a later webcast. But the brilliant taxonomy by the New Zealand surgery group, Doctor Windsor, peroral, it's either transluminal, transpapillary in the duct. And these are endoscopic routes, whether it's surgical, percutaneous, laparoscopic.

There's three routes for intervention-- transperitoneally through the stomach, transperitoneally missing the GI tract, and then most importantly, retroperitoneally. And we always strive for a retroperitoneal approach with catheter-based drainage, because the pancreas is a retroperitoneal organ. And the spread of the necrosis is usually retroperitoneal.

And if you go transperitoneal, you're risking dissemination of infection throughout the abdomen, which is peritonitis. It's sometimes necessary, but we try to avoid it. Percutaneous catheter drainage is widely established. Retroperitoneal route here, draining large amounts of infected necrosis. Systematic review shows it's quite effective.

But these are selected cases. An ideal patient for a retroperitoneal percutaneous catheter draining is acutely ill, three week into the course, dying of sepsis, on five pressors, poorly demarcated, no good window for endoscopic management, perfect for retroperitoneal. And in this case, intraperitoneal catheter drainage, which you can see here and here.

The problem with catheter drainage is external fistulas. Here, for whatever reason, somebody did a anterior transperitoneal drainage of walled-off necrosis that could have been treated through the stomach, led to six months of external fistula. You also can't debride large amounts of solid necrosis through percutaneous catheters such as this.

Video assisted retroperitoneal debridement was developed by Doctor Horvath and colleagues in Seattle, at the University of Washington, and is now widely used by some surgical center, a small incision through the retroperitoneal [INAUDIBLE] tract and debridement. And this classic paper in the *New England Journal* by the Dutch pancreatitis study group showed that a step-up approach, using percutaneous catheter drainage and video assisted retroperitoneal debridement as needed, was superior to open necrosectomy with morbidity, and short and long term morbidity, and a trend in other later studies and a definite improvement in mortality. That's just coming out now.

And I'll finally wrap up on endoscopic interventions, because that's really what we're all about. Here, this is a comprehensive systematic review we published in *The American Journal of Gastroenterology, 2014.* It goes through all of the aspects of endoscopic and multidisciplinary drainage.

Remember that there's transluminal drainage, which should be EUS guided. And then there's transluminal necrosectomy, where you actually put the scope through the fistula into the retroperitoneum and debride the necrosis directly. And this is sort of a summary of EUS guided puncture, dilation, and placement of stents and subsequent necrosectomy.

There is one randomized trial of endoscopic transgastric versus surgical necrosectomy in infected necrotizing pancreatitis, a very small study, again, by the Dutch pancreatitis study group. But it does show that significantly better outcomes with endoscopic versus surgical necrosectomy, a trend towards mortality difference.

What's interesting is they've now done in the press, a huge multi-national study, comparing open, minimally invasive, and endoscopic necrosectomy. And it looks like the mortality difference in endoscopic is dramatically better than open surgery. And it's also better for minimally invasive surgery than open surgery, but not by nearly as much.

So I just want to show you what a necrosectomy looks like. This is the video here. I don't know if it projects well. I'll try to use my shadow here. This is going through a AXIOS stent that has been placed at a previous session a few days earlier to drain infected necrosis, and using a variety of devices, snares, baskets. We used suction cap.

And a lot of time. This is under general anesthesia. This is about a two-hour procedure, using great care to not snare off the portal vein, the splenic artery, other vital structures back there. So multiple gateway, involved a very large infected collection like this walled-off necrosis.

A single cystogastrostomy won't do it. This is a cystduodenostomy and a cystgastrostomy. You can also use that retroperitoneal-- but again, not transperitoneal-- but retroperitoneal percutaneous catheter approach to do sinus tract endoscopy, and get at places in the abdomen you just can't reach through the mouth, such as this patient with pancreatic and huge extra-pancreatic necrosis going retroperitoneally down into the pelvis. The only way to get from there to there is multimodal.

And I'll just show you this quickly and end. This is a very ill patient, three weeks into necrotizing pancreatitis, with fever, sepsis, organ failure. Very poor candidate for surgery. And in this you can see how extensive the pancreatic and extra-pancreatic necrosis is. This is all infected.

Again, the cystduodenostomy, cystgastrostomy. Draining pus, but that will not be adequate. And nasojejunal tube, and then simultaneously left and right retroperitoneal percutaneous catheter placement. So that we have retroperitoneal, retroperitoneal, internal, internal, and a nasojejunal tube. And then followed by, not only peroral necrosectomy, but very limited what you can do through the mouth here. And this is some of the necrosis.

But then sinus tract endoscopy, where we take out the percutaneous drain in the operating room, put a scope through the back-- this patient is prone-- through the percutaneous tract. And you can explore the deep pelvis, go back to the cystgastrostomy. You can go through left and right. And the idea is to clean out the cavity. And that's the only way you are going to get to a good result. There is a chance of fistulas.

And then just to end on complications. This is really subject for another talk. But this is an example of massive bleeding from cystgastrostomy that failed clipping. Patient developed pseudoaneurysmal bleeding, and these sometimes dramatic, needs coil embolization. And you can have perforation during necrosectomy, especially with intraperitoneal dissemination of the necrosis, or root of the mesentery.

Air embolism is dreaded, should be able to be avoided. You must use carbon dioxide. And then, no matter what you do, these approaches fail sometimes. And this is a patient who had unbelievably aggressive-- three, six percutaneous drains, two cystgastrostomies, sinus tract endoscopy. Developed a colonic fistula and multi-organ failure, had to go to surgery and have all these resections and washouts.

And then there's many short and long term issues we won't touch on. GJ tubes are often necessary if an NJ can't be tolerated long term. And these are all subjects for later discussions, disconnected pancreatic duct.

And what I want to end on is an algorithm that we published in the *American Journal of Gastroenterology.* If intervention is indicated, try to wait four weeks. But if you can't, don't, if they're infected and deteriorating. Encapsulated, we do primarily endoscopic. If it's encapsulated and near the stomach, endoscopic. If it's distant from the stomach or it's non-encapsulated, you can't do endoscopy. You need percutaneous catheter management.

We only do surgery for failures. Using this approach in 221 interventions, you can see that only about 2/3 could be treated purely endoscopically. The rest needed some other modality. 17% didn't need any intervention. But the rest needed other modalities. We operated on 6%, and mortality in only 3%, which is pretty good. Most of these were infected necrosis.

Many other issues to cover. I just want to say this is our team that meets, believe it or not, weekly for an hour, just to go over necrosis cases in the hospital, and complex patients out of the hospital with follow up issues, general critical care surgery, interventional endoscopy, and interventional radiology. And this is our wonderful OR team, that make these endoscopic interventions possible in our clinics, and coordinating staffs.

So I want to thank you very much for your time. I'll stop there, only 12 minutes over. OK. Questions? Comments?

SPEAKER 1: So, Dr. Freeman, we have a few questions. So the first one is how do you determine infected versus uninfected patients?

MARTIN FREEMAN: Very good. That's an excellent question. The classic way of doing that was to do fine needle aspiration under CT guidance. That was described about 25 years ago. And it seemed like a reasonable idea, but it's basically completely obsolete now.

And if you read the IAP/APA guidelines and look at the evidence, here's why. If it's positive for bacteria and the patient isn't ready for intervention, it won't matter. You treat them with antibiotics. And there are false positives, too. If it's negative for bacteria, it can be a false negative. And especially if the patient's already been on multiple antibiotics.

Most of all though, the decision for intervention now for walled-off necrosis is made clinically. So suspicion of infection is, first of all, gas bubbles in the collection. Almost all the ones I showed you had obvious gas in the collection. That is by definition infected.

If they don't have gas bubbles in them, then it's spiking fevers, clinical deterioration, and a suitable collection. And rather than ponder whether it's infected or not, that patient needs intervention. So you intervene, usually endoscopically, percutaneously. Culture the material while you're doing that, and not so much as a diagnostic, but as a help guide antimicrobial therapy. But the real intervention is going in there and draining it and debriding it.

So to summarize, a clinical diagnosis and what drives intervention is not the result of a fine needle aspiration culture. So we had-- in the last 300 patients we have not done one single fine needle aspiration to determine presence or absence of infection.

SPEAKER 1: Are there any patients where a collection may mask, or a collection is masking as a walled-off?

MARTIN FREEMAN: Sure. That's always an issue is it really a neoplasm? Now honestly, the appearance of these is so different than neoplasm. I mean, for example, mucinous cystic neoplasm, typically in a patient without pancreatic disease who has a nice round collection, a nice round, not collection, but a nice round encapsulated lesion in the tail of the pancreas.

So it's pretty rare. I mean these collections result from severe pancreatitis. And that's usually obvious by clinical course, very rare for a patient to walk in with vague discomfort, no history of pancreatitis, and then have something that looks like infected necrosis.

SPEAKER 1: How about the patient after endoscopic intervention?

MARTIN FREEMAN: Most of these patients are quite ill. I'll be honest. Most of the conversations are with the family. And we have coined the term "Post-Pancreatitis Stress Disorder," or PPSD, for the syndrome the patients go through and the families.

And we typically have five to 10 patients in-house at any one time with necrotizing pancreatitis. And one of our main issues is to go by, reassure the patients and the family that this is an incredibly drawn out course. It's normal to be discouraged, because there's two steps forward, and one step back, or sometimes one step forward, two steps back.

And it's have faith that in six to 12 months, they may well be back to a more normal life. And they're very likely to survive. But that's one of the big challenges. Usually patients feel better right away after the drainage, and then the initial drainage. But they have no idea what an ordeal they're in for, which can be three, four, five, six interventions.

They get portal vein thrombosis. They get-- there's so many issues, nutritional issues. And it takes-- this is part of the support that you need to undertake treating this disease. It's why you need a multidisciplinary team, and really a dedicated service, because it's not just like even repetitive removal of bile duct stones, for example.