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A Unique Presentation of Abdominal Pain: Drug-Induced Hemorrhagic Cholecystitis

Brienne Ryan M.D. M.S., Cynthia Lin M.D., Jacob Sandor M.D., Antonio Picon M.D. F.A.C.S.
Stamford Hospital/Columbia University Vagelos College of Physicians and Surgeons

Introduction: Acute cholecystitis is a relatively common cause of abdominal pain, resulting from gallbladder (GB) inflammation secondary to cystic duct obstruction or impaired GB emptying. Untreated cases can lead to GB perforation, sepsis, and death. Hemorrhagic cholecystitis is a rare form of acute cholecystitis. Causes of hemorrhage within the GB lumen include trauma, iatrogenic intervention, neoplasms, or bleeding disorders. In existing literature, drug-induced cases have been reported in patients concurrently on anticoagulation (AC). Herein, we present the first reported case of drug-induced hemorrhagic cholecystitis in a patient who was not previously on AC.
Method(s): A 73-year-old female with a past medical history of idiopathic pulmonary fibrosis (IPF), osteoarthritis, and urinary incontinence presented with nausea and right upper quadrant pain for three days. The patient denied taking AC or any a personal or family history of bleeding disorders. Admission imaging showed that she had a distended GB with wall thickening and a hyperdense material within the lumen of the GB consistent with hemorrhage. The patient was diagnosed with hemorrhagic cholecystitis. A thorough review of her medical history revealed she was taking Ofev (Nintedanib) for 14 months, a tyrosine kinase inhibitor approved for IPF treatment, which has been shown to have an increased risk of minor bleeds (e.g. epistaxis).

Results: After careful discussion of the patient's comorbidities, the patient was admitted to the medical service, treated with antibiotics, bowel rest, and multimodal pain control. Pulmonology was consulted, and Ofev was held throughout her hospitalization. She was monitored with serial abdominal exams, and her diet was advanced as tolerated. Her pain improved, and operative intervention was deferred. The patient was discharged on hospital day 7 with plan for outpatient follow-up.
Conclusion(s): Hemorrhagic cholecystitis is a rare entity. To our knowledge, this is the first reported case of hemorrhagic cholecystitis secondary to Ofev, in a patient not concurrently on AC. Existing literature reports both non-operative and operative management options for patients with hemorrhagic cholecystitis. We hold that intervention should be guided by the patient's clinical status and degree of hemorrhage.

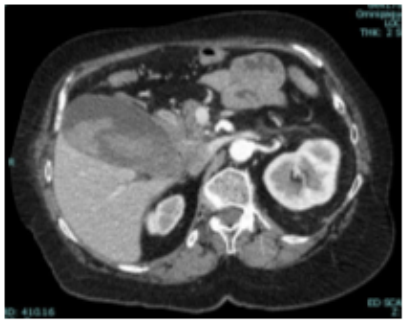

Figure 1. Abnormal Gallbladder. Admission CT Abdomen/Pelvis showing a 12 mm gallbladder with hyperdense material.

Characterization of Cryptoglandular Fistula Microbiome Using a Novel Technique

Muhammad H. Zafar MD, Anders Mellgren MD, PHD, Mohamad A. Abdulhai MD, Alejandra Perez-Tamayo MD, Gerald Gantt MD
Division of Colon and Rectal Surgery, University of Illinois at Chicago, Chicago, Illinois

Introduction: Most perianal fistulas are cryptoglandular in origin. Bacterial infection within the inter-sphincteric space is thought to be central to fistula formation, as suggested by Park's cryptoglandular hypothesis. However, this has never been proved due to difficulty in isolating the microorganisms in fistula specimens using conventional culturing techniques. We describe a novel technique to obtain fistula biopsy samples to characterize the cryptoglandular fistula microbiome using 16s ribosomal RNA (rRNA) gene amplicon sequencing. We also aim to correlate the microbiome with clinical outcomes.

Method(s): A prospective single institution observational study was performed. Fistula specimens were collected from patients as they underwent definitive surgical management for cryptoglandular perianal fistula disease between December 2021 and June 2022 via Video-Assisted Anal Fistula Treatment (VAAFT). Genomic DNA was extracted using a Microbiome DNA Kit (Promega). Deep sequencing of 16s rRNA gene amplicons was used to interrogate fistula microbial community structure. Differences in microbial community structure between groups were explored through comparison of alpha diversity, beta diversity analysis, and taxon-by-taxon differential abundance analysis. Patients were classified as either having a resolving or persistent fistula based on patient reported symptoms and anorectal examination findings at a 3-month postoperative visit.

Results: The final analysis included 6 patients with resolved and 3 with persistent fistula. The mean age in resolving vs. persistent fistula groups was 43 vs. 36 yo while the mean BMI was 28 vs. 31, respectively. Six patients were treated with a fistulotomy while one of each was managed through a rectal advancement flap, ligation of inter sphincteric fistula tract procedure, and a combination of VAAFT and fibrin glue. The most common overall phyla was *Firmicutes*. A trending difference in alpha diversity (Shannon index) was seen between the two groups with higher diversity observed in the resolving fistula group (p=0.26). The group with persistent fistula was found to harbor a significantly higher burden of the pathogenic phylum *Fusobacteria* (logFC value= 9.2) at all taxonomic levels (p<0.05). While patients with resolving fistula expressed enriched abundance of the normal gut flora phylum *Firmicutes*, and class *Negativicutes* (logFC value= 3.9, p=0.04).

Conclusions: To our knowledge, this is the first study to describe cryptoglandular fistula microbiome. Persistent and resolving cryptoglandular fistula appear to differ in their microbial community structures. Additional patients are being enrolled to further characterize the microbiome and investigate the possible relationship between the microbiome and fistula treatment outcomes.

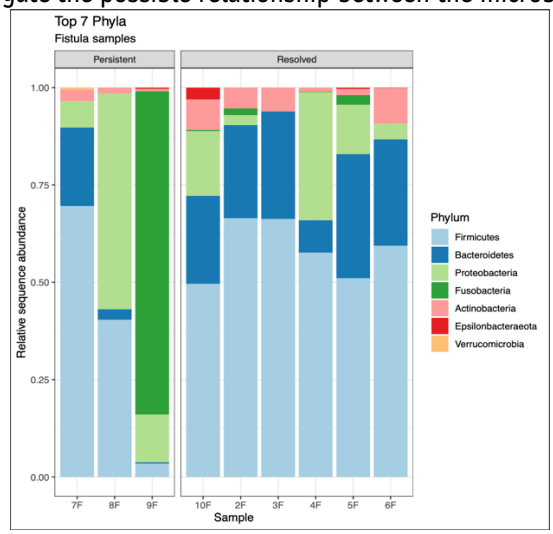

Figure 1: Top 7 Phyla isolated from cryptoglandular fistula tracts

Genetic Approach to demonstrate the Cardioprotective function of E3 ligase after Myocardial Infarction

[1]Seetur R Pradeep, PhD., [1]**Monica Maloney, MD.**, [1]Mahesh Thirunavukkarasu, PhD.,[1]Andrew Kemerley, DO., [1,2]Diego Accorsi, MD., [1,2]Santosh Swaminathan. MD., [1,2]Sue Ting Lim, MD., [1,2]Jennifer Hubbard, MD., [2]Alexander Palesty, MD, FACS., [1]Nilanjana Maulik Ph.D., FAHA

[1]Molecular Cardiology and Angiogenesis Laboratory, Dept of Surgery, University of Connecticut School of Medicine, Farmington, CT; [2]The Stanley J. Dudrick Department of Surgery, Saint Mary's Hospital, Waterbury, CT

Introduction: Ubiquitination is essential in cellular function, including cell death, cell migration/proliferation, angiogenesis, and immune response. Pellino-1 (Peli1), an E3 ubiquitin ligase, has emerged as a critical regulator of innate immune response; however, its role in repairing the injured myocardium remains to be elucidated.

Method(s): Control and genetic animals were exposed to left artery descending artery (LAD) ligation to induce myocardial infarction. Animals were divided into (a) Control wild type (WT), (b) AMPEL1 (Cardiomyocyte specific, Peli1 overexpression), and (c) CP1KO (cardiomyocyte-specific Peli1 deletion). The tissue collected at various time points was used for Western blot analysis (24 hours and 4 days after MI) and immunohistochemistry (7 days and 30 days after MI). Echocardiographic analysis was performed 30 days after MI.

Results: There was no change in cardiac function between Sham groups. AMPEL1$^{Tg/+}$ MI group showed preserved systolic function, represented by both EF [n=12-14, p<0.0001] and FS [n=12-14, p<0.0001] compared to WTMI. However, CP1KO MI showed a loss of systolic function, as represented by EF [n=13, p=0.03] and FS [n=13, p=0.03] compared to WTMI. The extent of fibrosis is also reduced in AMPEL1MI [n=5, p=0.0031] but increased in CP1KOMI [n=6-7, p<0.0001] compared to WTMI. Capillary [n=4-5, p=0.0010] density was increased in AMPEL1MI but reduced in CP1KOMI [n=6, p<0.0001] compared to WTMI. Western blot analysis documented increased survival and angiogenic factors (p-AKT, VEGF, and Bcl2) in AMPEL1MI compared to CP1KOMI and WTMI.

Conclusion(s): Using genetic approach, we have successfully demonstrated cardioprotection in Peli1 overexpressed mice subjected to MI. However, collaborative efforts are needed to translate our E3 ligase, Peli1-based therapy from bench to bedside.

Injectable Hydrogel Loaded with Modified Mesenchymal Stem Cells (MSCs) as a Potential Cure for Hind Limb Ischemia

[1,2]Virginia Parker, MD., **[1,2]Shayan Ahmed, MD, MPH,** [1]Rajesh Lakshmanan, PhD., [1,2]Benjamin Dahlberg, MD., [1]Mahesh Thirunavukkarasu, PhD., [1]Ajayan Mannoor Supran, PhD., [1]Andrew Kemerley, MD., [2]J. Alexander Palesty, MD, FACS., [1]Nilanjana Maulik, PhD, FAHA

[1]Molecular Cardiology and Angiogenesis Laboratory, Dept of Surgery, University of Connecticut School of Medicine, Farmington, CT; [2]The Stanley J. Dudrick Department of Surgery, Saint Mary's Hospital, Waterbury, CT

Introduction:

Mesenchymal stem cell (MSC) therapy has recently emerged as an alternative treatment strategy to cure terminal-stage peripheral arterial disease critical limb ischemia (CLI). Owing to poor MSC retention in ischemic conditions, the success of MSC therapy is very limited in clinical settings. Through gene therapy and transgenic model systems, we have effectively proven the proangiogenic and anti-apoptotic role of Trx-1 to promote blood perfusion and angiogenic protein expression in the murine model of hind limb ischemia. In the current study, we checked the feasibility of delivering Trx-1 overexpressing MSCs through injectable PLGA-PEG-PLGA hydrogel in a mouse model of hindlimb ischemia (HLI) and evaluated their therapeutic benefits.

Method(s):

ICR/CDI mice aged 8-12 weeks old were divided into four experimental groups: (i) PBS, (ii) Hydrogel (HG), and (iii) HG+MSC-Ad.LacZ, and (iv) HG+MSC-Ad.Trx1. MSCs were treated with *Ad.LacZ* or *Ad.Trx1* ($1x10^9$pfu) for 48 hours in vitro prior to injection along with hydrogel. All mice were subjected to femoral artery ligation. The left hind limb served as the internal control. All experimental animal groups underwent Laser Doppler Imaging (LDI) at pre- and postoperative levels until 28 days. Postoperative immunohistochemical analysis (IHC) was performed for fibrosis and VEGF expression.

Results:
LDI has confirmed improved blood perfusion levels (ischemic to non-ischemic limb) in HG+MSC-Trx1 group at day 7 [p=0.0008], day 21 [p=0.012] and day 28 [p<0.030] (n=8)] compared to HG+MSC-Ad.LacZ group. PBS and HG group showed no significant difference between them. IHC analysis further confirmed the increased expression of VEGF protein followed by reduced fibrosis in HG+MSC-Ad.Trx1 compared to HG+MSC-Ad.LacZ group [11.51 vs. 16.63; %; n=6; p=0.0062].

Conclusion(s):
Our experimental findings have proven enhanced cellular retention and restoration followed by blood perfusion, ischemic muscle repair and regeneration, and proangiogenic signaling due to the synergistic effect of Trx-1 and injectable delivery system in HLI. Through this study, we have proposed a solution to address the prevailing lacunas of MSC therapy in clinical settings.

Fournier's Gangrene: Successful Multidisciplinary Management at a Single Institution

Neville Patel MD, David Knight MD, Tammy Peterson RN, Zhongqiu John Zhang MD/PhD
Waterbury Hospital Department of General Surgery, Waterbury Hospital Wound Care Center, Frank H Netter Quinnipiac School of Medicine

Introduction: Necrotizing Fasciitis (NF) is a well-recognized surgical emergency that has a devastatingly high, from 11% to 22%,[1] mortality rate, which has not changed significantly from when first studied. Necrotizing fasciitis is a subset of the aggressive skin and soft tissue infections that cause necrosis of the muscle fascia and subcutaneous tissues. Typically, this polymicrobial infection travels along the fascial plane due to its poor blood supply. Fournier's Gangrene (FG) is a type of necrotizing fasciitis that affects the scrotum, penis and perineum and is associated with an even higher mortality rate of 20-30%[2]. Through this retrospective study, we discuss our multidisciplinary team management of these patients and the positive outcomes that resulted from our success over the past three years at our single institution.

Methods: Waterbury Hospital Center records were searched and recorded from January 2021 to September 2023 for all patients with a diagnosis code of FG (n=27), along with their clinical presentation, demographics, operative course, and post-operative ostomy care.

Patient care was started by the Emergency Department (ED) team after initial presentation of signs and symptoms of sepsis with a groin wound with clinical suspicion of NF. The diagnosis was based either on clinical examination, which revealed perineal skin necrosis or crepitus of the perineum, and/or on imaging studies revealing the presence of air in the perineal area. A patient with an elevated LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score[3] was also used to distinguish NF from severe cellulitis, and therefore prevent patients with NF from being admitted to a non-surgical service.

Upon diagnosing FG, antibiotics treatment was urgently initiated with mainstay therapy of Vancomycin, Piperacillin-Tazobactam and Clindamycin. We performed emergent operative wide excisional debridement of the affected tissue in the perineum. Post-operatively, a dedicated wound care team was consulted to assist in multimodal wound therapies, including collagenases, topical antimicrobials, and negative pressure wound therapies. Pre-operative stoma marking was completed prior to taking the patient for a diverting colostomy to protect the perineum from fecal incontinence and soilage of the wound bed.

After discharge, patients were treated at our outpatient wound care center where further advanced wound care techniques such as hyperbaric oxygen therapy were utilized with the aid of a nutritionist and physical therapist to aid in the healing process and prevention of future wounds, resulting in improved patient quality of life and decreased recurrence rates. Diverting colostomy was reversed after wound healing was complete.

With this method, we experienced minimal morbidity and mortality with one patient death and one patient requiring amputations of several distal phalanges secondary to vasopressor associated vasoconstriction. The remaining 25 patients recovered quickly and uneventfully with no loss of function.

Conclusion:
At our single institution study, early identification and diagnosis of Fournier's Gangrene (FG) was our primary objective. Secondary objectives included methods of efficient mobilization and proper utilization of resources to prevent the significant morbidity and mortality known to be caused from FG. Our third learning objective was how to effectively treat, heal, and prevent recurrence of wounds caused from excisional debridement of FG. Recurrence rates were zero after two year follow up. In conclusion we remark that survival can be improved in patients with Fournier's gangrene by this multidisciplinary approach.

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Interval Minimally Invasive Cholecystectomy for Severe Acute Cholecystitis

Jeremy Fridling MD, Jennifer Brewer MD, Ronald Gross MD, Stephanie Montgomery MD, Corrine Miller MD, Sarah Posillico MD, Elan Jeremitsky MD, Vijay Jayaraman MD, Thomas Russell Hill PA-C, Manuel Moutinho MD, Andrew Doben MD, Chasen Greig MD
University of Connecticut School of Medicine, Saint Francis Hospital and Medical Center

Introduction: Acute cholecystitis is a common surgical problem. Laparoscopic cholecystectomy (CCY) in the index admission has become the standard of care; however, recent evidence suggests a role for percutaneous drainage (PD) of the gallbladder as an initial approach in high-risk patients with severe acute cholecystitis. This treatment pathway remains incompletely evaluated with respect to timing and approach of interval CCY. We analyzed the outcomes of high-risk patients who underwent PD and interval minimally-invasive CCY for cholecystitis.

Method(s): We performed a retrospective chart review of patients undergoing either laparoscopic or robotic CCY after PD from January 2020 to June 2023. Demographic, clinical, and operative data were collected. Statistical analysis was performed using Excel.

Results: 29 high-risk patients underwent PD over the study period. 13 patients had laparoscopic CCY, and 16 patients had robotic CCY. The groups did not significantly differ in age, BMI, Charlson Comorbidity Index, or ASA. There were significantly more males in the laparoscopic group. Operative times and hospital length of stay were similar between the groups. The laparoscopic group had complications including open conversion with subtotal CCY (1), postoperative bleeding requiring transfusion (1), organ failure (1), and ICU admission (2). The robotic group had a single complication of postoperative ileus. There were no CBD injuries in either group.

Conclusion(s): Interval minimally invasive CCY after PD of the gallbladder for high-risk severe acute cholecystitis resulted in few operative and postoperative complications in our small series. The rate of open conversion or subtotal CCY was much lower than previous reports, and, notably, there were zero conversions or incomplete CCY in the robotic group. This pathway for management of severe cholecystitis with percutaneous drainage and interval surgery warrants further prospective study. *(table on next page)*

Table 1

	Laparoscopic CCY (13)	Robotic CCY (16)	p-value
Sex Male Female	 76.9% (10) 23.1% (3)	 43.8% (7) 56.2% (9)	 0.036
Mean Age (range)	67.8 (38-89)	69.5 (49-90)	0.38
BMI	26.9	27.7	0.33
Charlson Comorbidity Index	3.77	5.25	0.11
ASA	2.85	2.77	0.42

Table 2

	Laparoscopic CCY (13)	Robotic CCY (16)	p-value
Operative Time (min)	100.6	118.8	0.075
Hospital LOS (days)	1.19	0.81	0.18
Complication	Laparoscopic CCY (13)	Robotic CCY (16)	Total Event Rate (29)
Open Conversion or Subtotal CCY	7.7% (1)	0%	3.4%
CBD Injury	0%	0%	0%
Postoperative Ileus	0%	6.3% (1)	3.4%
Postoperative Bleeding (requiring transfusion)	7.7% (1)	0%	3.4%
Organ Failure	7.7% (1)	0%	3.4%
ICU Admission	15.4% (2)	0%	6.9%

Pediatric Surgery – Case Reports

Case Reports		
Brendan Stewart, MD	University of Connecticut School of Medicine	Adrenal Cortical Carcinoma With Associated IVC Thrombus in an Adolescent Patient: A Case Report
Elizabeth Hughes, MD		In vitro Testing of a Novel 4-in-1 Device to Treat Neonatal Esophageal Stricture

Adrenal cortical carcinoma with associated IVC thrombus in an adolescent patient: A case report

Brendan P. Stewart, MD[1], Kaitlyn M. Petitpas, BS[2], Maya Petashnick, MD[1], Jonathan D. Gates, MD, MBA, FACS[4], Christine M. Rader, MD[3], James Healy, MD, MHS[3]

[1]UConn General Surgery Residency Program, Farmington CT 06032

[2]UConn School of Medicine, Farmington CT 06032

[3]Connecticut Children's Medical Center, Hartford CT 06106

[4]Hartford Hospital, Hartford CT 06106

Introduction: There are many types of adrenal tumors, and when found in pediatric patients, there is a higher chance of malignancy. Prior case reports have demonstrated IVC thrombus associated with adrenal masses such as adrenal cortical carcinoma, paragangliomas, pheochromocytoma, Ewing sarcoma, adrenal leiomyosarcoma, and metastatic carcinomas. Nearly all adrenal masses with associated IVC thrombus occur in the adult population, and most have been confirmed through tissue cytology to be adrenal cortical carcinoma. We present a case of adrenal cortical carcinoma in a pediatric patient with an associated IVC thrombus.

Case Presentation: Our patient is a 14yo female with past medical history significant for morbid obesity (BMI 66.4 kg/m^2), type 2 diabetes, hyperlipidemia, vitamin D deficiency, and irregular menstruation presenting initially to our weight management program at Connecticut Children's Medical Center. The patient was without evidence of striae, round face, fat accumulation at her dorsocervical region, or bruised skin indicative of Cushing's syndrome on presentation. Work-up for etiologies of pediatric weight gain was significant for elevated cortisol and low DHEA-S. Low dose 1 mg dexamethasone suppression testing was performed and found cortisol level to be 15.8 mcg/dL. Due to the patient's weight, an extended two-day low dose dexamethasone test resulted in continued elevated cortisol to 17.2 mcg/dL, consistent with Cushing's syndrome. MRI revealed a right adrenal mass, 3.3cm at its largest diameter (Figure 1). CT scan performed to evaluate surrounding vasculature showed mass extension into the intra-hepatic IVC with a filling defect (Figure 2). MR-V demonstrated extension of IVC thrombus from the primary tumor in right adrenal gland to the level of hepatic veins. Cardiothoracic surgery, vascular surgery, pediatric general surgery, and pediatric anesthesia collaborated for adrenalectomy with thrombectomy via an open approach (Figure 3). The surgical subspecialists were involved due to the proximity to the heart and vascular invasion. Upon pathologic review, the tumor was determined to be adrenocortical carcinoma, inhibin positive, s100 and chromogranin negative.

Conclusion(s): Adrenal masses with associated IVC thrombus are rare entities, especially in the pediatric population. Thorough operative planning should include cross-sectional imaging to assess the full extent of mass and thrombus. A multi-disciplinary operative approach including general surgery, vascular surgery, cardiothoracic surgery, and pediatric anesthesia is essential in successful management of these patients, especially when there is close proximity to the heart and invasion of vasculature.

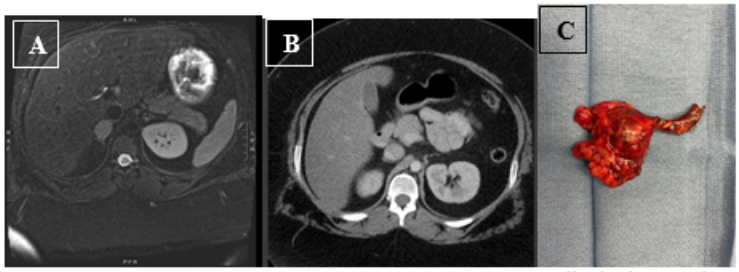

Figure 1: Adrenal Tumor imaging and operative findings. Panel A: MRI displaying R adrenal mass. **Panel B:** CT scan showing IVC Filling defect. **Panel C:** Adrenal gland with tumor specimen

In vitro Testing of a Novel 4-in-1 Device to Treat Neonatal Esophageal Stricture

Elizabeth J Hughes MD[1,2], Joanne Walker MS[1], Heather Wanczyk MS[1], Liisa Kuhn PhD[3], Christine Finck MD, FACS[1,2]
[1]Department of Pediatrics, University of Connecticut Health Center, Farmington, Connecticut
[2]Department of Surgery, Connecticut Children's Medical Center, Hartford, Connecticut
[3]Department of Biomedical Engineering, University of Connecticut Health Center, Farmington, Connecticut

Introduction: Esophageal atresia (EA) is a congenital defect where the proximal and distal ends of the esophagus fail to connect. Surgical repair may be complicated by postoperative anastomotic stricture, which occurs in 32-59% of cases. Current treatment involves serial balloon dilations, which requires multiple anesthesia events in neonates. To reduce the number of procedures, we developed a 4-in-1 device to perform multiple functions in the esophagus following repair of EA. This multi-tubular structure has 4 functions (Figure 1): delivery of enteral nutrition, stricture detection/balloon dilation, esophageal effluent aspiration, and delivery of topical drugs such as steroids or mitomycin C. After initial demonstration of functionality and general tolerability in a rabbit model, we sought to determine device compatibility with gastric and salivary fluids over time.

Methods: Benchtop testing of the 4-in-1 esophageal device was performed by submerging the balloon portion in rabbit gastric fluid (pH 3) for 1 week and simulated gastric fluid (pH 3-4) for 7 weeks, incubated at 37°C. As a control, a separate device was submerged in phosphate-buffered saline (PBS) at 37°C for 1 and 7 weeks. Each balloon dilator component was tested after 1 and 7 weeks by inflating to pressures between 6 and 8 ATM 7 times using a manometer. The same procedure was repeated using simulated salivary fluid (pH 5-6) at 1 and 7 weeks. Analysis was performed using student's t-test with significance set to $p \leq 0.05$.

Results: The balloon component of the device remained structurally and functionally intact over the course of experiments in both gastric and salivary fluids. At week 1 testing of the gastric fluid covered device, average balloon inflation pressure was 5.98 ATM and average diameter was 6.0 mm (typical diameter of the neonatal esophagus is 6 mm). For the salivary fluid covered device at week 1, average balloon inflation pressure was 7.68 ATM and average diameter was 6.3 mm. Average balloon pressures and diameters were similar at week 7 testing in both the gastric and salivary fluid covered devices, and there was no significant difference between parameters generated from the control device at week 7.

Conclusions: Preliminary studies with our novel 4-in-1 esophageal device to address esophageal stricture in neonates who undergo EA repair demonstrate stability of the material in gastric and salivary fluids over 7 weeks, as well as reproducible functionality of the balloon dilator component. Additional work will be done to optimize balloon dimensions and to evaluate for tube kinking, appropriate viscosity of tube feeds and medications, and integrity of the tubing connections over 30 days at body temperature. Next, we will move to *in vivo* testing of device multifunctionality in a rabbit model. This device affords an impactful reduction in the number of procedures requiring anesthesia during esophageal healing in the neonate. Use of this device for treatment, monitoring, and ultimately prevention of esophageal stricture may be widely applicable across many disease states in the future.

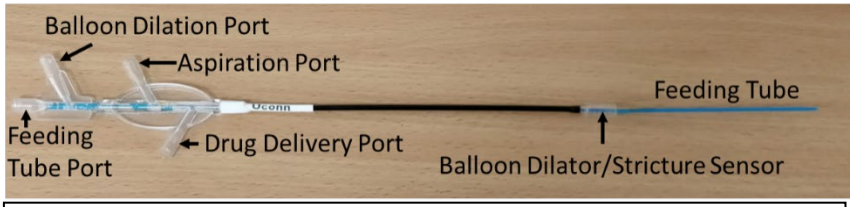

Figure 1. Complete 4-in-1 esophageal tube. This device would be placed in a neonatal patient using radiographic guidance and would allow for immediate feeding following EA repair surgery, as well as fluid sampling, drug delivery, and serial dilations- all without requiring additional anesthesia.