My talk will focus on risk factors and markers for severe acute pancreatitis. Acute pancreatitis is a major problem in the US and around the world, the incidence of acute pancreatitis is increasing probably because we are using more and more pancreatic enzyme measurements in the serum in the emergency room and as we can see in this diagram, has reached almost 1 per 1,000 US population per year.

The burden of the disease is significant, acute pancreatitis accounts for more than 300,000 hospital admissions annually in the US, with an average hospital stay of 4 days, a direct healthcare cost which exceeds $2 billion annually and an average cost per hospitalization which exceeds $11,000. Most of the patients with acute pancreatitis do have a mild uncomplicated course but we always have to remember that around 10 to 20% of them will develop severe disease. The mortality in this selected subgroup reaches up to 30%, but what exactly is severe disease? How do we define severity?

The first organized attempt was made 20 years ago where experts from around the world gathered in Atlanta and they came up with three different type of features to define severe acute pancreatitis to include the remote organ failure, local complications in the pancreas as well as unfavorable prognostic signs. And I have to say the Atlanta criteria served us well for a long period of time and it was the first organized attempt to classify pancreatitis and use a classification score or if you wish rules for research. However the last few years there have been major criticism of Atlanta criteria. This is because the criteria are very diverse and heterogeneous. They include as I showed you before remote organ dysfunction, but also local pancreatic injury and in addition that predictive scores.
There is no distinction between transient and persistent organ failure and we realize more and more how important persistent organ failure is. There is no distinction between pseudocyst and organized necrosis in pancreatic local complications whereas we know that it’s a completely different problem and the last few years from what I understand there is a revised version in progress but have not published yet.

Again persistent organ failure, we strongly believe that it’s extremely important. In a very nicely done study by Johnson and colleagues in 2004 in a good number of patients, 290 patients in a prospective fashion, the importance of persistent – the importance of persistence of organ failure is clearly demonstrated as you can see from 88 patients that developed persistent organ failure, meaning organ failure lasting for at least 48 hours, 32 died, 36% mortality. In contrast if you just look on the row above, from 60 patients that developed transient organ failure, only 1 actually expired.

The first 24 hours are critical for management of acute pancreatitis. It’s what we call our therapeutic window. Why is that? Because more than 50% of ICU transfers to occur within the first 24 hours of admission. In a nice study by Harrison and colleagues in 2007 you can see that organ failure peaks on day 1 in acute pancreatitis with more than 15%, 17% on day 1, whereas on day 2 only an additional 5 and on day 3 an addition 2%. So after the introduction of the burden of disease and severe acute pancreatitis we’re going to now focus on the risk factors.
Risk factors are factors that are present even before the onset, even before the development of acute pancreatitis. We usually divide them into environmental, which include age, obesity and alcohol as well as genetic factors. And in a part search that I did last week I found actually 80 articles on genetic polymorphisms related to acute pancreatitis and severity. So there is a lot of recent work on that and genes that have been identified include MCP-1, GSTT-1, TNF-a, IL-10, CD14, IL-8 and some new very interesting molecules as well.

How about age and severity? Two very interesting and well done papers that were 12 years apart have shown that patients with acute pancreatitis that are at least 70 years old reach a mortality which increases 20% versus only a mortality between 6 and 7% in younger patients. Going a step further, Lankisch and his colleagues in ’96 supported that the incidence of renal insufficiency increases with increasing age, but they could not find the same for respiratory insufficiency. There is a debate right now whether older age actually results in increased severity via augmented systemic inflammatory response versus just increased mortality, reflecting the limited reserves that the elderly patients have.

How about obesity? It is well known and documented now that obesity definitely results in more severe disease. By analyzing our prospective data we found that obese patients defined as a BMI of 30 or more have a risk of 31% in developing organ failure versus 14% for lean patients. So the risk for organ failure is more than 2 times. As you can see in the middle bar, the risk of necrosis is also more than 2 times, 17% for obese versus 8% for lean patients and impressively the risk of death in the third bar is 10 times more in obese patients, 14% in obese versus 1.4 in lean patients.
The third – and why is that? Because adipose tissue or fat releases a large amount of inflammatory cytokines, what we call adipokines, 50% of the amount of TNF-a and MCP-1 is released by adipocyte tissue, but also they are fat specific cytokines such as resistant with fat and adiponectin. We recognize more and more and there is a lot of interest the last few years of the importance, and of these molecules in augmented systemic inflammatory response and persistent organ failure.

The third environmental factor that is well documented to increase severity in acute pancreatitis is alcohol. In animal models alcohol shifts acinar cell death from apoptosis to necrosis, and it appears to worsen the local inflammation in the pancreas. In humans we found recently that alcohol increases the proportion of patients with pancreatic necrosis. If you look at the diagram on the left side where our prospective data were analyzed patients who drink 2 or more alcoholic drinks a day regardless of the etiology of acute pancreatitis have a 32% of developing necrosis, whereas the risk of necrosis is only 9% in patients that drink less than 2 drinks, alcoholic drinks a day. And we are able actually to reproduce these results in a retrospective fashion including almost 1500 patients.

So three well documented important environmental factors that are related to severe disease and now we are going to change gears to genetic factors. And I’m not going to go through all 20 genes that have been studied and published but I’m just going to focus on monocyte chemotactic protein 1 which is a very important and potent chemokine. By analyzing our prospective data we found that patients with severe acute pancreatitis have the G allele of the minus 2518 position present in more
than – in almost 90%, whereas the G allele as you can see in the bar to the left and middle is up around 45% in patients with mild acute pancreatitis and in controls. So subjects with acute pancreatitis again, regardless the etiology of disease and presence of the G allele on the MCP-1 minus 2518 position have a higher risk of severe disease with an alteration in our analysis reaching the impressive 7, meaning 7 times higher risk than patients that do not carry the G allele.

These are the risks, these are factors that are present before the development of acute pancreatitis. However as we said, acute pancreatitis can be a devastating disease. It is extremely important to be able to identify patients at the risk for severe disease early on, ideally on admission. And that’s where the prognostic, that all the prognostic markers is so important. They can guide patient triage to appropriate level of care such as intensive care unit in patients with increased risk for severe disease, and again guide our management, the amount and aggressiveness of either hydration, the need of urgent ERCP in biliary acute pancreatitis cases. Of course nutritional support as well a few days down the road. And we hope that by having an early accurate prognostic marker we might be able to apply target therapy trials early in the course of the disease by identifying at high – a selected group at high risk.

Where do we stand with the prognostic markers? First of all simply laboratory values have very well started to include hematocrit, BUN and creatinine. Recently a collaborative study by Brigham and Women’s Hospital in Boston, the Dodge Pancreatitis Study Group from the Netherlands of course, and University of Pittsburgh including more than 1,000 prospectively enrolled patients and by
studying our databases we found out that the admission BUN of more than 20 increases the odds of death more than 4 times, and interestingly a rise in BUN within the first 24 hours also increases the odds of death more than 4 times. By analyzing all our data as we can see in this flow sheet, if you wish, or classification tree the presence of elevated BUN on admission and increase of BUN at 24 hours resulted in all three groups in a mortality ranging between 10 and 20%, which is a very impressive number.

We are in the process of analyzing all three laboratory values on admission and 24 hours and try to develop classification rules that predict the development of pancreatic necrosis. As we can see here in data that were presented in the last DDW we have already identified a set of four classification rules starting from admission and advancing to 24 hour values. As you can see up here at the admission, the two admission classification rules followed by the two 24 hour classification rules that have – that can perform in predicting pancreatic necrosis with fairly good accuracy with an early AUC of 0.78.

Following the same laboratory values a lot of work have been done on multifactorial clinical scoring systems, which is another way to predict that have been used extensively in predicting severe disease. Recently we reviewed the literature and there are actually 9 clinical scoring systems published at the present time, excluding the radiologic scoring systems. These are plain clinical scoring systems. And interestingly enough, 5 of them, HAPS, PANC 3, BISAP, POP and the
RANSON score have been published the last 4 years. So there is still a lot of interest in – throughout the world of analyzing data and developing novel or new scoring systems.

Based on the plethora of scoring systems we went on using our prospective data and head to head compared all scoring systems in our data and see how they perform in predicting persistent organ failure. And what we actually found was that all 9 of them actually performed similarly with what I would call moderate accuracies. And again in our cohort Glasgow seemed to be the best classifier, not statistically significant from the rest of them with an area under the care of 0.84, a sensitivity of 0.85 and a specificity of 0.83. This is in predicting persistent organ failure as I already said.

Why do we believe – where are we going with the clinical scoring systems? Should we continue working on them? Should we continue developing what we call novel scores? I think there is an explosion in reporting as I showed to you of new scoring systems, and all of them seem to use singular parameter, clinical parameters. In addition to that the way that the scoring systems are developed is using cut offs and converting continuous variables into binary values and we do believe that this way we may fail to capture synergistic or multiplicative effects that might be very important in acute pancreatitis.

From the data that I already showed you through the international collaboration simple laboratory tests appear to perform as well as the multifactorial scoring systems and they are much easier to obtain and calculate on. I don’t think we need the development of more novel clinical scores, I think
clinical scores have reached their peak and probably it might be time to move onto new prognostic measures that directly reflect the outcome determining pathophysiology in acute pancreatitis, and this can be cytokines or genetic polymorphisms and also use new methods of analysis, not just pain cut offs but more sophisticated methods such as artificial neural networks or computational learning theories.

Following that novel approach, we have done some work at the University of Pittsburgh and by using information theory and information gain in analyzing a total of 30 cytokines in serum samples of patients with early acute pancreatitis there are 5 cytokines that we have selected, each of them appears to be linked to a different pathologic pathway and includes tumor necrosis factor alpha, receptor 1, interleukin 8, hepatocyte growth factor, angiopoietin 2 and resistin. These 5 biomarkers were modeled as a group using machine learning techniques and the help of our computer scientists. And actually the panel of these 5 cytokines appears to work very well and to be very promising by using Naïve Bayes Model the accuracy reaches 96% with a very high sensitivity and specificity. And we are almost done.

Okay, future directions just to finish. It’s not just important to identify and differentiate mild from severe disease, but we should actually focus in specific organs, the kidneys, the lungs, the heart which organ fails and how. We should focus on predicting markers of specific organ failure and hopefully in the next few years we’ll be able to perform small Phase I or Phase II specific therapy trials. Thank you for your attention.