Study title: Plastic stents vs fully covered self expanding metal stents (FCSEMS) for treatment of anastomotic bile leaks following orthotopic liver transplant: a randomized controlled trial

Principal Investigator: Patrick Yachimski, MD MPH Revision Date: October 11, 2017

Background:

Orthotopic liver transplant (OLT) can be a life-saving intervention for patients with decompensated liver disease. Typical surgical biliary reconstruction at the time of OLT is creation of an anastomosis between the donor common hepatic duct and recipient bile duct. Bile leaks arising from this anastomosis early in the post-transplant period are a known potential adverse event of OLT and may result in significant morbidity including intra-abdominal infection, need for repeat liver transplant, and death.

Standard endoscopic management for anastomotic bile leaks following OLT has been endoscopic retrograde cholangiopancreatography (ERCP) with placement of a temporary plastic biliary endoprosthesis (stent) across the site of anastomotic leak. While this intervention carries a high rate of technical success, clinical success is not universal. In a retrospective study of patients undergoing ERCP for post-OLT anastomotic bile leak at VUMC between 2009 and 2014, ERCP with placement of a plastic stent resulted in resolution of bile leak in 60% of patients. The remaining 40% of patients experienced refractory anastomotic bile leaks. Patients with refractory anastomotic leaks were found to be at increased risk of surgical re-intervention, repeat transplant, and death [1].

An alternative to placement of a plastic biliary stent is placement of a fully covered self-expanding metal stent (FCSEMS). FCSEMS have been granted United States Food & Drug Administration approval for categories of both malignant and benign bile duct disease. Whereas a plastic stent functions largely as a wick to siphon bile flow, the theoretical advantage of a FCSEMS is that the relatively larger expansile diameter and membrane coating provide an actual and effective seal at the site of leak. FCSEMS have been used successfully for salvage therapy of anastomotic bile leaks in the post-OLT population at VUMC [1], with no serious stent related adverse events and no cases of unsuccessful FCSEMS removal in this population.

The objective of this study is to prospectively randomize patients found to have anastomotic bile leaks following OLT to placement of either a plastic biliary stent or a FCSEMS at initial ERCP intervention.

Study hypothesis:

Placement of FCSEMS as initial treatment for anastomotic bile leak following OLT will result in a higher rate of leak resolution compared to placement of a plastic stent.

Study endpoints/outcome measures:

Primary endpoint:

Cholangiographic resolution of bile leak at follow-up ERCP 6 weeks following placement of a plastic stent or FCSEMS.

Secondary endpoints:

1) Need for repeat endoscopic intervention (ERCP) within initial 8 weeks following placement of a plastic stent or FCSEMS
2) Need for percutaneous drainage of biloma or intraabdominal fluid collection following placement of a plastic stent or FCSEMS
3) Need for surgical biliary reconstruction for refractory anastomotic bile leak
4) Need for repeat OLT
5) Death at 90 days
6) Rate of post-ERCP pancreatitis (PEP) following placement of a plastic stent vs FCSEMS
7) Rate of stent migration following placement of a plastic stent vs FCSEMS
8) Rate of anastomotic biliary stricture at follow-up ERCP 8 weeks following placement of a plastic stent or FCSEMS
9) Need for repeat ERCP for management of anastomotic biliary stricture within 90 days following leak resolution

Methods:

Eligibility: All adult patients undergoing ERCP for suspected anastomotic bile leak within 60 days following OLT with standard biliary reconstruction will be eligible for study participation. Clinical decision to proceed with ERCP will be at the discretion of the liver transplant service when a bile leak is suspected on the basis of bilious percutaneous drain output, imaging findings, or other clinical criteria.

Cognitively impaired population is eligible if surrogate has legal power of attorney.

Patients who have undergone OLT with hepaticojejunostomy will not be eligible for participation. Patients who have undergone percutaneous transhepatic cholangiogram with percutaneous biliary intervention following OLT and prior to ERCP will not be eligible for participation.

Study intervention: Potential subjects will be consented prior to ERCP. ERCP will be performed in standard fashion. If cholangiogram demonstrates a high-grade anastomotic bile leak (evident without occlusion cholangiogram) and successful transpapillary wire access across the leak is established, subject randomization will then take place. Study allocation to plastic stent vs FCSEMS will be determined by the contents of a sealed envelope. Patients randomized to plastic stents will receive a 10 French stent, with stent length sufficient to traverse both the anastomosis and papilla selected at the discretion of the endoscopist. Patients randomized to FCSEMS will receive an 8 mm diameter by 80 mm length Wallflex (Boston Scientific) FCSEMS. Consistent with current endoscopic practice among this population, biliary sphincterotomy will be performed prior to stent placement unless prohibited by coagulopathy and/or thrombocytopenia.

The study consists of a one-time intervention, randomization to plastic vs metal stent, during procedure while patient is under anesthesia. There is no further study intervention, and all subsequent clinical interactions and procedures (if necessary) will be performed as part of standard (non-study) clinical care. It is not expected that subjects will lose capacity or ability to withdraw consent. However, if a

subject is identified as incapable of consenting on his/her own behalf, the individual authorized to provide consent for ERCP procedure will be identified as the individual authorized to provide consent for study participation. That person must provide a legal power of attorney document.

Study follow-up: All patients will be assessed by the gastroenterology consult service on post-operative day 1 following ERCP for the presence of post-procedure adverse events, as is typical practice.

Patients will be scheduled for follow-up ERCP for stent removal at 6 weeks following initial placement of a plastic stent or FCSEMS. Repeat ERCP may be performed sooner than 6 weeks at the discretion of the transplant team if there is clinical suspicion for refractory bile leak following initial stent placement.

Adjudication of the primary study endpoint will be determined by the presence/absence of persistent anastomotic bile leak at first follow-up ERCP after initial stent placement, whether performed at 6 weeks or sooner.

Study participation for all subjects will be complete at this point in time, with continued standard care as directed by the transplant time. Additional secondary outcomes will be assessed by longitudinal follow-up during a 90-day period following initial stent placement.

Power calculation and statistical analysis plan: Statistical comparison of the primary study outcome, proportion of patients with refractory bile leak, will be performed using Chi-square statistic. Prior data indicate that the refractory anastomotic bile leak rate following placement of a plastic biliary stent is 40% [1]. Assuming that the refractory leak rate following placement of a FCSEMS is 10%, this study would need to enroll 32 subjects in the plastic stent arm and 32 subjects in the FCSEMS arm to be able to reject the null hypothesis that the refractory leak rate for plastic vs FCSEMS is the same with 80% power and a Type I error rate of 0.05.

Study timeline: Assuming an annual OLT volume of 150 patients at VUMC, and assuming 10% of OLT recipients will experience an anastomotic bile leak, we expect to enroll to study target (64) patients within a 4 to 5 year time frame.

Study funding: The study will not be supported or funded by industry, and the collection, analysis, interpretation, and publication of data will be independent of industry.

Reference:

1) Davee T, Geevarghese SK, Slaughter JC, Yachimski PS. Refractory anastomotic bile leak leaks after orthotopic liver transplantation are associated with hepatic artery disease. Gastrointest Endosc 2016 Sep 10. pii: S0016-5107(16)30556-9. doi: 10.1016/j.gie.2016.08.050. [Epub ahead of print]

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