[MUSIC PLAYING]

GEORGIOS PAPACHRISTOU: Today, we're going to be talking about acute and chronic pancreatitis. Probably we'll be able to finish with acute and maybe catch up on chronic. But you will have the slides. You can review them. And you can always ask me questions.

So the rate of acute pancreatitis hospitalizations has been increasing in the United States. And as you can see, through the years, it's rating almost 1 per 1,000 US population. So it's getting more and more common. It's the first cause, or one of the first causes, of GI-related hospital admissions in the US, more than 270,000 hospital admissions per year. The average hospital stay is relatively short. It's around four to five days. But despite that, the direct health care costs exceed $2 billion annually.

So as you can see, the burden of the disease is pretty significant. The cost of an average hospitalization exceeds $10,000. And as you know, the majority of these patients have a mild hospital course, and they're doing very well. That's why they can go home by day four or five. However, 10% to 20% of acute pancreatitis patients develop a severe course that has been traditionally reported having a mortality up to 30%.

We're going to start with a case. We have a 58-year-old gentleman that comes to the emergency room with acute onset of upper abdominal pain radiating to his back. He reports the pain as a band-like pain and is associated with nausea and vomiting. He has past medical history significant for hypertension, obstructive sleep apnea, and nephrolithiasis. And he was on an ACE inhibitor. But he has been on this medication for a long time.

He used to-- actually, he is an active smoker for 25 years. But he has a remote history of just social alcohol use and no drug use. So we go to examine the patient and we see that his vitals are abnormal. He's febrile, with a temperature of 38.5 degrees Celsius. He is tachychardic. He has a heart rate of 117. He's tachypneic. His respiratory rate is 24. And hypertensive his systolic blood pressure was 84.

On top of that, he is an obese patient with a BMI that exceeds 40. He is in moderate distress. His sclera is not [INAUDIBLE]. His lungs are clear. His abdomen is soft but tender to palpation, especially in the upper area. There is no guarding. And neurologically, he is still alert and oriented times 3.

Some initial blood work in the emergency room is significant for leukocytosis. You see the white count is more than 20,000 and hemoconcentration. He has a hematocrit of 52, with a hemoglobin of 17. Furthermore, his BUN and creatinine are elevated. His creatinine is 2.1. His BUN is 40.

The rest of his labs are significant for a lipase, which is significantly elevated at 27,000. His ALT and AST are also elevated. ALT is 800. That means that it's 20 times the upper limit of normal. Without-- with the alkaline phosphatase has been just slightly elevated. His triglycerides are normal or slightly elevated. The [INAUDIBLE] is around 150, very slightly, very mildly elevated at 153.

His chest X-ray is clear. As usual, there is a CT done at the emergency room. This time it's with no contrast because his creatinine is 2.1. And there is infiltration of pancreatic and peripancreatic fat planes. And the diagnosis from the emergency room is acute pancreatitis. So how do we diagnose acute pancreatitis? That's the first step. Correct?

Now we're going to go through some questions. And I want you to volunteer an answer. Is it an elevation of serum amylase and/or lipase? Is it elevation of amylase and/or lipase at least three times the upper limit of normal? Can we diagnose acute pancreatitis like that?

Do you need the elevation at least three times and characteristic abdominal pain? Do you need the elevation of amylase and/or lipase at least three times and evidence of pancreatitis on the CT scan? Is it both C and D?

AUDIENCE: Yes, C and D.

GEORGIOS PAPACHRISTOU: C and D. So what we really need to remember is that to diagnose acute pancreatitis, the clinical features in the case that I presented was the typical case of upper abdominal pain, which is usually band-like and radiates to the back. It's usually associated with nausea and vomiting. And it's pretty severe pain.

Now sometimes, I want you to remember, we have these patients with biliary pancreatitis that come in and they tell you, I have pain on my right upper quadrant on and off for two weeks after I eat. But yesterday, I developed severe pain. What happens in these patients? When is the onset of acute pancreatitis?

So usually, these patients have a biliary colic going on. They have a stone in the gall-- in the CBD, giving them symptoms for two weeks. And then eventually, the stone comes all the way down, impacts the papilla. And the pancreatitis the day before, it's the severe pain, OK?

Now we need two out of the three criteria that we use. You don't have to have all three of them. So if your amylase and lipase is more than three times the upper limit of normal and you have the typical upper abdominal pain, you don't need a CT to diagnose acute pancreatitis, correct?

But the third criteria, indeed, is this. It is evidence of pancreatitis on CT. And in this CT, you can see that the pancreas is enhancing. It's this brighter, long organ. But clearly, surrounding the pancreas in the peripancreatic area, there is a lot of stranding, which is consistent with acute pancreatitis.

Moving along, after the definition of the disease in respect to etiology-- this is a long list, but common causes include mechanical causes, such as gallstones. The way that we talked about it, a small stone is leaving the gall bladder, comes all the way to the distal CBD and is getting impacted to the papilla, where also the pancreatitis duct drains.

Cancer is actually a common cause of acute pancreatitis in patients that are more than 50 years old. So always remember that. Alcohol is the second big one. Then we have metabolic etiologies. That says hypertriglyceridemia. And usually, we have to have a triglyceride level which is at least 500, and in most of the cases, more than 1,000 to be considered as a cause of the disease.

Hypercalcemia, medications can give you pancreatitis. So it's always good to review the medication list. But we have to have a temporal association. If you're on an ace inhibitor for 15 years and you get pancreatitis, it's probably not the ACE inhibitor. It's a medication that has been started within the last couple of months.

The typical medications that we use in GI that you have to remember six [INAUDIBLE] [INAUDIBLE]. These are medications that can give you pancreatitis.

Infections are much more common in children, in pediatric gastroenterology. We don't see it that much in adults, with the most common virus being Coxsackie virus.

Finally, ischemia can give you pancreatitis, Patients that have complicated hospital course with hypotension, with an intra-abdominal operation, so on, so forth. You have to remember that.

And trauma, blunt trauma in the upper-- in the abdomen, either from a steering wheel or from bicycle falls. These are common also causes of acute pancreatitis.

But the two big ones that probably contribute for 70% of all cases are gallstones and alcohol. In this figure, you can see the gallbladder in the ultrasound. And the gallbladder is usually black, what we call anechoic, because it's filled with fluid. But here you can clearly see a layering of hyper echoic material that represents sludge.

And in this endoscopic ultrasound, you can actually see the bile duct. Again, you'll expect the bile duct to be black. But you can see clearly that there is a hyperechoic stone within it. And again, the incidence of gallstone pancreatitis is the highest among Caucasian women. Women tend to have gallstones more frequently than men over the age of 60.

And it's the small gallstones that migrate down. If you have a gallstone which is 3 or 4 centimeters, it's pretty hard to leave the gallbladder through the cystic duct.

Now we're going to move back to our patient. So as we talked about, this patient has all three out of three criteria for the diagnosis of actue pancreatitis. He was in moderate distress, correct? Remember, febrile, tachycardic, hypotensive, with hemoconcentration, with elevated creatinine. And then the ALT was high. The LDH was high.

Where should this patient go? Should we send the patient home without patient follow-up in the pancreas clinic with Dr. [INAUDIBLE] B, infuse one liter of normal saline and reassess and see how he does, if his blood pressure is improving. C, admit to the regular floor. D, admit to a higher level of care, such as ICU. None of the above. Would you send this patient home?

AUDIENCE: ICU.

GEORGIOS PAPACHRISTOU: ICU. Granted, option B, especially with the lactate. Then again, this is also something that you should adivce the emergency room physician to do, give one liter of bolus of IV fluids at the initial time of evaluation.

Now remember, we talked that 80% of pancreatitis is mild. However, we have 10% to 20% cases that are severe. But how do we define severity? What does severe acute pancreatitis mean? Mean This is very important so we can communicate between us, but also for research purposes.

Early in the course of acute pancreatitis, the first two weeks, all morbidity and mortality is driven by the systemic inflammatory response, correct? Which may result in a remote organ failure. And usually the organs that we assess are respiratory, cardiovascular, and renal. So these are the cases that even though the injury and the inflammation is local, for whatever reason, it leaves the pancreas and involves the whole body and becomes systemic. And that's when you run in trouble with both organ dysfunction, and in many cases, organ failure.

Delayed morbidity and mortality in acute pancreatitis, meaning after the first two weeks, usually occcurs in patients that have developed pancreatic necrosis which gets infected. And they develop sepsis, and they can develop septic shock as well.

So in this figure, you can see that one third of deaths, it's very early. It's within 72 hours of the disease. And they are all driven by the systemic inflammatory response that can lead to organ failure. And then, at some point, we'll be able to diagnose necrosis. We want the CT scan to be done after the first 72 hours. If you do a CT scan very early, you might miss the necrosis on imagin.

Initially, the necrosis is sterile. But especially in patients that have large necrosis, meaning necrosis that involves more than 50% of the pancreas. There is a risk of developing infection within the necrosis. And that's what drives all the severity after the first two weeks.

We know that persistent organ failure is extremely important. In a very nice study that was done a few years ago, the impact of transient organ failure, meaning organ failure that lasts for less than 48 hours, versus persistent organ failure on death. And that was a prospective study in 290 patients. It was pretty impressive.

You can see that patients with transient organ failure just above the red bar, out of 60, only 1 died. Whereas, you can see in patients with persistent organ failure, more than half of them-- actually, not more than half, but around 40% of them died. So it's mainly the persistent organ failure that drives the disease mortality.

For that reason, in late 2013, a panel of experts throughout the world came up with what we call the revised Atlanta Classification. And it's called the Revised, because there was an original Atlanta Classification back in 1992. So you don't have to worry about the 1992 Classification. Now, you have to know, though, the new one that divides disease in three different categories, as far as severity.

We have-- whoa, OK-- we have severe acute pancreatitis. These are the patients that develop persistent organ failure, organ failure that lasts more than 48 hours. And the three organs that we're interested in is renal, cardiovascular, and [INAUDIBLE]. The organ failure can be single, involving one of the three organs. Or it can be multiple, involving two or more organs. As you can assume those with multiple organ failures do worse than those with a single organ failure.

The second group is a little bit-- a heterogeneous group. But mainly, what I want you to remember is the first two lines. This involves a patient. First of all, it's called moderately severe. So we have severe, moderately severe, and mild. The moderately severe group involves all those patients that develop organ failure. However, it resolves within 48 hours. So it's what we call transient.

And those patients that develop local complications, and mainly, we're referring to those patients with pancreatic necrosis without organ failure or without persistent organ failure. So this is the group. I want you to remember that most patients with persistent organ failure will develop also necrosis, correct?

And finally, around 70% of patients will develop mild acute pancreatitis. And this is the uncomplicated group. They have no organ failure. They have no local complications. So three grades of severity.

And remember now, ti assess severity, you will need some sort of imaging down the road. So the first few days, you might not be able to say if it's moderately severe or mild until you have your follow CT scan to see if there's any necrosis or not. So it's a dynamic process. We'll not give a label on day one and this is it. The disease might even evolve into different levels of severity.

Now of course, we want to know who are those patients that will get severe disease down the road. So we want to have a good tool to predict severe acute pancreatitis. Do we have this tool? how can we predict severe?

First of all, we have risk factors. What are risk factors? Ris factors are factors that are present before the acute pancreatitis attack. You have them. You are obese, correct? You drink a lot of alcohol. These are risk factors.

Then once you get the acute pancreatitis attack, we have early markers. These markets can be simple laboratory values, such as BUN or hematocrit. Or we have clinical scores, with the original one being the Ranson's Criteria back in 1974.

So this is a little bit of a tricky question. I don't know why I made this question like that. But in fact, I am asking which one is not a risk factor. Remember risk factor, correct? A hematocrit of more than 44, cigarette smoking, creatinine of more than 1.8, two or more alcoholic drinks a day, and a BMI more than 30.

So this question should have been, which of the following is not a risk factor or market for severe disease, I think. So hemoconcentration is a marker. Cigarette smoking? It's not a risk factor. Creatinine of more than 1.8, it is a marker for severe disease. Drinking more than two alcoholic drinks a day, it is a risk factor. And being obese, it is a factor. So I think the correct answer is B.

Yeah, OK, thank God.

[LAUGHTER]

So it's markers and the risk factors. So in your mind, you have to try to clarify those. But they are both important, correct? So obesity does result in more severe disease. In a study that we did back when I was a fellow, we found out that those patients that have a BMI of more than 30, meaning they are obese, they have more than double the risk of developing organ failure. And in our population here at UPMC, it was 31% versus 14%. They have more than double the risk of developing necrosis, with 17%. And they have 10 times the risk of dying, with 14%.

And why is that? Because having a lot of visceral fat and adipose tissue, indeed, it does release a lot of inflammatory cytokines that we call adipokines, cytokines that they are produced within the fat. And these are TNF-alpha, monocyte chemoattractant protein 1, resistant with [INAUDIBLE] and adiponectin. So this is an important information to know. Is [INAUDIBLE] here? No. We have an expert, actually, in adipokines in your group.

Second risk is alcohol. In a study that we did a long time ago, again, we found out, in a small prospective cohort that we confirmed within a retrospective cohort, that regardless of your ideology. If you drink more than two or more than two alcoholic drinks a day, you develop more pancreatitis, more pancreatic necrosis. So you get biliary pancreatitis while you're drinking, You have a higher chance of developing necrosis.

And this was confirmed in animal models where alcohol shifts [INAUDIBLE] in our cell death from apoptosis to necrosis. And on top of that, it worsens local inflammation. So obesity, chronic alcohol consumption are risk factors. And these are environmentalist factors. These are the risk factors that we can intervene and correct.

On top of environmental risk factors, there are also genetic risk factors. In a very early pilot study that we did, we found out that a hormone, polymorphism, in the promoter region of a cytokine that is called MCP1, which stands for Monocyte Chemotactic Protein 1, the presence of the [INAUDIBLE] results in a significantly higher risk for developing severe disease. So subjects that have acute pancreatitis and the [INAUDIBLE] was present had an odds ratio of seven, so seven times more chance of developing severe disease, pretty impressive.

I'm sure there are many more other genes, especially genes that are involved in the inflammatory cascade, that we'll need to, further down the road, assess. And I'm sure that genetic predisposition will be a very important component in acute pancreatitis severity as well.

So moving from markers, either environmental or genetic-- I'm sorry, moving from risk factors, either environmental or genetics, to markers, the most common clinical score. And the original one is the Ranson's Criteria. The Ranson's Criteria has, overall, 11 points. The more important ones, and the ones that I use usually are the five ones on admission.

And as you can see, it's a combination of risk, such as older age and markers, such as a white count of more than 16,000, a high glucose of more than 200, an LDH, which we do not actually measure that much anymore, of over 350, and an ALT of over 250. And if you think of our patient, our patient on presentation had four out of five risk factors. And we know that if you have more than two risk factors on the Ranson's, you are at risk for severe disease.

So out front for this guy, we knew that the way that he presented, with being so tachycardic, hypotensive, he definitely moves towards organ failure, correct?

And then Ranson also used another set of criteria that we are assessing them at 48 hours. And this is a rising BUN, that we know very well that it's a risk. Actually, it's a marker for organ failure, a decrease of hematocrit of over 10%, and low serum calcium. Now remember, hypercalcemia is an etiology of acute pancreatitis. Hypocalcemia, within the disease, is a poor prognostic marker.

A pO2 less than 60, of course, then you're going a high base deficit. And when you have fluid sequestration, more than six liters, these are the second set of criteria assessed at the 48 hours that I do feel that most of us these days do not actually assess. And as you can see, in a nice study that was done, the more number of criteria that you have positive in the Ranson's, the higher your chance of not doing well. And as you can see, if you reach seven or eight criteria, your chance of going to the ICU is 100%. And your chance of dying is 100%. So if your calcium is 3, your p02 is 10, yeah, you're going to die, correct?

Now which one is a simple clinical score that it's easy to calculate and it's as accurate as the other ones and we should be using when we assess a patient like that? It's the SIRs. Remember, Systemic Inflammatory Response. But there is also a score that is called SIRS, standing for Systemic Inflammatory Response Syndrome.

And this score has four points. And it's very easy. Heart rate more than 90. In our case, the patient had a heart rate of 120. Core temperature of less than 36 or more than 38 degrees of Celsius, a very high or actually a high or a low white blood count of less than 4,000 or more than 12,000. And a respiration rate of more than 20 or a pCO2 of less than 32 millimeters of mercury.

So four very simple points. Three of them involve vitals. And the fourth one involves a CBC that almost any emergency room in the country or all over the world will be doing, correct? So it's very easy to calculate. If you have two or more criteria, then you are considered SIRS positive.

Moving from clinical scores to simple markers, a nice study that we did a few years ago showed that if your admission hematocrit and rising BUN is actually very good markers also of predicting severe disease. Yes, this is the one that I want to show you. It was a multi-center study. So it had a large number of patients, almost 1,000.

What we found out is that if your admission tomorrow it is less than 44. And then, within the first 24 hours, your BUN does not go up, then your risk of organ failure is 8%. It's relatively low. In contrast, if you have the high hematocrit. We give you fluid and despite the resuscitation, your BUN goes up in the first 24 hours, then your risk of organ failure is more than 50%.

So as you can see, with those two simple markers, following them on admission at 24 hours, you can get a good idea who's going to do well or not. So if you have a patient that you are aggressively resuscitating, and the BUN continues to go up, this is something that you guys should consider as a significant risk for this patient not doing well.

In a study that we did a few years ago, we tried to assess all the clinical scoring systems. And there is a long list of them. And the interesting thing is that many of them were developed in the last few years. And all of them, using a similar approach. There is a large retrospective cohort that they investigate or assess. They pick up those values that they come up as significant in univariate analysis. Then they are mixing them a little bit. And they come up with a score.

So all of these scores, more or less, have the same type of approach. So clearly, do we need any new scores? No, we have enough scores, correct. So if you come, and we do research together. And you tell me, you know what, how about creating a new score for predicting severe disease [INAUDIBLE] and we're going to call it the Pittsburgh score? No, that's not an option.

At least with this approach, this approach probably has reached a limit. And the question that I have of you is, which of the following scoring systems is proven to be the best predictor of severity? Either the Ranson's, Glasgow, Apache 2, [INAUDIBLE], [INAUDIBLE]-- you probably don't know them either-- or none of the above? So which one is the best predictor?

So we know very well that all of them have a moderate accuracy of around 80%. And we've proven that in a head-to-head comparison that we did a few years ago. In our cohort, Glasgow appeared to perform a little bit better. But frankly, overall, I want you to remember that that's where we are, correct? We are between high 60s and low 80s, as far as the scores.

And we have reached our limit with cutoffs, if your white count is more than 12 or less than 12, hematocrit more than 44, less than 44. We had an explosion in reporting of new scoring systems in the last 10 years that used more or less similar parameters as we talked about. By using cutoff and converging continuous variables like white count or hematocrit into binary values, we fail to capture synergistic or multiplicative effects, correct?

Simple laboratory tests appeared to perform as well as scores, so with BUN and hermatocrit. So we don't need no more clinical scores. What we need to do if we want to improve our predictive is probably to move in two different directions using measures that directly reflect outcome determining pathophysiology. And that could be genetic polymorphisms, cytokines, and new methods of analysis. Rather than using cutoff, probably, we'll have to move to artificial neural networks, computational learning theory. So that will be the future. Are we there yet? No, unfortunately.

So the holy grail of a very accurate and cheap clinical to predict severe diseases is still there. We do have a grant in our group from the VA that we are actually trying to validate. Our pilot resides at a panel of five cytokines. That each of them is linked to a different pathologic pathway might be a much more robust way to actually predict severe disease.

And the cytokines that are involved are tumor necrosis factor receptor 1, interleukin 8, [INAUDIBLE] growth factor, angiopoietin 2 and the resisting. And as you can see, all those cytokines are actually reflective of different pathways or cascades that likely are involved in the syndrome of acute pancreatitis.

So we have resistin,g which is one of the most prominent adipokines, cytokines that are produced by adipose tissue. We have angiopoietin 2 that appears to be a very good marker of the vascular leak syndrome. That seems to be a very important process in acute pancreatitis.

We do have interleukin 8 that actually outperformed interleukin 6, although they have very similar performance. So we hope that by validating our results, and we're going to be doing that m that we'll be able to come up with a more sophisticated way of predicting severity. We want a good-- we need a good predictor, why? Because if we have a good predictor, and we can accurately predict who's going to get severe disease early, then we can use selective agents.

If you have a selective biological agent, if you wish, or anti-inflammatory agent, and you give it to everyone, in a disease that 80% is mild, you dilute the fact of the treatment so much that it's very hard to reach statistically significant results. You really need to carry it down to a selective group, with high accuracy, though, of severe disease to try your treatment.

And this is a part of the proof study, correct? So for future reference, for the younger ones, whenever you are in the PB service and you have a patient with acute pancreatitis, you give my research team a call. And currently, [INAUDIBLE] is running the show. And this is his phone number. I don't know if some of you have met [INAUDIBLE] But it's really important for us to enroll these patients early in the disease course, because we want the early blood sample to assess the markers, OK? So always remember that.

Now moving around to local complications, we have acute fluid collections. They are common. They are cured early in the course of the disease. So many times, when you do a CT scan within the first days, you will see that there are some immature collections of fluid surround the pancreas.

They lack a defined wall. That's why we call them immature. And most of them regress. And you should just observe it. If you see some fluid surrounding the pancreas in the very early course, you don't need to do anything. You don't need to drain it. You don't need to sample it. Most of them would regress by themselves now. And 50%, actually, will go away within six weeks.

A small portion of them will progress in what we call mature fluid collections. And they're called mature because they become round. And they have a capsule. And those mature fluis collections, if they're just fluid, we call them pseudocysts. So pseudocysts are actually more common in patients with chronic pancreatitis, where there is a stricture. There is a pancreatic duct branch leak. And they're forming these fluid-filled collections.

In acute pancreatitis, most of the fluid collections also contain necrotic debris. So we tend to call them walled-off necrosis, rather than pseudocyst. So it's very important to be familiar with the terminology. When we call it a pseudocyst, we assume that there is no necrotic debris in it, because that's important. A pseudocyst, you can drain it. A walled-off necrosis, you need to debride it, correct?

So a pseudocyst is a collection of clear pancreatic juice, enclosed by a wall of fibrous or granulation tissue. And in acute pancreatitis, this process, for the collection to mature, requires at least four weeks. And then we have pancreatic necrosis, in contrast to pseudocysts, an organized pancreatitis necrosis, or what we call a walled-off necrosis, contains a significant amount of solid necrotic debris.

Then other types of local complications that we can see in acute pancreatitis is thrombosis of all the vessels that are going through or surrounding the pancreas. And then finally, we have also a more rare, but also important complications to remember, pseudoaneurysm, that are usually involving the splenic artery or the hepatic artery.

Now moving back to pancreatic necrosis, not all patients with pancreatitis develop necrosis, actually, a small portion of them. I would say it's probably 5% to 10%. In our hospital, because we're a referral center and we get a lot of transfers, this number is much higher. This number in our population of transferred patients is reaching up to 20%.

As we mentioned, the infectious complications predominate the second phase of necrosis. And I want you to remember that only around 20% to 30% with pancreatic necrosis will develop infected necrosis. And usually, these are large portions of the pancreas being necrosed, usually patients with more than 50%.

Septic complications from infected pancreatitis necrosis account of most delayed deaths in acute pancreatitis. We're going to go through some CT scans because that's, remember, the pancreas are a retroperitoneal organ. The physical exam can help you, but up to a point. Yes, if you have a 20 centimeter necroma, you're going to feel it. But many times, the physical examination of the pancreas is limited.

That's how the pancreas looks when it's not inflamed and normal. It's a long organ that starts on the right side of the abdomen, behind the stomach. This is the head of the pancreas. And then it moves towards the left side-- this is the body-- and ends up with a tail that goes all the way to the splenic hilum, OK? So it's a long organ crossing from the right, just right to the spine where the head is, all the way to the left, to the spleen, where the tail is.

And as you can see, when we use contrast-- and you know that we have contrast because the aorta here is bright-- the pancreas picks up the contrast, the pancreatitic [INAUDIBLE] and becomes bright as well, correct? Now look at the contrast of this picture of a pancrease that enhances normally throughout its course to this picture.

So you can see here that this pancrease does enhances in the head and in the tail a little bit. However, the larger portion of the pancreas, it does not enhance. It does not perfuse by contrast. And this is how pancreatic necrosis looks on the CT, correct? So this is a pancrease that has been necrosed more than 50%.

And I want you to remember, as I told you, that sometimes an early CT might not pick up the necrosis. I'm not sure if it's because the necrosis is evolving, the necrosis at the cellular level. Or the CT is not sensitive enough early. But you can see here a patient that got a CT in the emergency room with contrast. You see the [INAUDIBLE] is bright. And you see that the pancreas is a [INAUDIBLE] but enhances homogeneously throughout its course.

By the way, this patient has also gallstones. You see the gallbladder? And a large left renal cyst, correct? So this is the same patient, day one. You do the CT and you write in your note, no necrosis. Good, correct at this level. This is his CT on day four. He didn't do well. He crashed on day three. He went to the ICU.

And on day four-- this is the same patient. There is no pancreas there. You see that? It's all necrosed. So that's why what we really need and want to do is assess for necrosis after the first 72 hours of disease. And early CT won't be that helpful, because you have cases like that. And the same patient, look how immature is this collection, this necrotic collection, it's not formed. But as it progresses, you can see clearly that the forms a capsule, a wall.

Systemic complications, the three ones that we mainly need to focus is cardiovascular with hypotension and shock, pulmonary with hypoxia, pleural fusion and respiratory failure, and renal with oliguria, azotemia, and acute tubular necrosis. However, I want you to remember-- and these are the three that define severity, correct? But I want you to remember that these patients tend to develop hypocalcemia, hyperglycemia, and metabolic acidosis as well.

Back to our patient, so up to now, we have talked as to how we diagnose acute pancreatitis, the etiologies of acute pancreatitis, how we define severity, what are the risk factors for severities, how do we predict severity with markers or scores. We talk about which are the local complications, which are the systemic complications, correct?

The patient, I got him into the ICU. He developed multisystem organ failure. He got intubated because of his respiratory failure. He was started on pressors because of his cardiovascular failure. What's next? How do we treat complicated acute pancreatitis?

When the disease is mild, still, we have to be on top of things. We have to support this patient. We usually keep this patient when they come into the hospital NPO. We have to be aggressive with IV fluids.

If you wish a better word rather than aggressive is "adequate." And the most important are the first 12 to 24 hours. So when you get this call in the emergency room, and they tell you, I have a patient with acute pancreatitis, after you discuss the patient, you ask the emergency room resident, have you been giving them any fluids?

They tell you they're getting a little bit. Tell them, give a liter of lactated ringers wide open. That's the best way that we can help our patients these days. I do the same thing when I get phone calls from emergency rooms from outside hospitals. I accept the patients. But I tell the emergency room doctor, give them a liter of IV fluids wide open.

Patients will need control of their pain. Usually we'll start with IV narcotics. And by day two or three, if they are doing well, we switch them to PO narcotics. And we start feeding them. You can start either with clear liquids. Or you can start with low-fat diet. What really irritates the pancreas is the fat. So we tend to tell the patients for the first two or three weeks after their attack to stick on a low-fat diet.

And then we have to try to identify the etiology of acute pancreatitis, so as to prevent future attacks. If the etiology is biliary, what do we need to do? A cholecystectomy. And many studies have shown, including Kishore's studies, that the best time to do a cholecystectomy is during the index admission, if it's mild disease. If your gallbladder is not removed during the day of admission, you have 25% chance of coming back to the hospital within the first one month, either with pancreatitis or biliary complications or just cholangitis. So it's really important to try to twist our surgical colleague's arm a little bit to get the gallbladder out during the index admission. It's important.

If we have hypercalcemia, we have to assess the causes and correct it. If we have hypertriglyceridemia, we have to involve endocrine, make sure that the patients have good outpatient follow-up.

If it's alcoholic, a very nice prospective study have shown that counseling the patient during their index attack of alcoholic acute pancreatitis, it's extremely important. It can change the natural history of the disease. So it's important to spend a few minutes with a patient, explain to them what is going on and what they have to do.

If the disease is severe, patients need a higher level of monitoring. Not only if the disease is severe. But if you're in the emergency room and you have a patient that is SIRS positive, is tachycardic, and has a wife kind of 20,000, I would probably have this patient either on a telemetry bed or in the ICU up front, rather than waiting for the patient to crash in the middle of the night. Again, aggressive hydration.

There is conflicting evidence now. There are some recent studies that have shown if you're overdoing it with hydration, that might not be a good thing either. Oxygenation, most of these patients will require oxygen. If pancreatic necrosis is present, there is a large debate, there's now good data of the need of prophylactic antibiotics to prevent infected necrosis. And then in patients with severe biliary pancreatitis, clearly, an ERCP in a selective group of them can be of help.

Fluid resuscitation, unfortunately, that's our main and major therapeutic tool that we have. We don't have specific medications for acute pancreatitis. If you compare where we are in pancreatitis diseases in comparison to IBD, for example, it's day and night, correct? How many medications are already approved out for IBD?

AUDIENCE: A lot.

GEORGIOS PAPACHRISTOU: A lot. So all of you that are going to follow a career in IBD, I have to warn you, IBD has already peaked. We found all the medications. We know how to treat the patients. Pancreas is the way to go. We have nothing.

[LAUGHTER]

It's a joke.

[LAUGHTER]

So severe acute pancreatitis accumulate vast amounts of fluid in the third space from the vascular leak. All their endothelium is leaking and all the fluid is going out, correct? And this is can result in ARDS, and so on and so forth.

Inadequate hydration, there is a hypotheses that it will lead to hypotension, acute tubular necrosis, and even damages the pancreatic microcirculation. The exact amount and composition of fluids is unclear. However, I would advise you, the most important is the early first few hours where giving a couple of liters of LR is the best thing that you can do for your patient.

And you can assess if you are adequately replacing fluids in your patients by the improvement in the vital signs. If they're tachycardic, their tachycardia might improve in their hypotension. By their urine output-- you want adequate urine output. And then you can follow the hematocrit and the BUN. And ideally, you're going to see a reduction over the first 24 hours.

Now do we have good studies on IV fluids? No. The study that we're using, actually, we base our evidence to give lactated ringers is a study of 40 patients, believe it or not, that was done now six years ago, where the investigators at Brigham compared goal-directed resuscitation with standard resuscitation. And they found that there is no impact, a systemic inflammatory response, at 24 hours. However, the patients that were resuscitated with lactated ringers had the reduced SIR and CRB at 24 hours.

So again, they used surrogate markers, correct? They didn't use . severity. They used a drop in SIRS and CRB at 24 hours. So the hypothesis that we're using these days for LR, Lactated Ringers, is that it results in less metabolic acidosis. And it's a pH-mediated effect.

And granted, they have done a-- the goal-directed resuscitation was a very nice protocol where the patients received a bolus of 20 mLs per kilogram. So a patient who was around 70 kilograms or 75 got 1.5 liters, bolus. And then they started them on 3 mLs per kilogram. So a patient who is around 70 kilos got 200 mLs per kilogram per hour, correct? So a bolus of 1 and 1/2 liters, and 200 mLs per hour.

And their first checkpoint was at eight hours, so very intense. And then they followed them, mainly their vitals and their BUN. And if they were fluid-responsive, then they dropped their 81.5 to 100. So it's the early fluid resuscitation that matters. If they non-responsive, they were fluid-refractory. Then at that point, they gave a second bolus. And they continued with a higher infusion rate. And then they had the second checkpoint at 16 hours.

AUDIENCE: [INAUDIBLE]

GEORGIOS PAPACHRISTOU: Why the goal-directed did not do better than standard? Because by then, everyone at Brigham knew that we have to be aggressive with fluids. And actually, the standard group got amino 4.6 liters for the first 24 hours. So I mean, even though it was not goal-directed, it's more or less the same amount of fluid, which is good, in a way, because Brigham's seems that they are on top of things. But it's bad for your study, correct?

[INAUDIBLE] in the ERCP, do we need to do [INAUDIBLE] in the ERCPs on everyone with biliary pancreatitis, on most patients with biliary pancreatitis? No, because by the time that they come to the hospital, they probably have already passed the stone. So there is no controversy about early ERCP in subjects with biliary pancreatitis and concomitant cholangitis. Yes, if you're cholangitic, or you do an MR and there is a stone in the distal CBD, you have to do an ERCP.

However, the rest of the patients with biliary pancreatitis, the vast majority, the role of early ERCP in those patients is controversial. And we don't do it in our practice, correct? I'm sure you're getting familiar with the ERCP. It's also an endoscopic procedure. We're using, instead of a forward viewing scope, a side viewing scope. And we access through [INAUDIBLE] that we get down through our endoscope channels. We access through the ampulla, the biliary tree or the pancreatic duct.

And we can remove stones. We can sample tissue. We can place stents, either plastic or metal. It's a procedure that was initially started to be performed in the late '70s, actually in Japan. And I think it has picked up through the mid '80s. So this is a procedure that it's out now 30 years or so.

In the older days, we used to do a of diagnostic ERCPs. This is not what we do these days, correct? ERCPs are purely a therapeutic procedure. We don't go in to see to look how things are. We have MRCP for that, which is a safe test. I want you to remember that ERCP carries some risks, with the most devastating risk being [INAUDIBLE] pancreatitis. Always remember that. So we have to select our patients appropriately.

Nutritional support is required in patients that are predicted to remain fasting for seven days or more. So if you are in the ICU, and you have a patient intubated on pressors, and it's day 4 of his disease, this patient won't be eating by day 7. You know that. So you have to address this patient's nutritional support.

And we know these days that when we compare internal nutrition that in our hospital, we tend to provide it through nasojejunal tubes. It's better than total [INAUDIBLE], because mainly it maintains the intestinal barrier. You use your intestines, and it eliminates catheter sepsis.

And this is not just a hypothesis. A large meta-analysis have proven that the use of internal nutrition results in significant reduction in infectious morbidity, hospital [INAUDIBLE] stay by four days, and a trend toward reduced organ failure when compared to TPN.

The way that place our NJ tubes are endoscopically through a nasal scope where we try to advance as far as we can into the duodenum. Then we feed a guidewire through the nasojejunal scope and the fluoroscoping the guidance into the proximal jejunum.

We exchange out the scope, and we advance over the wire, the nasojejunal tube. Our goal is to pass the ligament of Treitz by 30 centimeters. This is the area where when we provide internal feedings, the stimulation to the pancreas is minimal.

So you are succeeding in two goals. Number one, adequate nutritional support in patients that cannot eat because of their moderately severe or severe pancreatitis. And number two, resting the pancreas. We usually keep these tubes in for at least four weeks. And then we bring the patients back in clinic. At that time, we usually perform a follow-up CT scan, because you want to see how are these patients doing with respect to their pancreatic necrosis.

In our data analysis, we found out that we need to drain or debride less than 50% of patients with pancreatic necrosis. So I want you to remember, if you follow this conservative approach, a good portion of your patients, actually the majority of your patients, will develop a collection that slowly will regress. It will never become symptomatic. And they will actually be able to go into oral diet after four weeks. And they won't need a pancreatic intervention, such as debridement.

An easier alternative to the NJ tube is an NG tube, a nasogastric tube. And actually, studies have shown that it may be as efficient and effective as the nasojejunal tube. In our experience, and especially in patients with large necrosis, there is a lot of extrinsic compression to the stomach. They tend to have a lot of residuals. That's why an NJ and sometimes an NGJ tube might work better.

We use a semi-elemental feeding formula. And some patients might not be able to tolerate the NJ tube. So always remember that. Always follow your patients after we place the tubes. These tubes tend to migrate, get clogged, get kinked. So many of these patients may need close follow-up and follow-up procedures as well.

Prophylactic antibiotics, I will tell you that a Cochraine meta-analysis in 2010, yeah, using seven randomized controlled trials, meaning good data, showed no difference in mortality or infected pancreatic necrosis with the use of prophylactic antibiotics. However, in the post-work analysis. In the independent group, there was a significant reduction in pancreatic infection.

Sometimes we tend, when you see large necromas, to use prophylactic antibiotics. But if you're going to do that, use carbapenems that have a good penetration into the pancreatic [INAUDIBLE].

Pancreatic necrosis management, there has been an evolution from open necrosectomy into minimal access necrosectomy these days. So these days, it's unacceptable to have surgeons doing an incision from up here to there and leave the drains out. We can have minimal access in the [INAUDIBLE] done percutaneously via interventional radiology, laparoscopically. Our surgeons are experts at doing either laparoscopic or robotic cystogastrostomies through the stomach.

Or another technique that is used a lot in Europe from the Dutch pancreatitis group is actually a retroperitoneal approach surgically with small incisions. And of course, we also have endoscopic approach. Or there are centers, especially centers in Seattle, that they advocate dual approach. You place a percutaneous drain and also an endoscopic cystogastrostomy as well at the same time. And these patients tend to do very well.

This is our patient with a huge necrosis. We can go in through the scope, access it through the stomach, coil a wire in, balloon dilate the track, leave stents. Back in the days. we used to leave plastic stents. Now we tend to use more metal stents. And actually, many times, you can go inside the collection and use our endoscopic tools to debride the necrotic debris. And you can see here, the scope is actually through the stomach into the [INAUDIBLE]. You can see a stent. And you can see the remnants of necrotic debris in here that we can clear.

So the results can be impressively good. And actually, in a pilot study, comparing endoscopy versus surgery, but I have to warn you that most of the surgical candidates got open surgery and endoscopic necrosectomy did better. So it's a viable option.

In our hospital, we tend to do a lot of endoscopic work. But those patients that have biliary pancreatitis, and they need their gallbladder out too, I think it's more appropriate to go to a laparoscopic route and with one shot kill both birds. Take care of the necroma and remove the gallbladder.

Which of the following is wrong? Another question that we're looking for the wrong answer. Prophylactic use of antibiotics reduces mortality in patients with pancreatic necrosis, early SCP is indicated for patients with biliary pancreatitis and cholangitis or persistent stones.

Internal feedings reduce infectious complications and length of stay compared to TPN. The exact amount and composition of fluids is not clear. But we'll have to be aggressive the first 48 hours. Which answer is wrong?

AUDIENCE: [INAUDIBLE]

GEORGIOS PAPACHRISTOU: Correct. So we don't know that-- we have not proven that prophylactic antibiotics reduce mortality. So this is the dynamic cascade of acute pancreatitis. You have an injury, and you can see the [INAUDIBLE]. The insult involves both the [INAUDIBLE] and the ductal cell, will develop tissue injury and then a local inflammatory response.

Most of the patients will stop there and will have a fight between pro-inflammatory and anti-inflammatory agents. But around 20%, the inflammation will leave the pancreas and it involves the whole body. It will become systemic. And around 50% of those patients will also develop the vascular leak syndrome. And those are the patients that will develop pulmonary edema. They will be hypovolemic and in shock. And now we are on hour 12. That's why the early fluid resuscitation is so important.

And then down the road, there is also acute visceral organ injury and dysfunction, including the odd injury in ileus. That's why internal feedings are also preferred. And remember, if you don't feed the gut at all, you increase the risk of bacteria translocation that even more enhances the systemic inflammation.

Back to the patient, there [INAUDIBLE] an ERCP with [INAUDIBLE] extraction, had an NJ tube placed for pancreas rest. Follow-up CT scan showed more than 50% necrosis, had a slow recovery. And at the end of the day, there was no need on this patient for pancreatic debridement. He did, though, develop diabetes. Remember, if you necrose most of your pancreas, you are at risk for both endocrine and exocrine pancreatitis insufficiency.

In summary, acute pancreatitis diagnosed and based on having two out of the three criteria. Gallstones and alcohol are the most common causes. 10% to 20% of patients develop severe disease. There are preexisting risk factors. There are simple markers that are as good as complex scoring systems to predict disease.

Conservative management, IV fluids early is what I want you to remember. Prevention of future [INAUDIBLE] for those with severe disease will leave the ICU starting more interventions--