Good evening. I want to thank Dr. Whitcolm and Jay for inviting me to speak. So we’ve got 20 minutes, usually I tell jokes, no time for jokes today we are going to get right to the talk.

So today my talk is going to focus on patients who are admitted with an active esophageal variceal bleed, so I’m not going to be discussing noncirrhotic portal hypertension, gastric or ectopic variceal bleeding prophylaxis. I’m not going to be touching on medicine or therapies that are not approved for use in the U.S. and I’m not going to be talking on follow-up management, so just a very focused talk on a patient with an active variceal bleed.

So esophageal varices develop and are at a risk of bleeding when portal pressure rises to greater than 12 mm of mercury. Although the majority of patients with cirrhosis will never bleed studies suggest that variceal hemorrhage occurs in about 1/3 of patients with cirrhosis. So how do we predict who is at a higher risk of bleeding? Well it depends on basically 5 things. So one is location, varices in the distal esophagus or closer to the GE junction are more at risk than those that are in the mid or proximal esophagus. Large varices are at a higher risk of bleeding than small. We are going to talk a little bit about appearance or what we call high risk stigmata and I’m going to show some pictures to display those specific entities I mentioned there. A sicker liver patient is more prone to bleed than one that is well compensated. If a patient has a history of a prior variceal bleed they are obviously more at risk of bleeding again. And then hepatic venous pressure gradient, so the risk of bleeding is greater, is greater than 50% when the portal pressure exceeds 16 mm of mercury.
So this is what a normal esophagus looks like and we basically grade varices as small, medium or large so you can – you may be able to make these out, these small protrusions. These are relatively bland or what we call small esophageal varices. This is a gentleman I scoped a few weeks ago, you can see these cords protruding out, these are what most of us would label as medium sized esophageal varices and the large ones kind of look like grapes where they are almost occluding the lumen. So how do we determine endoscopically who has high risk varices? So believe it or not this is a relatively rare occurrence, only about less than 10, 15% of the time do we go in and a patient is actively spurting from a varix.

So this is a patient I scoped just about 10 days ago and I don’t know if you can make it out but there is a fibrin plug or what we call a nipple sign on what’s a relatively small varix, but this is considered a very high risk stigmata, so what we did was we ended up banding under the actual fibrin plug and you can see that the varix basically resolved. This is what we call red whale signs, so you can see these red lesions on the varices.

These are cherry red spots sitting on medium size varices and these are basically blood blisters. So these things basically portend a high risk of bleeding. So putting this all together if you take a sick liver patient for example a Child’s C cirrhotic with large ascites with large varices, with red whale signs, that particular patient would have about a 75% likelihood of variceal bleed within one year.
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So the ideal treatment of an active variceal bleeder it would be a therapy that’s universally effective, completely safe, easy to administer and inexpensive and we have none of those so obviously we are not 100% effective. Although most of us would consider an upper endoscopy safe it’s not a completely safe procedure, there are risks involved. We like to think that there is some expertise in terms of administering the procedure and like everything in America it is expensive. So what we do currently have is a combination of medical and endoscopic therapies, so current guidelines recommend and I’m going to touch on these briefly before I get into the difficult bleeder. Antibiotics, vasoactive drugs, endoscopic ligation and to consider tips or a shunt in high risk patients.

So prophylactic antibiotics there is a high incidence of bacterial translocation associated with variceal bleeding and antibiotics have been shown to reduce infection complications and possibly decrease mortality in patients with variceal bleeding. It may also reduce the risk of bleeding in these patients so all cirrhotics who come in with an upper GI bleed whether it’s variceal or not should be given antibiotics. It should preferably be done before the upper endoscopy.

The most evidences for Ceftriaxone 1 g/day for about 5 to 7 days. At our hospital we use Amp Sulbactam. It’s not unreasonable to change to an oral Quinolone is patients who are taking PO and it’s not unreasonable to cut the duration of antibiotics to 5 days in patients who are otherwise deemed stable.
Vasoactive drugs, so Somatostatin and its analogs indirectly cause splanchnic vasoconstriction and therefore decrease portal inflow. Somatostatin has been shown to be more effective for control of variceal bleeding than placebo or Vasopressin. In the United States we use an analog of Somatostatin called Octreotide, the general dose is 50 mc bolus followed by a drip at 50 per hour for about 5 days.

Timing of EGD, so should the EGD be done early? So most experts say yes, if you look at current guidelines in all upper GI bleeders recommendations are that the scope be done within 24 hours. If you look at the specific liver recommendations in a cirrhotic with an upper GI bleed both the American and the European guidelines recommend that the scope should be done within 12 hours, and it’s important to note that that’s regardless of the severity of the bleed. So I think one of the mistakes maybe we make is a patient comes in at night and is deemed stable hemodynamically even though they have a history of hematemesis, and potentially waiting on that patient to the next day is probably be best if that patient is done sooner than later and that seems to be evidence based.

When it comes to endoscopic therapy there is two things we can provide. One is called sclerotherapy or injection of a sclerosing agent into the actual varices. The two most commonly used drugs in the United States are Sodium Morrhuate and Ethanolamine.

Then ligation has kind of taken over sclero and we are going to talk about why that is. So band ligation is placement of a small elastic rubber band around a varix. It works by capturing all of part
of the vein resulting in occlusion from thrombosis. It’s normal for the tissue to necrose then and then sluff off leaving a superficial ulceration. There are several commercial kits available. Once the kit is applied anywhere from 4 to 10 bands can be deployed without the need of the scope coming out. There is no study yet comparing the different kits one to each other. Bands are typically placed distally and work upwards, you place anywhere from 1 to 3 bands per column. There is one study suggesting that there is no benefit to more than 6 bands but it kind of depends on the situation and the endoscopist.

So here is a cartoon that represents. Here is the scope and you can see the kit. The banding cap just fits over, there are 7 bands on this particular kit. The varix is sucked into the catheter and then you can see this blue thing is the rubber band that shot off. So here is an actual life pictorial. You see these medium size varices, there is a fibrin plug sitting right here on this varix and the physician then has the suction catheter centered on the plug, he pulls it in and then the band is deployed. So there seem to be less complications associated with band ligation versus sclerotherapy, so less mediastinitis, less strictures, less pain, less esophageal dysfunction and less bacteremia.

So when you look at the synthesis of the available literature on these therapies basically it boils down to this, medical therapy alone is beneficial based on randomized controlled trials. Early EGD based on consensus, endoscopic therapy is beneficial so ligation superior to sclerotherapy superior to a sham endoscopy. And ligation plus medical therapy seems to be more beneficial than either therapy alone. Just one quick note on sclerotherapy guidelines do state as do some experts that
sclero may be preferable when visibility is an issue but when possible, band ligation is the preferred method of endoscopically treating varices.

So using the above therapies; antibiotics, vasoactive drugs plus endoscopic therapy in the last 30 years failure to treat variceal bleeding has decreased from 50% to around 10-20%. So basically treatment failure is still in 2013 about 10-20% and that’s what I would label as the difficult variceal bleeder.

So who are patients that rebleed and who are patients that are at increased risk of mortality with the variceal bleed? So patients who are at a high risk of rebleeding defined as 6 weeks from the index bleed are older age. If it’s a severe initial bleed, meaning the patient is basically in shock, renal failure, severity of underlying liver disease, if they have ascites, if there’s active bleeding at the time of endoscopy, if the varices are large or have very high risk stigmata. And then risk factors associated for a 6 week mortality if you’re HVPG, so if the pressure gradient is greater than 20 it’s consistently associated with a greater treatment failure and you can see the odds ratio is very high on that at 10. If you’re very sick, meaning a Childs-C the MELD score does correlate with mortality so a MELD score of 26 in a variceal bleeder portends about a 50% 6 week mortality. Again if there’s active bleeding, if there’s hemodynamic instability, bacterial infection, liver cancer and portal vein thrombus.
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So the most important variables and probably one of the more important slides I’m going to show you tonight consistently associated with treatment failure of variceal bleeding is a high HVPG defined as greater than 16-20, active bleeding at the time of the EGD, and the severity of the underlying liver disease.

So what’s the typical next step in patients who fail endoscopic medical therapy owns the placement of a shunt or a tib, so transjugular meaning these are procedures that are performed mostly by interventional radiologists where a wire is passed through the jugular vein fed down into the liver, it’s intrahepatic meaning the shunt itself sits within the liver and it connects the portosystem to the systemic system and it’s a very effective means of decreasing portal pressure.

So TIPS for salvage meaning a patient comes with a bleed and you can’t stop the bleed endoscopically using TIPS is very effective in control of bleeding so most studies suggest that you can stop the bleeding with placement of TIPS in greater than 90% of patients. However, the mortality in this group still remains high based on literature anywhere from 27-55%. So the best treatment for treatment failure is to prevent the failure to begin with and this is what formed the basis of the early TIPS study. So this was published in the New England Journal in June 2010 and is probably one of the more controversial studies published in liver disease within the last 10 years and you can see just within 2.5 years this study which was published by the Barcelona Group has already been cited over 200 times. So basically this was a study done in Europe, 9 European centers and what they did was based on previous studies they identified a high risk group of patients. So these
were patients that were Childs-C cirrhotic but less than a CTP score of 13 or Childs-B who are actively bleeding at the time of the endoscopy, all of these patients underwent an EGD. Therapy was performed at the discretion of the endoscopist so either banding and sclero and then patients were randomized to one of two groups. So one was standard care meaning the patients would get Octreotide or a vasoactive drug for another 5 days and then started on a beta blocker with repeated endoscopy until the varices were eradicated or those patients were sent directly for an early TIPS all done within 72 hours. So in this study 359 patients were admitted amongst these 9 centers with an acute variceal bleed, in the end only 63 met inclusion criterion or what they deemed as the high risk group and I think that’s important to note. So this is a very select group of patients that only turned out to be around 18%.

So what did these studies show in the standard of care group, failure to control bleeding was 50% at one year so 14 patients in the standard group rebled or ended up dying. Remember these are high risk patients so if you look specifically at those 14 patients 7 eventually went on for TIPS, 4 of these patients eventually died, 5 were deemed too sick for TIPS, they all died, and then 2 patients continued to get band ligation. So this is versus the TIPS group where the failure was only in 1 patient and you can see that was very highly statistically significant. And then more importantly the survival in the TIPS group was much higher than compared to standard therapy so 86% versus 16% so again this is the failure to control bleeding; 50% in standard therapy versus only 1 patients in the early TIPS and then the survival being significantly higher in the early TIPS group versus standard of care.
When you look at other outcomes surprisingly encephalopathy was actually lower in the TIPS group although it didn’t reach statistically significance compared to standard therapy. Not surprisingly ascites was better controlled in the TIPS group and then the time in the ICU and overall hospitalization was significantly lower in patients who were TIPSed versus patients who underwent standard therapy.

Two additional centers since that paper have come out, one from the UK and one from France confirming the early TIPS basically showing again a decreased risk of rebleeding and improved survival of both of these studies are only in abstract form. These later studies did suggest that earlier TIPS meaning even before 72 hours may be more beneficial so again 24 hours may be better than waiting 3 days.

So we were asked to write a critique on this paper and I thought cleverly I’d name the paper the TIPSing point. I spent more time on the title than actually writing up the paper but anyway if you look specifically at this study and of course it was a very well done study I think the devil is a little bit in the details. Seventy percent of patients sent for TIPS were alcoholic with the majority of these patients actively drinking and for those in the audience who take care of liver patients you know patients specifically with alcoholic liver disease if you can get them to stop drinking it’s not uncommon in the patients who do well for a fair amount of their liver disease to reverse. The mean MELD score in the TIPS cohort was relatively low it was 15 plus or minus 5 so not one patient was
sent for TIPS with a MELD score greater than 21 and I think also it’s a little difficult to explain why there was a lower incidence of encephalopathy in the TIPS group. Maybe a smaller critique sclerotherapy was used in about 25% of cases, I think most endoscopists are very rarely using sclerotherapy at least certainly less than a quarter % of the time.

So here’s a case just to I think exemplify the problem with the early TIPS study so for example a 64 year old patient with NASH cirrhosis, a Childs C with a MELD of 25 with 2 prior episodes of encephalopathy in the last 2 months, one requiring intubation is admitted with their first variceal bleed. And EGD reveals a medium sized esophageal varices with a clear nipple sign in the distal esophagus on the larges varix, a band ligation is performed with good decompression. So just a poll of the audience I don’t know how many hepatologists we have, how many patients here would or how many physicians here would send this patient for an early TIPS? So we got one. So based on that study this patient would meet criterion for an early TIPS but I think a lot of us who take care of liver patients would be concerned that this patient would be a high risk of at least developing worsening of encephalopathy post TIPS so I think the verdict is still out.

So these are my steps the last 2 slides for a patient with cirrhosis and upper GI bleed. I’ve put smiley faces on the things that are evidenced based and frowny faces on things where there is not a lot of evidence. So ABCs obviously if a patient comes in you want to type and cross them, hold at least 3 units large-bore IV access, of course get basic labs, x-rays. You want to transfuse patients conservatively and there’s good data to transfuse only to about a hemoglobin of 8. INR is typically
not reliable in these patients and most of us are not correcting the INR with FFP and that is based on pretty good data. Most of us are transfusing to a platelet count above 50 but again that’s not based on great data, most of us are admitting these patients to an ICU. You know I personally am not a big fan of an NG tube in a cirrhotic patient because in my opinion it’s just delaying what you need to do which is to get in there and look. There have been specific studies though looking at NG tubes in patients with both upper GI and variceal bleeding and it doesn’t seem to necessarily change the outcome. Surprisingly there’s not a lot of good data on intubation, you know our default in our ICU is that all cirrhotics who come in with an upper GI bleed are intubated. Again it’s not based on great data I’ll just tell you anecdotally I’ve never regretted intubating someone, I have regretted in the past not intubating. Octreotide is based on pretty good evidence. A PPI should be started until you can confirm that it is in fact portal hypertension, antibiotics we talked about. There is some evidence for Erythromycin which is a prokinetic agent to move all the blood hopefully out of the stomach into the small bowel. The EGD should be performed within 12 hours of presentation. You should have some type of balloon Tamponade device available at bedside whether that’s a Blakemore or Minnesota tube. After you’ve done your endoscopy you should order a right upper quadrant ultrasound in case the patient does require a TIPS mainly just to check for vessel patency. Band ligation preferable compared to sclero and then I basically would summarize by saying if the patient is a Childs class C with less than a score of 13 or a B with active variceal bleeding I would think maybe fast and hard about early TIPS. Thank you.