Reviewer comment and subsequent reviewer responses:

Reviewer: 1

1) Paper must include a background and aim of the biliary stents, especially drug eluding stents

Thank you for this suggestion. The following background and aims has been added to our paper:

Background & Aims
Biliary stents can offer quick resolution of both malignant and non-malignant biliary obstructions; however they suffer from high rates of subsequent failure due to a variety of reasons including bile clogging, ingrowth of both malignant and non-malignant tissue, and migration of the stent. Local drug delivery through incorporating novel agents into biliary stents holds promise as a means to decrease the rates of stent failure through multiple mechanisms, thus decreasing patient morbidity, mortality and costs. In this review we will discuss the most up to date relevant studies of drug eluting biliary stents in benchtop, animal models, and human trials, as well as discuss directions for future study.

2) Animal and human studies must be presented in different parts

This is an excellent point, as animal and human studies should be distinguished. The following changes have been made to our paper.

(Table 3) Studies evaluating drug elution or coating to prevent Internal failure:

In Vitro

Author	Journal	Study Design	Study Results
Rees	Journal of Hospital Infection (1998)	in vitro - control (polyurethane) - benzalkonium chloride (BZC) - ePTFE (Teflon)	BZC and Teflon reduced the number of organisms attached to stents
Cetta	The European Journal of Surgery (1999)	in vitro 5 stents - control (polyurethane) 5 stents - heparin +	heparin and hyaluronic acid coating reduced biofilm development

		hyaluronic acid	
Weickert	Advances in Medical Sciences (2011)	*in vitro* 7 stents - control (polyethylene) 4 stents - hydrophobin (H) 3 stents - H + ampicillin/sulbactam 3 stents - H + levofloxacin 3 stents - H + heparin	stents coated with hydrophobin or both hydrophobin and heparin reduced clogging material (SEM images)

Animals

Author	Journal	Study Design	Study Results
Gwon	Acta Radiologica (2012)	canine model 3 stents - control (ePTFE) 3 stents - 10% wt/vol cefotaxime 3 stents - 20% wt/vol cefotaxime	cefotaxime did not prevent biofilm development (gross inspection, SEM images)

Humans

Author	Journal	Study Design	Study Results
Farnbacher	Scandinavian Journal of Gastroenterology (2012)	randomized prospective 13 stents - control (polyethylene) 13 stents (same patients) - heparin	heparin is effective in preventing encrustation on stents (encrustation weighed)

(Table 4) Trials evaluating systemic treatments to prevent internal failure:
In vitro

Author	Journal	Study Design	Study Results
Tsang	Journal of Laboratory and Clinical Medicine (1997)	in vitro 4 - porcine bile 4 - porcine bile + ampicillin + sulbactam	ampicillin and sulbactam inhibited biofilm formation
Humans			
Author	**Journal**	**Study Design**	**Study Results**
Smith	Gastrointestinal Endoscopy (1989)	randomized prospective 30 patients received either - placebo or - doxycycline or - aspirin	both doxycycline and aspirin reduced the dry weight of sludge. doxycycline improved patient survival
Barrioz	Lancet (1994)	randomized prospective 25 - conservative treatment 21 - ursodeoxycholic acid & norfloxacin	drugs were associated with longer stent patency and shorter hospital stay
Coene	Scandinavian Journal of Gastroenterology (1994)	randomized prospective 60 patients received either - co-trimoxazole or - N-acetylcysteine	bile clogging did not correlate with bile viscosity. mucolytic agents or antibiotics only effective when bile is highly viscous
De Lédinghen	Digestive Diseases and Sciences (2000)	randomized prospective 29 - conservative treatment 33 - ursodeoxycholic acid & norfloxacin	no difference in stent patency and patient survival
Halm	Endoscopy (2001)	randomized prospective 26 - ursodeoxycholic acid 26 - ursodeoxycholic acid + ofloxacin	no difference in patient survival or stent occlusion

(Table 5) Studies evaluating drug elution or coating to prevent external failure:

Animals

Author	Journal	Study Design	Study Results
Lee DK	Gastrointestinal Endoscopy (2005)	porcine model 2 pigs - control (metallic) 2 pigs - 10% wt/vol Paclitaxel 2 pigs - 20% wt/vol Paclitaxel	paclitaxel-eluting stents caused mild adverse effects, but are safe to use in porcine models
Lee SS	Gastrointestinal Endoscopy (2009)	canine model 5 dogs - control (metallic) 6 dogs - 20% wt/vol paclitaxel	paclitaxel-eluting stents caused mild adverse effects, but are safe to use in canine models
Lee JW	International Journal of Pharmaceutics (2012)	in vitro, murine model 5 mice - no stenting 5 mice - polyurethane 5 mice - 0% wt/vol gemcitabine 5 mice - 8% wt/vol gemcitabine 5 mice - 12% wt/vol gemcitabine	stents coated with gemcitabine reduced the size of subcutaneous tumor in vitro and in mice
Chung	Journal of Gastroenterology and Hepatology (2012)	porcine model 2 pigs - 0% wt/vol gemcitabine 2 pigs - 10% wt/vol gemcitabine 2 pigs - 15% wt/vol gemcitabine	gemcitabine-eluting stents cause mild to severe inflammation, but are safe to use in porcine models

		2 pigs - 20% wt/vol gemcitabine	
Jang SI	Endoscopy (2012)	porcine model 2 pigs - 0% wt/vol paclitaxel 2 pigs - 0% Pluronic + 10% taxol 2 pigs - 10% Pluronic + 10% taxol 2 pigs - 20% Pluronic + 10% taxol	greater patency observed when stents were coated with pluronic with paclitaxel. stents are safe to use in porcine models.
Kim	International Journal of Nanomedicine (2013)	in vitro, murine model 10 mice - control (no stenting) 10 mice - PCL film 10 mice - sorafenib-loaded film	sorafenib-loaded film inhibited the growth of human cholangiocarcinoma cells in vitro and in mice
Shi	European Journal of Gastroenterology and Hepatology (2013)	canine model 10 dogs – control (no stenting) 10 dogs – Poly-L-lactic acid coated metallic stents (PLLA) 10 dogs – PLLA + 1mg paclitaxel/stent 10 dogs – PLLA + 2mg paclitaxel/stent	no adverse effects. less granulation tissue and glandular hyperplasia in dogs with paclitaxel stents.
Bang	Gastroenterology Research and Practice (2015)	murine model 8 mice - control (polyurethane)	tumor angiogenesis inhibited in mice with Paclitaxel stents through multiple molecular

		8 mice - control + Pluronic 8 mice - Pluronic + 5% paclitaxel 8 mice - Pluronic + 10% paclitaxel	mechanisms.
Humans			
Author	**Journal**	**Study Design**	**Study Results**
Suk	Gastrointestinal Endoscopy (2007)	randomized prospective 21 patients - 10% wt/vol paclitaxel	paclitaxel-eluting stents are safe and effective. occlusion in 9 patients, mean patency was 429 days.
Jang SI	Digestive Diseases and Sciences (2013)	randomized prospective 46 patients - control (metallic) 60 patients - 10% wt/vol paclitaxel	no significant differences in stent patency or patient survival, but stents proved safe to use in humans

3) Some abbreviations in the tables must be defined at the end of table 3

Thank you for catching this, the abbreviations have been identified as follows:

(Table 3) Studies evaluating drug elution or coating to prevent Internal failure:

In Vitro

Author	**Journal**	**Study Design**	**Study Results**
Rees	Journal of Hospital Infection (1998)	in vitro - control (polyurethane) - benzalkonium chloride (BZC) - ePTFE (Teflon)	BZC and Teflon reduced the number of organisms attached to stents
Cetta	The European	in vitro	heparin and hyaluronic

	Journal of Surgery (1999)	5 stents - control (polyurethane) 5 stents - heparin + hyaluronic acid	acid coating reduced biofilm development
Weickert	Advances in Medical Sciences (2011)	*in vitro* 7 stents - control (polyethylene) 4 stents - hydrophobin (H) 3 stents - H + ampicillin/sulbactam 3 stents - H + levofloxacin 3 stents - H + heparin	stents coated with hydrophobin or both hydrophobin and heparin reduced clogging material scanning electron microscopy (SEM) images

Animals

Author	**Journal**	**Study Design**	**Study Results**
Gwon	Acta Radiologica (2012)	canine model 3 stents - control (ePTFE) 3 stents - 10% wt/vol cefotaxime 3 stents - 20% wt/vol cefotaxime	cefotaxime did not prevent biofilm development (gross inspection, SEM images)

Humans

Author	**Journal**	**Study Design**	**Study Results**
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4) References are relatively old, however there are very nice papers published in 2014 and 2015, they must be added to the text and discussed.

There were several papers published recently that are relevant to our paper, thank you for suggesting them. The following text has been added,

"Most recently, Shi *et al.* used a canine model to study the effect of paclitaxel biliary stents when used as biliary-enteric anastomosis following Roux-en-Y cholangiojejunostomy.[49] Histology of the bile duct was observed 1, 3, 6, 9 and 18 weeks following the surgery. Paclitaxel-coated stents were found to release paclitaxel for 9 weeks, and dogs that had paclitaxel-coated stents placed had less granulation tissue and granular hyperplasia of the biliary-enteric anastomosis. No adverse effects of paclitaxel were observed."

"Bang and colleagues recently developed a mouse model xenografted with both pancreatic cancer and cholangiocarcinoma cell lines which they exposed to paclitaxel-eluting membranes, in an attempt to determine the molecular mechanisms of tumor inhibition.[50] Paclitaxel, they discovered, inhibited tumor angiogenesis, through multiple mechanisms including suppression of mammalian target of rapamycin (mTOR) through regulation of hypoxia inducible factor (HIF-1) and increased apoptosis, as well as inhibiting tumor-stromal interaction by effecting regulation of CD44, SPARC, matrix metalloproteinase-2, and vimentin."

These were from the following references:

- Shi J, Lv Y, Yu L, Zhang B, *et al.* Interest of a new biodegradable stent coated with paclitaxel on anastomotic wound healing after biliary reconstruction. Eur J Gastroenterol Hepatol. 2013 Dec;25(12):1415-23.

- Bang S, Jang SI, Lee SY, et al. Molecular Mechanism of Local Drug Delivery with Paclitaxel-Eluting Membranes in Biliary and Pancreatic Cancer: New Application for an Old Drug. *Gastroenterology Research and Practice*. 2015;2015:568981..