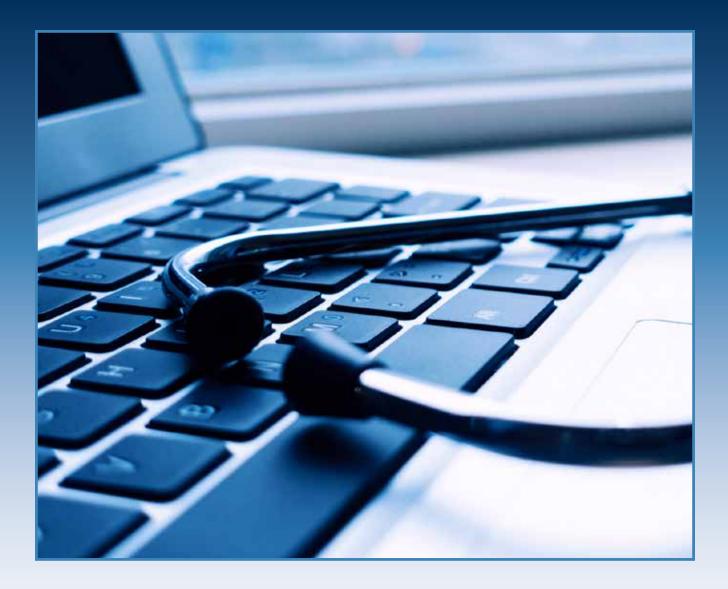
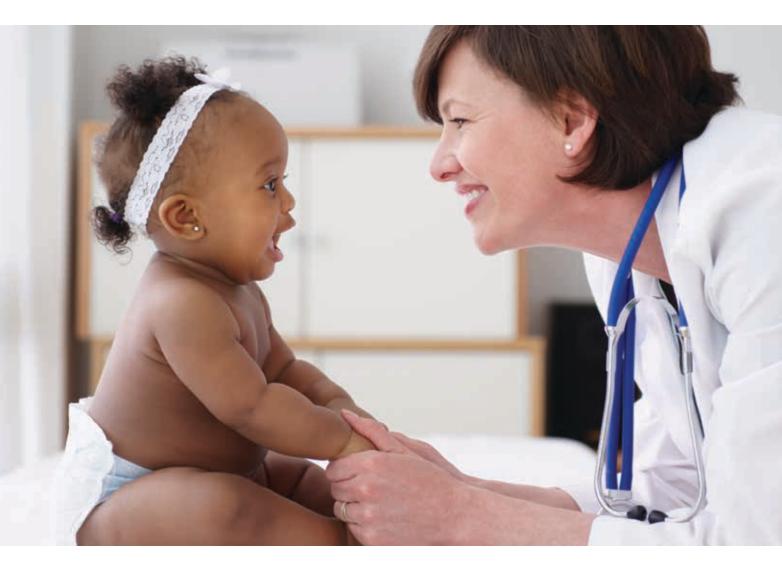
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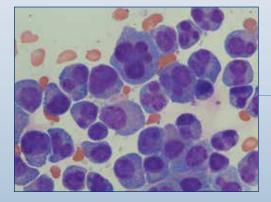
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## Appendicocecal Loop Urinary Diversion in a Transplant Kidney: Case Report, Literature Review

APARNA ASHOK, MEng, MD; FAIZAN MUNSHI, MD; DANIELLA PORTAL, BS; BORIVOJ GOLIJANIN, BS; PAUL MORRISSEY, MD; ADENA OSBAND, MD; KENNON MILLER, MD; DICKEN S. C. KO, MD, FRCSC

#### ABSTRACT

Urinary diversion in renal transplant patients can take a variety of forms - bladder augmentation, continent cutaneous pouch, or intestinal conduits, to name a few. Herein, we present a unique case of an appendicocecal urinary diversion in a patient with history of end stage renal disease, pelvic radiation, and complex surgical history who underwent deceased-donor renal transplantation. During the renal transplant, the transplant ureterovesical anastomosis could not be performed due to inherent anatomical hindrances. A temporary modified cutaneous ureterostomy using a single-J stent was therefore used for drainage of the transplant kidney. Given that the cutaneous ureterostomy was not a durable, long-term option, we sought to develop a creative surgical solution. This report presents a unique case of urinary diversion post renal transplant and reviews the literature of renal transplantation in patients with anatomical abnormalities.

**KEYWORDS:** renal transplant, urinary diversion, ureter, appendicocecal loop

#### INTRODUCTION

In the United States, more than 500,000 adults live with end stage renal disease (ESRD).<sup>1</sup> Renal allograft transplantation is the gold standard therapeutic option for these patients. Approximately 6% of patients undergoing renal transplant have lower urinary tract (LUT) abnormalities, and 15% of patients have secondary LUT anatomical abnormalities.<sup>2</sup> The native bladders in these patients are often unsuitable for transplantation, due to loss of detrusor muscle and bladder compliance from infrequent bladder cycling and underlying medical comorbidities, resulting in a unique operative challenge for renal transplant surgeons. Given that graft survival can be compromised by a high-pressure non-compliant bladder, urinary diversion or augmentation cystoplasty either prior to or following transplantation, are methods to ensure long-term transplant success.3-5 In genitourinary reconstructive surgery, the appendix has been used for over 100 years as an interposing segment.6 In pediatric renal transplantation specifically, the appendix has been used as a ureteral substitute in patients with extended ureteral strictures.<sup>7,8</sup>

We present here a unique case of a 71-year-old male patient with ESRD and history of pelvic radiation with atrophic bladder who underwent renal transplantation. Due to lack of an adequate urinary reservoir at the time of transplant, a cutaneous ureterostomy was initially created. A urinary diversion in the form of an appendicocecal loop was subsequently created to overcome a shortened allograft ureter and an end-stage bladder. This, to our knowledge, is the first record of such a procedure.

#### PATIENT BACKGROUND AND INITIAL RENAL TRANSPLANT

The patient was a 71-year-old man with past medical history of left colon cancer status post radiation and colectomy with end colostomy, gastroesophageal reflux diseases, restless leg syndrome, deep vein thrombosis/pulmonary embolus, ESRD who was evaluated for renal transplantation. At the time of his deceased-donor kidney transplantation (DDKT), the patient's native non-functioning bladder was noted to be contracted with a 20-cc capacity and obliteration of bilateral native distal ureteral lumina. These findings made for an unsuccessful attempt at ureteroureteral anastomosis. The transplant ureter, therefore, was secured to the posterior rectus fascia and a single-J stent was placed percutaneously via the transplant ureter into the transplant renal pelvis. The stent was secured to the skin and an ostomy appliance was placed over this modified cutaneous ureterostomy. The tract epithelialized post-operatively, but the patient had delayed graft function which is defined as increase in creatinine within 48 hours after transplant or acute kidney injury (AKI) necessitating dialysis within one week after transplant.9 After studies suggesting post-obstructive AKI and acute tubular necrosis, the patient underwent placement of percutaneous nephrostomy tube into the transplant kidney. He improved gradually post-operatively and recovered urine output. His creatinine stabilized several weeks later to 3.1 mg/dL.

Four weeks post-operatively, the patient presented to the emergency room with decreased urine output, which raised concern for ischemia of the ureterostomy, urinary tract infection, and dehydration. Physical exam revealed drainage of urine as expected from the ureterostomy. The patient underwent percutaneous nephrostomy exchange and received IV antibiotics and fluids for the infection. Renal



ultrasound demonstrated preserved vascular flow, trace perinephric fluid, and no significant hydronephrosis. The patient was thereafter discharged home.

The patient was followed closely in the transplant clinic, by both nephrology and urology. His creatinine continued to improve, stabilizing at 2.15 mg/dL, and urine output remained consistent. Once he was medically optimized, the patient was recommended for exploratory laparotomy, ureterostomy with possible buccal mucosal graft, possible ileal loop creation, and all indicated procedures.

#### APPENDICOCECAL LOOP URINARY DIVERSION

The patient underwent an exploratory laparotomy that revealed extensive intraabdominal adhesions. After the adhesions were taken down carefully, the right colon was identified from the ileocecal junction to the hepatic flexure. The cecum was identified, along with an attached long appendix, in the right lower quadrant with robust mesenteric blood supply. The transplant kidney was palpable in the extraperitoneal space, just inferolateral to the cecum. The transplant ureter was identified by following the ureteral stent from the cutaneous ureterostomy to the posterior fascia. There was limited length of the transplant ureter. Given the proximity of the ureter to the distal aspect of the appendix, the decision was made to use to appendix and cecum for the ureteral anastomosis and the urinary conduit, respectively.

Transplant ureterolysis was performed to mobilize the ureter off the posterior fascia. The distal end of the ureter was excised sharply, and the ureter was spatulated posteriorly approximately 1.5 cm with Potts' scissors. Next, appendiceal and proximal cecal mesenteric blood supply was inspected and confirmed to be appropriate with transillumination. A mesenteric window in between the vessels was made using a right-angle clamp. A vessel loop was passed through the mesenteric window, after which the window was carefully widened to fit the stapler. The proximal cecum with the attached appendix was divided just inferior to the ileocecal valve using an endoGIA<sup>®</sup> 80 mm stapler load. The staple line was inspected and found to be hemostatic on both sides.

To construct the appendicocecal conduit (Figure 1), the distal end of the cecum was sharply excised with scissors and the distal end of the appendix was sharply excised with scissors. After covering the abdominal opening with towels, the conduit was irrigated with warmed saline to remove the succus. The appendix was spatulated posteriorly approximately 1.5 cm with Potts' scissors. A single J 6x26 stent was passed through the conduit. A sensor wire was then passed through the stent to straighten it and the wire was passed through the transplant ureter to the renal pelvis of the transplant kidney. The stent was passed over the wire and positioned, after which the wire was removed. The stent was secured to the cecal mucosa of the conduit with a 3-0

Figure 1. View of the appendicocecal conduit and surrounding anatomy.
[A] Prior transplant ureterostomy at posterior fascia; [B] Final ureteral stent; [C] Appendicoureteral anastomosis; [D] Appendicocecal conduit;
[E] Cecal urostomy.

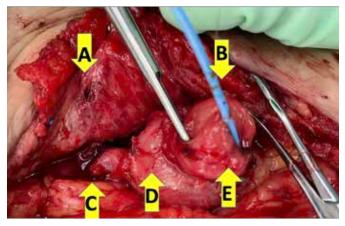
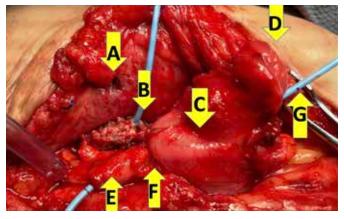


Figure 2. Closer view of the appendicocecal conduit with visible appendicocecal junction and the final ureteral stent in the appendix. **[A]** Prior transplant ureterostomy at posterior fascia; **[B]** Transplant ureter with previously placed ureteral stent; **[C]** Cecal conduit; **[D]** Cecal urostomy; **[E]** Appendix with final ureteral stent; **[F]** Appendicocecal junction; **[G]** Final ureteral stent.



chromic simple interrupted suture. Next, we anastomosed the distal end of the appendix to the transplant ureter using 5-0 PDS sutures in an interrupted fashion from the apex on each side, taking care to avoid the stent (**Figure 2**). The site of the marked right lower quadrant ostomy was incised with a #15 blade to create a circular opening for the urostomy. We made a cruciate fascial incision wide enough to pass two fingers through. A Babcock clamp was passed through the fascial opening and into the abdomen. The distal end of the appendicocecal conduit was grasped and pulled through the abdominal incision with the stent in place. The urostomy was matured to the skin with 2-0 Vicryl sutures in four quadrants in a Brooke fashion and additional 4-0 chromic interrupted sutures were placed through the mucosa and dermis



to create a protuberant viable rosebud urostomy. The stent was flushed, and urine output was noted from the conduit. The abdomen was closed in the standard fashion. A stomal appliance was placed around the urostomy and the ureteral stent was placed into the urostomy appliance.

#### **POST-OPERATIVE COURSE**

The patient progressed well post-operatively and had consistent return of bowel function 6 days after surgery. He was restarted on immunosuppression and had excellent urine output throughout his recovery. The patient's creatinine improved from his pre-operative baseline of 2.15 mg/ dL to 1.7 mg/dL. Once he was stable from a medical and surgical standpoint, he was discharged to a rehabilitation facility for short-term physical therapy. His capped transplant percutaneous nephrostomy was removed 4 weeks later post-operatively and his ureteral stent was removed 6 weeks post-operatively. The patient thereafter continued to have stable graft function. There were no reported anatomic complications in this time.

#### **REVIEW OF LITERATURE AND DISCUSSION**

Patients with anatomically abnormal or dysfunctional lower urinary tracts (LUT) pose distinct challenges for renal transplant and reconstructive surgeons. Implantation of the transplant ureter into a non-compliant bladder should be avoided due to the significant risk of graft loss due to high-pressure urinary storage. In transplant patients with end-stage bladders, urinary diversion options include bladder augmentation, continent cutaneous pouches and intestinal conduits.<sup>10,11</sup> All these techniques have unique advantages and disadvantages that should be considered on a case-bycase basis depending on patient factors. Additionally, timing of a urinary diversion procedure, prior to, during, or after transplant, is also important to graft success. In transplant patients, a key aspect of pre-operative evaluation involves determining which patients will need staged versus simultaneous urinary reconstruction to achieve a structurally and functionally unobstructed, low-pressure urinary tract. This involves a thorough history to establish a timeline of LUT dysfunction in relation to development of ESRD. Furthermore, oliguria and eventual anuria in ESRD can result in a poorly compliant bladder due to the absence of routine autonomous bladder cycling with storage and emptying. Extensive urodynamic studies in patients who have undergone renal transplant defined inadequate bladder cycling as less than 300 mL urine cycled daily.12 It is also essential to distinguish defunctionalized bladders with recoverable function from those with end-stage bladders due to pathologic contracture from extensive fibrosis.

In addition to bladder function, reflux of urine into the upper tracts is also important to consider, voiding cystourethrogram (VCUG), more commonly performed in the pediatric pre-transplant population, has been suggested as part of the standard workup for adult transplant candidates. The high likelihood (85.3–97.5%) of finding clinically insignificant reflux has eschewed the cost-effectiveness of VCUG for general transplant candidates.<sup>13,14</sup> However in patients with evidence of end-stage bladders and LUT abnormalities, VCUG and urodynamics demonstrated abnormal findings in 45% of patients.<sup>12</sup>

Lastly, a patient compliance assessment is key to ensuring transplant success in the setting of a urinary diversion. The transplant team must ensure patients have the education and capability to manage their diverted urinary systems. Improper or inadequate management of ostomy drainage or intermittent catheterizations can result in a variety of complications ranging from UTIs to graft failure, which can cause significant morbidity and mortality.<sup>15</sup>

One of the main urologic considerations in renal transplant is the transition from upper to lower urinary tract. In patients with normal anatomy, the donor ureter is anastomosed to the native bladder via a ureteroneocystotomy. In our patient, the bladder was contracted and retropubic, making it unfavorable and difficult to access for transplant ureter implantation. We therefore anastomosed the transplant ureter to the ipsilateral native ureter to provide the needed length to access the bladder. After completion of the ureteroureterostomy, no urine outflow from the native ureter into the bladder was observed. Furthermore, attempted intraoperative cystoscopy revealed obliterated bladder mucosa and no identifiable ureteral orifices. Due to a short transplant ureteral length, the ureter could only be brought up to the level of the anterior rectus fascia, where it was secured after placement of an externalized single J ureteral stent which served to drain the transplant kidney. While transplant cutaneous ureterostomy has fallen out of favor due to the high ureteral stricture rate, stomal stenosis, and infectious complications, at the initial time of surgery for our patient it was the only feasible option to pursue until the ischemic reperfusion injury of the allograft had resolved.<sup>16</sup> We also wanted to ensure that the patient passed the initial phases of recovery for the kidney transplant under standard immunosuppression protocols. As detailed above at the time of urinary diversion, patient-specific anatomic characteristics which included dense adhesions requiring extensive lysis, prior pelvic radiation, limited length of the transplant ureter, placement of the transplant kidney in the right lower quadrant, and an appendix with considerable length, led to the decision to use the appendix and cecum for the ureteral anastomosis and urinary conduit, respectively. Our unique use of an appendicocecal loop for urinary diversion in a transplant patient was accomplished by utilizing a key tenet of reconstructive urology: use viable, easily available, well-vascularized, and anatomically practical tissue in a tension-free manner that avoids any significant functional compromise



to donor and recipient sites. Use of the appendix has several benefits. The appendix harbors gut-associated lymphatic tissue (GALT) and commensal microbes, which could be protective against urinary tract infection.<sup>17,19</sup> It can also lower overall pressure in the conduit and provide a continence mechanism due to length.<sup>18</sup> Disadvantages include similar metabolic effects (dehydration and B12 malabsorption) and serum electrolyte abnormalities (hypokalemic, hyperchloremic, metabolic acidosis) as ileal and colonic conduits.

Although the literature on the subject is scant, long-term follow-up of renal transplant patients with appendicocecal junction urinary diversions may require surveillance for colonic and gastric metabolic effects due to inherent tissue types. The 5-year graft survival for any type of urinary diversion in renal transplantation is between 63% and 78%, amongst both pediatric and adult population, with limited data including long-term follow up at 15 years reporting 69% graft survival rate.<sup>4,5</sup> Additionally, while UTI is noted in approximately 65% of patients with urinary diversion, interestingly, no graft loss due to infection has been noted. Furthermore, graft survival has been reported to be comparable in patients with and without urinary diversions.<sup>10,20-22</sup> Chronic bacteriuria is frequently encountered in diverted patients, however no effect on transplant survival is noted despite the colonization.<sup>16,23-25</sup> This observation allowed for a shift towards less aggressive treatment of asymptomatic bacteriuria and greater acceptance of urinary tract reconstruction, which was historically viewed with caution due to the perceived risks of sepsis.26 The risk of UTI (24%) and pyelonephritis (13%) in post-transplant patients with urinary diversions, in fact, remains reasonably low and has not proven to translate into worse patient outcomes.2,27-29

Complications specific to lower urinary tract reconstruction include stomal stenosis, prolapse of the conduit, fistula, dehiscence, urine leak, and metabolic abnormalities. Physical changes of the reconstructed urinary tract function are often symptomatic and early indicators for examination and even revision. These surgical complications can occur in the long- or short-term and should be monitored for regularly. Metabolic acidosis, a well-known phenomenon of ileal or colonic intestinal diversion due to excretion of bicarbonate and reabsorption of urinary solutes, such as chloride, by the mucosa, is more nuanced.<sup>30-35</sup> While transplant literature has focused on graft and infectious outcomes, the inherent incidence of metabolic derangements in the ESRD population may cause transplant teams to overlook the sequelae of reabsorption in transplant patients with reconstructed lower urinary tracts. Close follow up, electrolyte repletion, and urine and blood pH measurement are therefore important throughout the post-transplant course of these patients' lives. Monitoring both blood and urine pH allows to establish the type of acidemia in patients with metabolic acidosis. Lastly while the literature is limited on the incidence of secondary malignancy of intestinal segments after urinary diversion in the transplant population, transplant patients remain at an uncertain risk for malignancy given their immunocompromised state. While no consensus has been reached on surveillance, an appropriate level of concern should be maintained with interval endoscopy and surveillance imaging as clinically indicated.

#### CONCLUSION

ESRD is a life-limiting diagnosis that can be successfully mitigated by renal transplantation. While the main focus of transplant literature has been graft function and complications, it is important to consider urinary drainage and storage. Lower urinary tract evaluation prior to transplantation is essential to the longevity of the patient. In patients with dysfunctional or incompetent lower urinary tracts, reconstruction and augmentation restore functionality.

Our patient not only had insufficient bladder capacity, but also had multiple prior surgeries and pelvic radiation that precluded traditional reconstruction with an ileal or a colonic segment. We therefore had to develop a creative solution with accessible tissue to provide reliable egress for the urine from the transplant kidney. Given the location of the graft in the right lower quadrant, we identified adjacent the appendix and cecum as favorable tissues for incontinent diversion of urine. This is the first documented use of an appendicocecal conduit with a transplant kidney. The appendix segment served to augment the transplant ureter length and to provide a natural transition to a cecal reservoir and urostomy. The patient's transplant function improved significantly after definitive lower urinary tract reconstruction, and he has not had any major complications in the short term. While the long-term durability of our appendicocecal loop urinary diversion remains to be seen, we hope to offer an example of how reconstructive urologic techniques can supplement renal transplantation and provide lasting graft function for ESRD patients.

#### References

- 1. Benjamin O, Lappin SL. End-Stage Renal Disease. StatPearls. Treasure Island (FL)2022.
- 2. Hatch DA. Kidney transplantation in patients with an abnormal lower urinary tract. Urol Clin North Am 1994;21:311-20.
- Kocot A, Spahn M, Loeser A, Lopau K, Gerharz EW, Riedmiller H. Long-term results of a staged approach: continent urinary diversion in preparation for renal transplantation. J Urol 2010;184:2038-42.
- 4. Rigamonti W, Capizzi A, Zacchello G, et al. Kidney transplantation into bladder augmentation or urinary diversion: long-term results. Transplantation 2005;80:1435-40.
- Surange RS, Johnson RW, Tavakoli A, et al. Kidney transplantation into an ileal conduit: a single center experience of 59 cases. J Urol 2003;170:1727-30.
- O'Rourke TK, Gn M, Patel HV, et al. The Urologist and the Appendix: A Review of Appendiceal Use in Genitourinary Reconstructive Surgery. Urology 2022;159:10-5.



- 7. Corbetta JP, Weller S, Bortagaray JI, et al. Ureteral replacement with appendix in pediatric renal transplantation. Pediatric Transplantation 2012;16:235-8.
- Adani GL, Pravisani R, Baccarani U, et al. Extended Ureteral Stricture Corrected With Appendiceal Replacement in a Kidney Transplant Recipient. Urology 2015;86:840-3.
- 9. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. Am J Transplant 2011;11:2279-96.
- Eltemamy M, Crane A, Goldfarb DA. Urinary Diversion in Renal Transplantation. Urol Clin North Am 2018;45:113-21.
- Altan M, Bozaci AC, Asci A, Dogan HS, Tekgul S. Autoaugmentation: A Feasible Option before Ileal Augmentation in Selected Cases. Eur J Pediatr Surg 2022;32:370-5.
- 12. Errando C, Batista JE, Caparros J, Vicente J, Arano P. Urodynamic evaluation and management prior to renal transplantation. Eur Urol 2000;38:415-8.
- Shandera KC, Rozanski TA, Jaffers G. The necessity of voiding cystourethrogram in the pretransplant urologic evaluation. Urology 1996;47:198-200.
- 14. Glazier DB, Whang MIS, Geffner SR, et al. EVALUATION OF VOIDING CYSTOURETHROGRAPHY PRIOR TO RENAL TRANSPLANTATION1. Transplantation 1996;62.
- O'Flynn SK. Care of the stoma: complications and treatments. Br J Community Nurs 2018;23:382-7.
- Prieto M, Sierra M, de Francisco AL, et al. Long-term outcome in renal transplantation with terminal cutaneous ureterostomy. Br J Urol 1993;72:844-7.
- Laurin M, Everett ML, Parker W. The Cecal Appendix: One More Immune Component With a Function Disturbed By Post-Industrial Culture. The Anatomical Record 2011;294:567-79.
- English SF, Pisters LL, McGuire EJ. The use of the appendix as a continent catheterizable stoma. J Urol 1998;159:747-9.
- Randal Bollinger R, Barbas AS, Bush EL, Lin SS, Parker W. Biofilms in the large bowel suggest an apparent function of the human vermiform appendix. Journal of Theoretical Biology 2007;249:826-31.
- 20. Hatch DA, Belitsky P, Barry JM, et al. Fate of renal allografts transplanted in patients with urinary diversion. Transplantation 1993;56:838-42.
- 21. Warholm C, Berglund J, Andersson J, Tydén G. Renal transplantation in patients with urinary diversion: a case-control study. Nephrology Dialysis Transplantation 1999;14:2937-40.
- 22. Fournier R, Codas-Duarte R, Daily T, Martin X, Badet L, Fassi-Fehri H. Long-term kidney transplant survival in patients with continent urinary diversion. International Journal of Urology 2017;24:787-92.
- 23. Shigemura K, Tanaka K, Arakawa S, Miyake H, Fujisawa M. Postoperative bacteriuria, pyuria and urinary tract infection in patients with an orthotopic sigmoid colon neobladder replacement. J Antibiot (Tokyo) 2014;67:143-5.
- Dawahra M, Martin X, Tajra LC, et al. Renal transplantation using continent urinary diversion: Long-term follow-up. Transplantation Proceedings 1997;29:159-60.
- Tsai SY, Chang CY, Piercey K, Kapoor A. Terminal loop cutaneous ureterostomy in renal transplantation: an under utilized urinary diversion technique. J Urol 2005;174:1906-9; discussion 9.
- Alfrey EJ, Conley SB, Tanney DC, et al. Use of an augmented urinary bladder can be catastrophic in renal transplantation. Transplant Proc 1997;29:154-5.
- Chaykovska L, Deger S, Wille A, et al. Kidney transplantation into urinary conduits with ureteroureterostomy between transplant and native ureter: single-center experience. Urology 2009;73:380-5.
- Parada B, Figueiredo A, Mota A, Furtado A. Renal transplantation in patients with lower urinary tract dysfunction. Transplant Proc 2003;35:1089-90.

- 29. Sullivan ME, Reynard JM, Cranston DW. Renal transplantation into the abnormal lower urinary tract. BJU Int 2003;92:510-5.
- 30. ajima S, Nakanishi Y, Matsumoto S, Ookubo N, Tanabe K, Masuda H. Hyperchloremic Metabolic Acidosis with Hyperglycemic Hyperosmolar Syndrome after Robot-Assisted Radical Cystoprostatectomy with Ileal Conduit Urinary Diversion: A Case Report. Case Rep Oncol 2021;14:1460-5.
- 31. Dsouza LB, Hussein RJH. Urinary Diversion and Metabolic Acidosis: A Case Report. Cureus 2021;13:e14638.
- 32. Domínguez García A, Muñoz Rodríguez J, Prats López J, et al. Metabolic acidosis after ileal urinary diversion and radical cystectomy. Do we know as much as we think we do? A systematic review. Actas Urol Esp (Engl Ed) 2022.
- Stein R, Rubenwolf P. Metabolic consequences after urinary diversion. Front Pediatr 2014;2:15.
- 34. Roth JD, Koch MO. Metabolic and Nutritional Consequences of Urinary Diversion Using Intestinal Segments to Reconstruct the Urinary Tract. Urol Clin North Am 2018;45:19-24.
- Stein R, Hohenfellner M, Pahernik S, Roth S, Thüroff JW, Rübben H. Urinary diversion--approaches and consequences. Dtsch Arztebl Int 2012;109:617-22.

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## Cardiogenic Rhinorrhea: Evidence for an Unrecognized Heart Failure Symptom

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#### ABSTRACT

There have been anecdotal observations of rhinorrhea as an isolated symptom indicating volume overload and impending congestive heart failure (CHF). We present a case of apparent cardiogenic rhinorrhea presaging acute systolic CHF, with hemodynamics supported by thoracic impedance data (Medtronic OptiVol 2.0).

**KEYWORDS:** cardiogenic rhinorrhea, acute heart failure, intrathoracic impedance, hypervolemia

#### BACKGROUND

With large numbers of hospitalizations due to congestive heart failure (CHF), early identification and interventions become increasingly necessary. Understanding and recognition of the signs and symptoms portending to volume overload can allow a physician to provide care early and potentially prevent hospitalization. Rhinorrhea in the setting of CHF exacerbation has yet to be considered a clinically relevant symptom, despite anecdotal observations that have been made over the years.<sup>1,2</sup> In this case, we observed a direct association between a patient experiencing new onset rhinorrhea in concordance with changes in thoracic impedance and volume overload. This was followed by a CHF exacerbation episode and hospitalization, thus suggesting idiopathic rhinorrhea as a sign of volume overload.

#### **CASE REPORT**

A 77-year-old woman presented to the emergency department with acute onset of increased dyspnea and was noted to be in congestive heart failure. This patient has a history of systolic heart failure, with non-ischemic cardiomyopathy and ejection fraction of 20% as measured by echocardiogram. She had undergone biventricular intracardiac device implantation (Medtronic Claria MRI Quad CRT-D) and had mild obstructive coronary artery disease (50% stenosis of LAD by 2013 heart catheterization), stage III CKD, hypertension, depression, and GERD. Preceding her presentation, she had felt no other symptoms including orthopnea, PND, edema, weight change, dyspnea on bending or changes in diet. The only prodromal symptom that was noted was anterior as well as posterior rhinorrhea for the past 2–3 days. On exam, an audible S4 was heard and JVP was elevated, without any signs of peripheral edema. Lungs demonstrated bibasilar crackles. At presentation, she was afebrile, tachycardic without chest pain and normotensive. Her oxygen saturation on room air was 84% that increased to 100% upon administration of 2 liters of oxygen via nasal cannula. Relevant labs showed no electrolyte abnormalities, stable elevated creatinine, and BNP elevated to 505 pg/mL. There were no signs or symptoms of an upper respiratory tract infection, sinusitis or allergic rhinitis. Procalcitonin was negative and a nasal swab PCR was negative for COVID-19. She had no prior history of allergic or vasomotor rhinitis. IV diuresis was initiated.

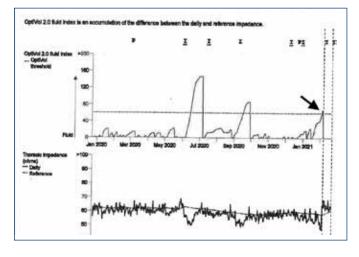
Initial chest X-ray (Figure 1) taken at presentation to the ED showed cardiomegaly that was more prominent when compared to a previous study. A left-sided triple lead implantable cardiac device was noted with leads terminating in appropriate positions. Broncho-vascular markings were blurred suggesting pulmonary edema with small bilateral pleural effusions. During the patient's hospitalization, her intrathoracic impedance and volume status changes were assessed through interrogation of OptiVol 2.0 parameters on

**Figure 1.** Chest X-ray taken upon initial patient presentation. Biventricular Pacemaker-Defibrillator device (Medtronic Claria MRI Quad CRT-D) is visible and intrathoracic impedance monitor.





**Figure 2.** OptiVol 2.0 hemodynamics: three separate episodes of clinical CHF are represented on the Optivol data, two of which were prior to the presenting episode, represented by the arrow.



her Biventricular Pacemaker-Defibrillator device (Medtronic Claria MRI Quad CRT-D). Four days prior to admission, the patient's OptiVol 2.0 Fluid Index was 0. The next day it raised to 30 and on the day of admission peaked at 70, which is above the threshold indicative of volume overload (**Figure 2**).

The patient was given IV furosemide for diuresis and was able to wean off of supplemental oxygen. The patient was discharged after two days with her medication reconciled and a planned follow-up. Two days following discharge, the patient's rhinorrhea had completely resolved and her ICD measured a fluid index return to baseline of 0.

At 2-month follow-up, the patient remains free of rhinorrhea and free of all decompensated CHF symptoms, with stable Class 1 CHF. Optivol 2.0 thoracic impedance parameters remain within normal limits.

#### DISCUSSION

It is estimated that more than 1 million hospital admissions in America are directly related to congestive heart failure.<sup>3</sup> Patient education of the earliest signs and symptoms of impending exacerbation of heart failure is an important tool employed by practicing physicians in the prevention of hospital admission and readmission. Early identification and intervention is increasingly necessary, as hospital admissions account for the majority of the direct cost burden for patients with heart failure.4 Traditional manifestations of volume overload such as weight gain, peripheral edema, orthopnea, paroxysmal nocturnal dyspnea, and abdominal bloating remain essential for its early recognition. Recent identification of a novel symptom, shortness of breath bending (termed bendopnea<sup>5</sup> or flexo-dyspnea),<sup>6</sup> has also been shown to correlate well with changes in patient hemodynamics and impending CHF exacerbation. In this case report, we present a patient whose impending exacerbation was preceded by a newly characterized clinical sign, which we propose terming "cardiogenic rhinorrhea."

Anecdotes exist positing the relationship between the onset of anterior rhinorrhea ("runny nose") and/or posterior rhinorrhea ("post nasal drip") as a preceding symptom to heart failure exacerbation in some patients, which can completely resolve with IV diuresis and appropriate CHF treatment.<sup>1,2</sup> This manuscript is the first, to our knowledge, to provide hemodynamic evidence suggesting the associated onset of rhinorrhea as a clinical correlate for volume overload and impending exacerbation of CHF.

We can only speculate on a possible mechanism for this association. Peripheral and generalized edema in CHF is caused by disordered intravascular volume control, in which there is disproportionate activation of vasoconstrictor-sodium retaining systems, along with failure of vasodilatory natriuretic factors, resulting in excessive salt and water balance.7 This leads to an increase in capillary pressure,8 causing movement of fluid from the intravascular space to the interstitium, with the net result of expanding extracellular volume as clinical edema.9 It is feasible that a similar process causes CHF to sometimes manifest as rhinorrhea, in which an expansion of fluid volume in subepithelial capillary beds of the nasopharynx leads to fluid dripping from the nose.<sup>10</sup> Autonomic dysfunction also plays a role in the pathophysiology of CHF<sup>7</sup> as well as that of nonallergic rhinitis and rhinitis of the elderly.<sup>11</sup>

The OptiVol device is able to indirectly measure increases in lung fluid congestion by sensing a decrease in intrathoracic impedance. Measurements are taken throughout the day and referenced to the baseline measured upon initial placement of the device. OptiVol 2.0 has been shown in multiple trials to be a highly sensitive measure for elevated LV volume and filling pressures.<sup>12</sup> Increases in OptiVol 2.0 index are correlated with increases in Pulmonary Capillary Wedge Pressure (PCWP), fluid balance, and NT-pro BNP.13,14 Measurements of reduced impedance (increased OptiVol 2.0 fluid index) typically precede symptom onset by multiple days.15 There are two earlier episodes of clinical CHF represented on the Optivol data, during which Optivol index rose to an even higher level than it did during the present case, (155 and 95) (Figure 2). Clinically, these episodes involved more florid symptoms of CHF, during which the patient experienced rhinorrhea in addition to more traditional CHF symptoms, including orthopnea and weight gain. The episode of CHF documented in this case report was subjectively milder, and the only prodrome symptom was rhinorrhea.

Rhinorrhea is an extremely common and bothersome medical condition. The prevalence of non-allergic rhinitis in the United States is estimated at 19 million.<sup>11</sup> The cause of most cases of non-allergic rhinorrhea is unknown.<sup>16</sup> The prevalence of CHF is expected to increase by 25% over the next 10 years, with a particularly large increase in the



incidence of heart failure with preserved left ventricular function (HFpEF).<sup>17,18</sup> Asymptomatic diastolic dysfunction, a precursor to HFpEF, is characterized by elevated left ventricular filling pressures, and is highly predictive of the development of CHF.<sup>17</sup> We hypothesize that many cases of "asymptomatic" diastolic dysfunction are not truly devoid of symptoms. It is feasible that there is crossover between these two common conditions, and that the recognition and further investigation of cardiogenic rhinorrhea may have a significant impact on the recognition, prevention, and treatment of CHF.

#### CONCLUSIONS

Further clinical studies utilizing chronic hemodynamic monitoring such as Cardiomems or others will be useful to further characterize the role of traditional as well as novel symptoms of decompensated CHF, enhancing the early recognition of CHF and further reducing unnecessary hospitalizations.

#### References

- 1. Brandon N. Characterization of a novel symptom of advanced heart failure: bendopnea. JACC Heart Fail 2014 Oct;2(5):540.
- Personal Communication, Mandeep Mehra, MD, Medical Director, Brigham and Women's Heart and Vascular Center, June, 2013. Dr. Mehra discussed his experiences with patients undergoing heart transplantation for advanced heart failure, after which their chronic rhinitis resolved, potentially due to resolution of their CHF.
- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, et al. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. Circulation 2016;133:e38–60.
- Urbich M, Globe G, Pantiri K, Heisen M, Bennison C, Wirtz HS, Di Tanna GL. A Systematic Review of Medical Costs Associated with Heart Failure in the USA (2014–2020). Pharmaco Economics 38, 1219–36.
- Thibodeau JT, Turer AT, Gualano SK, Ayers CR, Velez-Martinez M, Mishkin JD, Patel PC, Mammen PP, Markham DW, Levine BD, Drazner MH. Characterization of a novel symptom of advanced heart failure: bendopnea. JACC Heart Fail 2014;2(1):24-31.
- Brandon N, Mehra MR. «"Flexo-dyspnea": a novel clinical observation in the heart failure syndrome". J Heart Lung Transplant 2013;32:844.
- Abassi Z, Khoury EE, Karram T, Aronson D. Edema formation in congestive heart failure and the underlying mechanisms. Front Cardiovasc Med 2022; 9:933215.
- Crandall ED, Staub NC, Goldberg HS, Effros RM. Recent developments in pulmonary edema. Ann Intern Med 1983;99:808.
- 9. Reed RK, Rubin K. Transcapillary exchange: role and importance of the interstitial fluid pressure and the extracellular matrix. Cardiovasc Res 2010; 87:211.
- 10. Sin B, Togias A. Pathophysiology of allergic and nonallergic rhinitis. Proc Am Thorac Soc Vol 8.pp106-114, 2011.
- Liva GA, Karatzanis AD, Prokopakis EP. Review of rhinitis: classification, types, pathophysiology. J Clin Med 2021;10:3183.

- Yang XW, Hua W, Ding LG, Wang J, Zheng LH, Li CQ, Liu ZM, Chen KP, Zhang S. OptiVol fluid index predicts acute decompensation of heart failure with a high rate of unexplained events. J Geriatr Cardiol 2013;10(3):253-57.
- Wang L, Lahtinen S, Lentz L, Rakow N, Kaszas C, Ruetz L, Stylos L, Olson WH. Feasibility of using an implantable system to measure thoracic congestion in an ambulatory chronic heart failure canine model. Pacing Clin Electrophysiol 2005 May;28(5):404-11.
- Lüthje L, Vollmann D, Drescher T, Schott P, Zenker D, Hasenfuss G, Unterberg C. Intrathoracic impedance monitoring to detect chronic heart failure deterioration: relationship to changes in NT-proBNP. Eur J Heart Fail 2007 Jun-Jul;9(6-7):716-22.
- 15. Yu CM, Wang L, Chau E, Chan RH, Kong SL, Tang MO, Christensen J, Stadler RW, Lau C. Intrathoracic impedance monitoring in patients with heart failure: correlation with fluid status and feasibility of early warning preceding hospitalization. Circulation 2005;112(6):841-48.
- Kaliner MA. Classification of Nonallergic Rhinitis Syndromes With a Focus on Vasomotor Rhinitis, Proposed to be Known henceforth as Nonallergic Rhinopathy. World Allergy Organ J. 2009;2(6):98-01.
- Kosmala W, Marwick T. Asymptomatic left ventricular diastolic dysfunction: predicting progression to symptomatic heart failure. J Am Coll Cardiol Img 2020;13:215-27.
- Kittleson MM,Panjrath GS, Amancherla K, Davis LL, Deswal A,Dixon DL, Januzzi JL Jr, Yancy CW. 2023 ACC expert consensus decision pathway on management of heart failure with preserved ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. Published online April 19, 2023

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The South County Hospital Institutional Review Board (IRB) has reviewed our Case Report, and determined that it is exempt from a full IRB review according to 45 CFR 46.104. The IRB has affirmed its ethical oversight of our work.

#### **Conflict of Interest**

There are no conflicts of interest for the authors to declare.

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### Diplopia after Sleeve Gastrectomy: The Canary in the Coal Mine

ANNA WHITHAM, MD; KUNTAL BHOWMICK, MD; SARAH FREEMAN, MD

#### ABSTRACT

Wernicke's encephalopathy (WE) is a neurologic emergency requiring timely intravenous thiamine supplementation to prevent permanent neurologic deficits. Historically, the WE diagnosis was limited to individuals with alcohol use disorder. However, it is now widely recognized to occur in patients who are chronically malnourished, post-bariatric surgery, pregnant with hyperemesis gravidarum, and with severe anorexia nervosa. Here we present a young woman who developed WE after undergoing a recent sleeve gastrectomy followed by protracted emesis for several days. This case underscores the importance of performing a thorough neurological review of systems and physical exam in high-risk patients and having a low clinical threshold to initiate appropriate thiamine treatment.

**KEYWORDS:** Thiamine Deficiency; Wernicke's Encephalopathy; Obesity; Bariatric Surgery; Medical Tourism

#### INTRODUCTION

Sleeve gastrectomy (SG) has become the most common bariatric surgery performed worldwide.<sup>1</sup> Its popularity arises from it being a technically simpler surgery with similar weight loss results and presumed lower postoperative risk of nutritional deficiencies compared to other bariatric surgeries.<sup>2</sup> However, significant nutritional deficiencies frequently occur, even with restrictive operations such as SG.<sup>1</sup> Here we present a cautionary tale of diplopia with progressive neurological deficits in a patient admitted with protracted emesis shortly after undergoing sleeve gastrectomy.

#### CASE

A 26-year-old female with class III obesity (BMI = 40) and rapid 60lb weight loss following sleeve gastrectomy in Turkey two months prior, presented with severe fatigue and three-day history of non-bloody, nonbilious emesis with inability to tolerate oral intake. Starting one month after surgery, this patient developed progressive weakness and nausea with occasional postprandial vomiting. She also described more recently two days of dizziness and altered Figure 1. Inability to abduct left eye on extraocular movement exam.



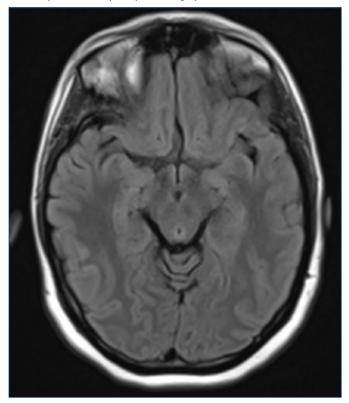
balance without any falls and one day history of double vision, all of which she self-attributed to her decreased oral intake. She reported adherence with the postoperative bariatric diet and vitamins prescribed by her medical provider in Turkey, except for the four days prior to presentation due to emesis. She did not have any fevers or chills.

On presentation, the patient was in no acute distress, well nourished, and alert and oriented to self, date, and place. New right esotropia at rest was identified prompting a more thorough neurological exam. Cranial nerve exam revealed inability to abduct her left eye (Figure 1) and evoked bidirectional horizontal nystagmus. Binocular diplopia was present on primary gaze and worse on leftward gaze. Visual fields were intact to frontal confrontation in all four quadrants. Cranial nerves were otherwise intact. The patient did not show signs of appendicular ataxia and gait testing was deferred. Her lab studies, Complete Blood Count (CBC), Basic Metabolic Panel (BMP) and Magnesium (Mg) were all within normal limits, except for a mildly elevated anion gap of 14 mEq/L. Computerized tomography (CT) of the abdomen/pelvis did not reveal any surgical complications. She was admitted to the general internal medicine service after receiving 2 L of IV normal saline and 200mg of thiamine IV.

A repeat neurological exam, approximately 12 hours after the first exam, was significant for progression of her ophthalmoplegia with now complete inability to abduct her eyes bilaterally, as well as a mild truncal ataxia with standing and wide-based gait. Her exam otherwise showed a negative Romberg sign and normal finger-to-nose testing. Thiamine supplementation was increased to 500mg IV every 8 hours. Magnetic resonance imaging (MRI) with and without contrast did not show areas of increased or decreased intensity, including no cranial nerve or mamillary body enhancement (**Figure 2**). CT angiogram did not show signs of anterior or posterior circulation aneurysm or stenosis.



**Figure 2**. MRI Axial Flair imaging showing lack of enhancement at mamillary bodies and periaqueductal gray.



After her third administration of 500mg IV thiamine, her ophthalmoplegia and ataxia had resolved, but she continued to have diplopia on left gaze. After her sixth dose of thiamine, her diplopia had completely resolved. Esophagogastroduodenoscopy (EGD) showed sharp angulation of the stomach but no functional gastric stenosis. Her ability to tolerate oral intake improved throughout the hospital stay. She was discharged with thiamine 100mg daily in addition to her bariatric vitamins. After discharge, the patient's thiamine level, drawn after receiving three doses of IV thiamine, resulted at 48 nmol/L (normal 70–180 nmol/L). Her vitamin B12 and folate were within normal limits and myasthenia gravis antibodies were negative.

#### DISCUSSION

This case of diplopia shortly after sleeve gastrectomy is an unusual presentation of severe thiamine deficiency with neurological involvement consistent with Wernicke's encephalopathy (WE). WE is a clinical diagnosis made when a patient has two of the following four updated Caine criteria: thiamine deficiency, oculomotor abnormalities, cerebellar dysfunction and either altered mental status or mild memory impairment. The classic Wernicke's triad of ophthalmoplegia, ataxia, and altered mental status presents in a minority of patients, raising concerns for under-diagnosis.<sup>3</sup> Historically, in developed countries, this diagnosis was limited to individuals with alcohol use disorder, but it is now widely recognized to occur in patients who are chronically malnourished, post-bariatric surgery, pregnant with hyperemesis gravidarum, and with severe anorexia nervosa.<sup>1</sup>

Thiamine pyrophosphate (TPP) is integral to the anabolic metabolism of neuronal and glial cells. Without TPP, astrocyte-related functions are impacted, leading to increased blood brain barrier permeability. Edema and accumulation of lactic acid lead to eventual neuronal necrosis I.<sup>4</sup> The presence of mammillary body or other diencephalic or periventricular lesions on MRI can support the diagnosis of WE, but MRI is only 53% sensitive.<sup>5</sup> The postulated blood brain barrier alterations from thiamine deficiency take weeks to develop on imaging, so it is not uncommon for MRI findings to lag behind the progression of the clinical picture.

Up to 25% of post-sleeve gastrectomy patients experience thiamine deficiency. However, progression to Wernicke's encephalopathy is rare, occurring in less than 1% of patients.<sup>6,7</sup> The majority of WE cases develop within the first 6 months after surgery but cases of post-SG WE have been reported up to six years after surgery.8 Thiamine deficiency in non-malabsorptive restrictive weight loss surgery (gastric banding, sleeve gastrectomy, vertical gastroplasty, gastric balloon) has been attributed to preexisting nutritional deficiency, impaired thiamine absorption from gastric wall edema, and dietary non-compliance post-operatively.<sup>7,9</sup> In a systematic review, 84% of post-SG WE patients were women and 38% were aged 21 to 30 years old.<sup>10</sup> Other risk factors for development of post-SG WE are functional gastric stenosis, excessive or rapid weight loss, prolonged vomiting and those not attending an outpatient nutrition clinic.<sup>9,11</sup> Our patient was young, female, and had rapid postoperative weight loss. Her 60 lbs. of weight loss at 2 months was at least double the expected weight loss. She may also have been sub-clinically deficient in thiamine prior to the procedure, as a high-calorie malnutrition picture is demonstrated in 15.5-29% of patients with obesity.9

Consensus clinical guidelines cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery advise daily thiamine supplementation of 50 to 100mg as part of the bariatric vitamin regimen. Updated guidelines in 2019 now also recommend routine thiamine screening after bariatric surgery for all patients.<sup>12</sup> Due to our patient's participation in medical tourism, any preoperative nutritional screening results are not available for review, and she did not have the typical longitudinal bariatric surgical nutrition counseling.<sup>10</sup> The contents of her prescribed vitamins could not be confirmed. The specifics of the prescribed supplementation are vitally important as general multivitamins have been shown to be inadequate in preventing deficiencies in patients after sleeve gastrectomy.<sup>11</sup>

Patients with suspected thiamine deficiency should be



treated before or in the absence of imaging confirmation and monitored for signs of neurologic recovery following thiamine supplementation.<sup>10</sup> Strength and duration of treatment for Wernicke's is less clear, but it is widely accepted that oral supplementation is inadequate to prevent permanent disability.14 The majority of studies have been in patients with alcohol use disorder, which may not be generalizable in the bariatric patient population. The 2019 consensus guidelines recommend changing from 200 mg IV 3 times daily to 500 mg IV 1-2 times daily for 3-5 days, followed by 250 mg IV daily for 3–5 days or until symptoms resolve. Following symptom resolution, patients should be maintained on oral thiamine supplementation of 100mg daily indefinitely or until risk factors have been resolved. In patients with recalcitrant or recurrent thiamine deficiency with one of the above risks, the addition of antibiotics for small intestine bacterial overgrowth should be considered.

In conclusion, WE is a neurologic emergency requiring timely intravenous thiamine supplementation to prevent permanent neurologic deficits. This case underscores the importance of performing a thorough neurological review of systems and physical exam in high-risk patients, including those with a history of bariatric surgery patients and protracted vomiting. As IV thiamine is a well-tolerated treatment without known independent toxicity risks, there should be a low threshold to treat patients presenting with acute neurological deficits with a history of any gastric surgery. If their condition fails to improve, supplementation should be stopped after three days. With a low threshold for clinical suspicion, this low-risk therapy can prevent long-standing neurological deficits in our progressively younger bariatric surgery patients.

#### References

- Kizy S, Jahansouz C, Downey MC, Hevelone N, Ikramuddin S, Leslie D. National trends in bariatric surgery 2012-2015: demographics, procedure selection, readmissions, and cost. Obes Surg 2017;27:2933-2939.
- Young MT, Gebhart A, Phelan MJ, Nguyen NT. Use and outcomes of laparoscopic sleeve gastrectomy vs laparoscopic gastric bypass: analysis of the American College of Surgeons NSQIP. J Am Coll Surg 2015;220:880-885. EL 2; ES
- Harper CG, Giles M, Finlay-Jones R. Clinical signs in the Wernicke-Korsakoff complex: a retrospective analysis of 131 cases diagnosed at necropsy. J Neurol Neurosurg Psychiatry. 1986 Apr;49(4):341-5. doi: 10.1136/jnnp.49.4.341.
- Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. Lancet Neurol. 2007 May;6(5):442-55. doi: 10.1016/S1474-4422(07)70104-7. PMID: 17434099.
- 5. Antunez E, Estruch R, Cardenal C, et al. Usefulness of CT and MR imaging in the diagnosis of acute Wernicke's encephalopathy. AJR Am J Roentgenol. 1998;171(4):1131–7.
- Tang, Liyang, et al. "Prevalence and predictors of postoperative thiamine deficiency after vertical sleeve gastrectomy." Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery vol. 14,7 (2018): 943-950. doi:10.1016/j.soard.2018.03.024.

- Emile, Sameh & Elfeki, Hossam. (2017). Nutritional Deficiency After Sleeve Gastrectomy: A Comprehensive Literature Review. European Medical Journal, Gastroenterology. 6. 99-105. 10.33590/emjgastroenterol/10313202.
- Negri M, Macerola N, Mancarella FA, et al. A Late Onset of Wernicke-Korsakoff Encephalopathy After Biliopancreatic Diversion: a Case Report. OBES SURG 29, 2309–2311 (2019). https://doi.org/10.1007/s11695-019-03894-5.
- 9. Aesheim ET, Hofso D, Hjelmesaeth J, et al. Vitamin status in morbidly obese patients: a cross-secitonal study, Am J Clini Nutr, 2008 87:362-9.
- Singh S, Kumar A. Wernicke encephalopathy after obesity surgery: a systematic review. Neurology. 2007 Mar 13;68(11):807-11. doi: 10.1212/01.wnl.0000256812.29648.86. PMID: 17353468.
- Kröll D, Laimer M, Borbély YM, et al. Wernicke Encephalopathy: a Future Problem Even After Sleeve Gastrectomy? A Systematic Literature Review. OBES SURG 26, 205–212 (2016).
- 12. Mechanick J, Apovian C, Brethauer S, Kothari S, Seger MV, Still CD, et al. "Clinical Practice Guidelines For The Perioperative Nutrition, Metabolic, and Nonsurgical Support of Patients Undergoing Bariatric Procedures 2019 Update: Cosponsored By American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society For Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiology." Obesity 2020. DOI:https://doi.org/10.4158/GL-2019-0406
- Heusschen L, Schijns W, Ploeger N, et al. The True Story on Deficiences After Sleeve Gastrectomy: Results of a Double-Blind RCT. Obesity Surg (2020) 30:12890-1290.
- Galvin R, Bråthen G, Ivashynka A, et al. EFNS. EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy. Eur J Neurol. 2010;17(12):1408–1418.

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## Kaposi Sarcoma Associated with Tofacitinib Use in a Patient with Rheumatoid Arthritis

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#### ABSTRACT

Kaposi sarcoma is a rare vascular malignancy associated with HHV-8 infection. Four variants of Kaposi sarcoma have been described: Classic, African, HIV-associated, and iatrogenic. Iatrogenic Kaposi sarcoma is typically associated with immunosuppression and organ transplantation. We present a case of iatrogenic Kaposi sarcoma associated with tofacitinib therapy. A 69-year-old woman with rheumatoid arthritis receiving tofacitinib presented with multiple firm, purple-red nodules and brown plaques on the left lower extremity and a single lesion on the right medial calf. Clinicopathologic correlation confirmed a diagnosis of Kaposi sarcoma. Tofacitinib was discontinued and she was started on Alitretinoin 0.1% gel bid. The purple-red Kaposi sarcoma nodules decreased 50% in size after 4 months and resolved at 1 year off the tofacitinib and initiation of alitretinoin gel. As the use of immunomodulators and biologics continues to expand, awareness of this association is important for prompt diagnosis and management.

**KEYWORDS:** Kaposi sarcoma, tofacitinib, rheumatoid arthritis, immunosuppression, HHV-8

#### **CASE REPORT**

The patient is a 69-year-old Hispanic woman with rheumatoid arthritis on tofacitinib 5 mg daily for 1 year. She presented with bilateral lower extremity edema and skin lesions primarily on the left lower extremity and single lesion on the right medial calf. The lesions were asymptomatic and slowly growing over the previous 6 months. There was no history of trauma. Physical examination revealed a well-appearing patient with multiple purple-red nodules and brown plaques ranging from 2–10 mm in size on the dorsal left foot, left lateral ankle and left calf (**Figure 1**). One 4mm round dull red-purple macule was present on the right medial calf. No other similar lesions were found on full body skin examination and no mucosal involvement was detected. Laboratory testing confirmed that the patient had a negative human immunodeficiency virus (HIV) status.

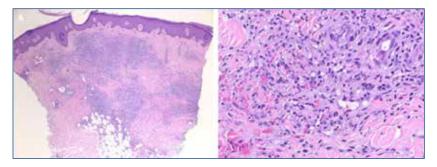
Shave and punch biopsy of the left dorsal foot and left lateral calf, respectively, was performed. The shave of a purple nodule revealed focal human herpesvirus-8 (HHV-8) Figure 1. A and B show red-purple Kaposi sarcoma nodules on brown patches of dorsal left foot [A] and left ankle [B] region at time of presentation. C and D show resolution of the nodular lesions 1 year after stopping at tofacitinib and starting alitretinoin 0.1% gel.



positivity and increased vascularity confirmed by CD31 staining. Punch biopsy of a brown plaque demonstrated hyperkeratosis and an acanthotic epidermis. Within the upper and mid dermis, there was a subtle proliferation of slit-like vascular spaces, interspersed interstitial spindle cells, numerous dermal endothelial cell lined well-formed small blood vessels, occasional plasma cells and moderately dense lymphohistocytic inflammation (**Figure 2**). Background fibrosis, extravasated erythrocytes and hemosiderin was also present. The prominent angioplasia, inflammation and fibrosis suggested concomitant acroangiodermatitis features. Immunohistochemical staining with CD68 revealed intermingled histiocytes. CD4/CD8 immunostaining confirmed an admixed lymphoid infiltrate with a CD4:CD8



**Figure 2.** Punch biopsy H&E stain demonstrates nodular proliferation and admixed interstitial spindle cells with slit-like vascular spaces, extravasated erythrocytes, endothelial cells lining well-formed small blood vessels, occasional plasma cells, and moderately dense lymphohistiocytic inflammation. 4X **[A]** and 40X **[B]** magnifications.



ratio of 4:1. HHV-8 immunostaining showed occasional scattered positive nuclei. Clinicopathologic correlation confirmed a diagnosis of Kaposi sarcoma in the setting of tofacitinib therapy. Tofacitinib was discontinued. Skin lesions have notably decreased in size following cessation of tofacitinib and the start of alitretinoin gel.

#### DISCUSSION

Kaposi sarcoma is a vascular endothelial proliferation caused by an infection with HHV-8. Cutaneous findings of Kaposi sarcoma have a predilection for the lower extremities and they include red-purple nodules, patches, and macules, as seen in our patient. Mucocutaneous manifestations and visceral involvement have been reported, most commonly affecting the gastrointestinal tract.<sup>1</sup> Histopathologic analysis is required for diagnosis, particularly in order to distinguish Kaposi sarcoma from mimickers such as bacillary angiomatosis. The key histological characteristics of Kaposi sarcoma include angiogenesis of banal appearing spindle cells forming aggregates and slit-like to ectatic vascular spaces. There is accompanying microhemorrhage, single intracellular and few to many extravasated erythrocytes, hemosiderin deposition and inflammation. Immunostaining for HHV-8 aids in diagnosis. Rare cases of HHV-8 negative have been reported.<sup>2</sup>

Although Kaposi sarcoma may be classic, endemic/African or acquired immunodeficiency syndrome (AIDS) associated, it may present in patients with immunosuppression due to reactivation of latent HHV-8 infection. With the increased availability of antiretroviral therapy (ART), the incidence of HIV-associated Kaposi sarcoma has decreased.<sup>3</sup> Nevertheless, iatrogenic Kaposi sarcoma can be seen in various clinical contexts. In a large retrospective study of 137 patients with Kaposi sarcoma in Turkey by Baykal et al, 37 cases of iatrogenic Kaposi sarcoma were reported: sixteen following systemic steroid use, ten transplant patients (renal and liver) on varying immunosuppressive medications, four with myasthenia gravis (some patients receiving either systemic corticosteroids or IVIG therapy), three with rheumatoid arthritis (some patients receiving systemic corticosteroids, methotrexate, and/ or leflunomide), three with topical steroid therapy use and one with congenital immunodeficiency syndrome.<sup>4</sup>

The development of Kaposi sarcoma in patients with rheumatoid arthritis receiving various therapies, including TNF-alpha inhibitors and triptolide, a diterpene triepoxide found in a traditional Chinese herbal remedy have been reported.<sup>5,6</sup> However, as noted above, there are infrequent reports of Kaposi sarcoma developing specifically in patients with rheumatoid arthritis who are receiving immunosuppressive drugs. Tofacitinib is a

small-molecule immunomodulator that primarily inhibits Janus Kinase (JAK) 1 and JAK 3 (and to a lesser extent JAK 2), which are cell surface proteins that mediate cytokine-dependent signal transduction.<sup>7</sup> Inhibition of JAK signaling interferes with lymphocyte activation, proliferation, and function.<sup>7</sup> Tofacitinib is used to treat severe cases of rheumatoid arthritis, even in the setting of an incomplete response to methotrexate therapy.<sup>7</sup> This drug is also used in the management of other inflammatory conditions, including ulcerative colitis, psoriasis, and alopecia areata.<sup>8-10</sup> More recently, tofacitinib has been shown to reduce the risk of death among patients hospitalized with COVID-19 pneumonia.<sup>11</sup>

Adverse events related to tofacitinib therapy primarily result from immunosuppression. For example, the incidence of herpes zoster (HZ) has been found to be higher in individuals with rheumatoid arthritis on tofacitinib compared to those not on this treatment.<sup>12</sup> Similarly, it has been shown that the risk of cancer and cardiovascular disease is higher with tofacitinib relative to tumor necrosis factor (TNF) therapy.<sup>13</sup> Tocilizumab, a humanized antihuman interleukin-6 (IL-6) receptor monoclonal antibody developed in Japan has demonstrated safety and efficacy in the management of rheumatoid arthritis refractory to various treatment options including other biologics and methotrexate.<sup>14</sup>

Moreover, one case report has associated tofacitinib with the development of Kaposi sarcoma. Wetwittayakhlang et al describes biopsy-confirmed Kaposi sarcoma in an HIV-negative 61-year-old man after two years of tofacitinib therapy for treatment-resistant ulcerative colitis. In this patient, the Kaposi sarcoma in lesions improved slowly within 2 months of discontinuation of tofacitinib, thus suggesting a causal relationship.<sup>15</sup> Notably, there is one case report of an HIV-negative patient with essential thrombocythemia (ET) treated with ruxolitinib, another JAK inhibitor, who developed biopsy-confirmed Kaposi sarcoma.<sup>16</sup>

Our patient was treated with alitretinoin gel 0.1% which, along with the discontinuation of tofacitinib, resulted in resolution of the red-purple nodular Kaposi sarcoma cutaneous lesions. Repeat biopsy of residual brown plaque at 1



year revealed no evidence of KS; only findings consistent with drug deposition attributed to her ongoing Plaquenil use. Alitretinoin is a Vitamin A derivative that offers a non-invasive, patient-administered topical therapy to treat Kaposi sarcoma with minimal adverse effects.<sup>17</sup> Randomized controlled studies have confirmed the utility of alitretinoin 0.1% gel in the treatment of AIDS-related Kaposi sarcoma, although case reports have suggested that it may also be effective in patients who develop Kaposi sarcoma in the setting of a HIV negative status.<sup>17,18</sup>

This case highlights the importance of close surveillance for new skin lesions, particularly in the lower extremities, in iatrogenically immunosuppressed patients. With the increased use of biologics and immunomodulators to treat chronic autoimmune conditions, physicians must be familiar with the clinical presentation of Kaposi sarcoma and maintain a low level of threshold for skin biopsy to establish a prompt diagnosis.

#### References

- Finesmith TH, Shrum JP. Kaposi's sarcoma. Int J Dermatol 1994;33(11):755–62.
- 2. Kumar P. Human herpes virus-8-negative kaposiform sarcoma in a HIV-positive male: Novel variant. J Cancer Res Ther 2020;16(1):177–9.
- Engels EA, Pfeiffer RM, Goedert JJ, et al. Trends in cancer risk among people with AIDS in the United States 1980–2002. AIDS 2006;20(12):1645.
- Kutlay A, Baykal C, Atci T, Buyukbabani N. The spectrum of underlying causes of iatrogenic Kaposi's sarcoma in a large series: A retrospective study [Internet]. Indian Journal of Dermatology. 2019;64(5):392. Available from: http://dx.doi.org/10.4103/ijd. ijd\_217\_18
- Grzegorzewska AE, Frankiewicz D, Bręborowicz D, Matławska I, Bylka W. Disseminated cutaneous Kaposi sarcoma in a patient receiving triptolide/tripdiolide for rheumatoid arthritis. Med Sci Monit 2012;18(8):CS67–71.
- Mariappan AL, Desai S, Locante A, Desai P, Quraishi J. Iatrogenic Kaposi Sarcoma Precipitated by Anti-Tumor Necrosis Factor-Alpha (Anti-TNF-α) Therapy. Cureus 2021;13(2):e13384.
- van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012;367(6):508–19.
- Berekmeri A, Mahmood F, Wittmann M, Helliwell P. Tofacitinib for the treatment of psoriasis and psoriatic arthritis. Expert Rev Clin Immunol 2018;14(9):719–30.
- Craiglow BG, King BA. Tofacitinib for the treatment of alopecia areata in preadolescent children. J Am Acad Dermatol 2019;80(2):568–70.
- Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med 2017;376(18):1723–36.
- Guimarães PO, Quirk D, Furtado RH, et al. Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med 2021;385(5):406–15.
- Curtis JR, Xie F, Yun H, Bernatsky S, Winthrop KL. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. Ann Rheum Dis 2016;75(10):1843–7.
- Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. N Engl J Med 2022;386(4):316–26.

- Kaneko A. Tocilizumab in rheumatoid arthritis: efficacy, safety and its place in therapy. Ther Adv Chronic Dis 2013;4(1):15–21.
- Wetwittayakhlang P, Golovics PA, Afif W, Bessissow T, Lakatos PL. Tofacitinib-Associated Iatrogenic Kaposi Sarcoma in a Patient With Ulcerative Colitis. ACG Case Rep J 2021;8(11):e00678.
- Loscocco GG, Vannucchi M, Paoli C, et al. Kaposi sarcoma in a patient treated with ruxolitinib. Ann Oncol 2017;28(7):1670–1.
- Bodsworth NJ, Bloch M, Bower M, Donnell D, Yocum R, International Panretin Gel KS Study Group. Phase III vehicle-controlled, multi-centered study of topical alitretinoin gel 0.1% in cutaneous AIDS-related Kaposi's sarcoma. Am J Clin Dermatol 2001;2(2):77–87.
- González de Arriba A, Pérez-Gala S, Goiriz-Valdés R, Ríos-Buceta L, García-Díez A. Kaposi's Sarcoma Treated with Topical Alitretinoin. Actas Dermo-Sifiliográficas (English Edition) 2007;98(1):50–3.

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## SVC Syndrome With Hepatic Pseudolesion

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#### INTRODUCTION

SVC syndrome is collection of clinical and radiographic symptoms commonly associated with lung malignancy. The compression of the superior vena cava leads to neovascularization and collateralization of several vascular beds. This process may lead to unusual radiographic findings which can lead the unfamiliar clinician astray. Recognition of these findings is therefore paramount to ensure timely diagnosis of the underlying malignancy and avoid unnecessary testing.

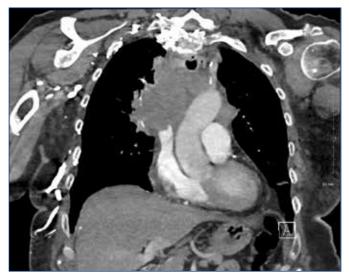
#### CASE

A 72-year-old female with a medical history significant for cigarette smoking and provoked PE presented to the emergency department complaining of 1 week of flulike symptoms which progressed to severe dyspnea at rest. She had recently been diagnosed with a lung mass and was scheduled for outpatient workup. She endorsed unintentional weight loss over the preceding months and, notably, progressive swallowing difficulty that began several days prior to presentation. In the emergency department, chest X-ray revealed a large mass within the anterior mediastinum with subtle nodular thickening of the right upper lobe and associated volume loss. There were also several small sub-centimeter nodules within the right upper lobe. (Figure 1) Given her history of tobacco use, age, and clinical prodrome, these findings were concerning for an aggressive pulmonary malignancy perhaps with a developing post-obstructive pneumonia. A follow-up CT angiography (CTA) of the chest was ordered to both rule out PE and better assess the extent of this mass. The CTA revealed a 4.5 cm mass in the right upper lobe confluent with a 14 cm bulky mediastinal lymphadenopathy which completely encased and occluded the superior vena cava. Focal enhancement of the liver was also appreciated in addition to extensive chest wall collateralizations. (Figures 2,3)

Subsequent abdominal imaging to investigate for potential metastatic spread revealed sub-centimeter cyst-like hypodense liver lesions, as well as hyperenhancement of the left lobe of the liver in segment IVa which subsequently normalized on delayed phase imaging (**Figure 4**). While the hyper-enhancing liver lesion was initially considered to be potentially suspicious for metastasis, the lesion location, washout on delayed-phase imaging, clinical prodrome, and Figure 1. X-Ray Chest a/p view revealing large RUL mass.



Figure 2. CTA Chest coronal view re-demonstrating large RUL mass with encasement of the SVC.



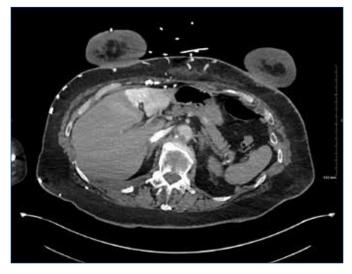
presence of a known SVC obstruction together formed a more convincing picture for a hepatic pseudolesion due to collateralization of the superior vein of Sappey.



Figure 3. CTA Chest coronal view showing a large mass encasing the great vessels with mediastinal invasion and multiple contrast-enhanced thoracic wall collaterals as well as heterogenous nodular enhancement of the liver.



**Figure 4.** CT Abdomen axial view showing nodular hyperenhancement of hepatic segment IVa and engorgement of the surrounding hepatic and thoracic veins on the right.



#### DISCUSSION

SVC syndrome is a cluster of clinical symptoms associated with pathologic obstruction of venous return through the superior vena cava. These symptoms include upper extremity edema, JVD, and facial plethora. Many patients also present with cough and dyspnea or other complication of the underlying malignancy as this patient did. An estimated 80% of cases are caused by solid right-sided pulmonary malignancies, particularly small cell carcinomas, though rare cases associated with diffuse large B cell lymphoma have also been reported.<sup>1</sup> SVC syndrome tends to develop insidiously, as the SVC becomes gradually obstructed and venous collaterals form. These collaterals, particularly of the thoracic veins, are so frequently associated with SVC syndrome that their presence on chest CT carries a diagnostic sensitivity of 96%, and specificity of 92%, and they are essentially pathognomonic for SVC syndrome.<sup>2</sup> However, less commonly recognized is the collateralization of distant vessels such as the vein of Sappey which connects the internal thoracic vein to the hepatic portal system and eventually to the IVC. This vein normally arises within segment IVa of the liver and can produce a convincing lesion that enhances during contrast phase on CT. It can easily be mistaken for a primary liver or metastatic lesion.<sup>3,4</sup> Thus, a high degree of suspicion should be held for SVC syndrome in patients with known or suspected lung cancer and an arterial phase hyper-enhancing liver lesion to avoid unnecessary testing and diagnostic pitfalls.

#### References

- 1. Escalante CP. Causes and management of superior vena cava syndrome. Oncology: Williston Park. 1993;7:61–68.
- Mansour A, Saadeh SS, Abdel-Razeq N, Khozouz O, Abunasser M, Taqash A. Clinical Course and Complications of Catheter and Non-Catheter-Related Upper Extremity Deep Vein Thrombosis in Patients with Cancer. Clin Appl Thromb Hemost. 2018 Nov;24(8):1234-1240.
- Dahan H, Arrive L, Monnier-Cholley L. Cavoportal collateral pathway in vena cava obstruction: imaging features. AJR Am J Roentgenol. 1998 Nov;171(5):1405–1411
- Vummidi D, Bhargava P, Medverd JR, Virgin JB, Oliveira GR, Vaidya S. Pseudolesion in segment IV A of the liver from vein of Sappey secondary to SVC obstruction. Radiol Case Rep. 2015 Nov 6;5(3):394. doi: 10.2484/rcr.v5i3.394. PMID: 27307867; PM-CID: PMC4898296.

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## Dysmorphic Cells of Anaplastic Plasma Cell Leukemia

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**KEYWORDS:** Plasma cell leukemia, anaplastic myeloma, multiple myeloma

#### **CASE PRESENTATION**

An 86-year-old man presented with anemia (Hgb 6.1g/dL) and renal failure (serum creatinine 2.7 mg/dL). Hematological evaluation revealed serum protein electrophoresis (SPEP) with IgG lambda 1.66 g/dL, urine protein electrophoresis (UPEP) positive for lambda light chains, serum free light chain assay with abnormal kappa/lambda ratio of 18.63/16007.27 (0.00116), erythrocyte sedimentation rate of 71, lactate dehydrogenase (LDH) of 277 Units/L (125-243), serum calcium and albumin were normal. Peripheral blood smear showed rouleaux formation, occasional tear drop cells, and ~15% circulating plasma cells (PC), some of which were 'multilobulated' (Figure 1). Peripheral blood flow cytometry reported 7.4% PC. CT imaging of chest, abdomen and pelvis without contrast displayed a right pleural effusion, pelvic lymphadenopathy, and diffuse osteopenia. Bone marrow evaluation showed hyper-cellularity (~70%), with an increase in PC (~75%), many multilobulated with peculiar

**Figure 1.** Peripheral blood smear showing rouleaux formation and circulating anaplastic plasma cell with multilobulated nucleus (x 1000 original magnification).

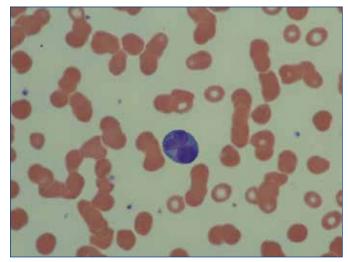
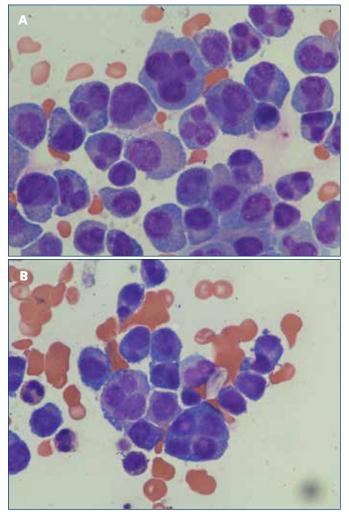


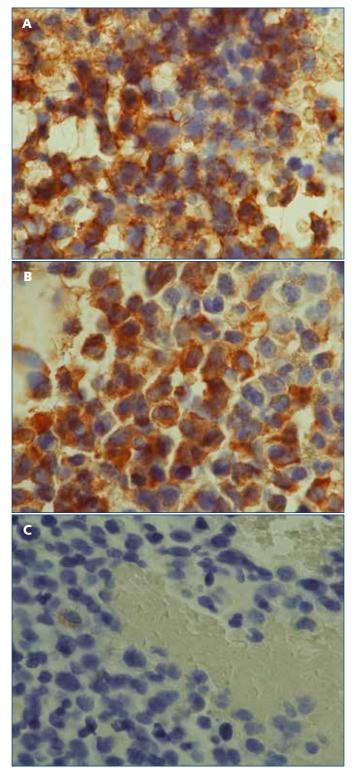
Figure 2A, 2B. Bone marrow aspirate revealing markedly pleomorphic plasma cells with multilobulated nucleus (x 1000 original magnification).



nuclear segmentation (**Figures 2A, 2B**), expressing CD138 and lambda (**Figures 3A, 3B, 3C**) on immunohistochemistry. Flow cytometric analysis on bone marrow aspirate revealed CD38 positive PC neoplasm (84% of WBC, >99% lambda light chain. Cytogenetics showed 46XY, fluorescent in situ hybridization (FISH) revealed monosomy 13; deletion 1p +duplication of 1q; Tp53 deletion; IgH rearrangement (14q32) with t(4;14); trisomy 15; gain 19; trisomy 7 and gain 3/3q. Based on the morphology and number of circulating PCs,



**Figures 3A, 3B, 3C.** Immunohistochemistry of the bone marrow aspirate (x 1000 original magnification) showing CD138 positivity **[A]**, lambda positivity **[B]** and kappa negativity **[C]**.



anaplastic plasma cell leukemia (APCL) was diagnosed; treatment was initiated with cyclophosphamide, bortezomib, and dexamethasone.

APCL (de novo or evolved) represents an extraordinarily rare variant of myeloma, with adverse cytogenetics, an aggressive course, poor responsivity to conventional chemotherapy, and poor survival. Lymphadenopathy and pleural effusions can be found. LDH can be elevated, and FISH (PCL) may express monosomy 13, del 17p, and abnormalities of chromosome 1. The morphology of the PCs is bizarre, and might be confused with carcinoma, an aggressive lymphoproliferative disorder, osteoclastic giant cells, or dysplastic megakaryocytes.

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### Epidemiology of Ankle Dislocations in the United States: 2009 to 2018

GABRIEL I. ONOR, JR., MD; ANDREW P. THOME, JR., MD; NICHOLAS J. LEMME, MD; KELSEY E. BROWN, MD; ALAN H. DANIELS, MD

#### ABSTRACT

**BACKGROUND:** Injuries to the ankle joint are common and often sustained during participation in athletic activities. There is little information regarding the overall epidemiology of ankle dislocation, both with and without associated fracture.

**DESIGN AND METHODS:** The National Electronic Injury Surveillance System (NEISS) database was queried to characterize ankle dislocation presentations to U.S. Emergency Departments (ED) from 2009-2018. Ankle dislocations were analyzed by age, sex, mechanism, and race.

**RESULTS:** From 2009–2018, 30,477 patients with ankle dislocations presented to U.S. EDs with a majority (59.8%) occurring in male patients. The overall incidence of ankle dislocations increased by 54% from 2009–2018 (p = 0.017). Over half (53%) of ankle dislocations occurred in association with sports. Ankle dislocations peaked in the third decade of life at 16.94 per million person-years. For male, the age at which ankle dislocations peaked at 39.27.

**CONCLUSION:** Preventive strategies are necessary to decrease the risk of sustaining ankle dislocations in the adult population participating in jumping sports.

**KEYWORDS:** ankle dislocations; epidemiology; sports medicine; sports

#### INTRODUCTION

Injuries to the ankle joint are common and often sustained during participation in athletic activities.<sup>1</sup> An ankle dislocation can occur with or without concomitant malleolar fracture(s), based on the magnitude and vector of forces transmitted during a traumatic event.<sup>2</sup> Pure ankle dislocation without an associated fracture is a rare occurrence because of the bony constraints of the ankle joint.<sup>3-5</sup> Wight et al reported simple ankle dislocations to account for only 0.46% of 5,000 ankle dislocations in their study.<sup>6</sup> For simple ankle dislocations, they demonstrated that 31% were a result of sporting accidents, and 30% were attributed to motor vehicle accidents.<sup>6</sup>

Though both the short- and long-term potential sequelae of an ankle dislocation have been discussed, there is little information regarding the overall epidemiology of ankle dislocation both with and without associated fracture. In this study, we investigated the incidence of ankle dislocations presenting to United States (U.S.) emergency departments (EDs). We hypothesized there to be a high incidence of ankle dislocation associated with athletic activities and the greatest rate of ankle dislocation occurring in the 18–64 age group.

#### METHODS

#### **Data Source**

The NEISS database was queried to identify rates of ankle dislocation presenting to U.S. EDs from 2009–2018. NEISS is a publicly available database published by the Consumer Product Safety Commission (CPSC). The database consists of data from ED visits from 100 sample hospitals nationwide. This sample data is then used to provide national estimates of consumer product-related injury visits to U.S. EDs. National estimates produced by NEISS have previously been used in epidemiologic studies of orthopedic injuries.<sup>7-9</sup>

#### **Patient Selection**

Records from 2009–2018 were queried to identify ankle dislocation data using body part code 37 for ankle and injury diagnosis code 55 for dislocation. Isolated ankle dislocations and ankle fracture-dislocations were grouped together for the purposes of this study. Data available for each case included treatment date, age, sex, race, anatomic site of injury, patient disposition from ED, location of injury, and narrative description of injury. Ankle dislocation rates were evaluated by age, sex, race, location of injury, product/activity, and patient disposition. Patient disposition was evaluated as either treated and released from the ED or admitted to the hospital.

#### **Statistical Analysis**

All statistical analysis was performed using Stata (StataCorp, College Station, TX), RStudio (RStudio Inc., Boston, MA), and Microsoft Excel (Microsoft Corporation, Redmond, WA). The incidence of ankle dislocation was calculated by each of the following characteristics: age, sex, race, and product/activity using US Census Bureau data. Incidence rates were reported in 1,000,000 person-years. ANOVA and chisquare analyses were performed. Statistical significance was defined as P < 0.05.



#### **Results**

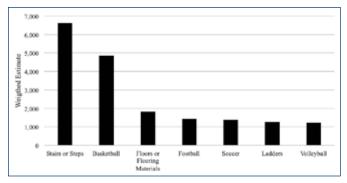
A total of 30,477 patients with ankle dislocations presenting to U.S. EDs were identified from 2009–2018. Over half of the ankle dislocations occurred in male patients (59.8%, n = 18,240), while 41.2% (n = 12,237) occurred in females. There was an overall incidence rate of 9.32 (95% CI: 7.52, 11.1) ankle dislocations per million person-years.

The leading product groups responsible for ankle dislocation were sports and recreation equipment, home structures/ construction materials, and home furnishings, fixtures, and accessories. Sports and recreation equipment were responsible for 53.0% (n = 16,149) of ankle dislocations with an incidence rate of 4.93 (95% CI: 3.96, 5.91) per million person-years. Home structures and construction materials were responsible for 33.7% (n = 10,284) of ankle dislocations with an incidence rate of 3.14 (95% CI: 2.12, 4.17) per million person-years. Home furnishings, fixtures, and accessories were responsible for 11.9% (n = 3,636) of ankle dislocations with an incidence rate of 1.11 (95% CI: 0.80, 1.42) per million

The leading causes of ankle dislocation in descending order by product code were stairs/steps, basketball, floors/ flooring materials, football, soccer, ladders, and volleyball (**Figure 1**, **Table 1**).

In males, simple ankle dislocations and complex ankle fracture-dislocations occurred, in descending order, as a







Product/ Activity	N (National Estimate)	%	Incidence Rate	95% CI
Stairs/Steps	6,623	21.7	2.02	(1.23, 2.82)
Basketball	4,856	15.9	1.48	(1.10, 1.87)
Floors	1,816	6.0	0.56	(0.34, 0.77)
Football	1,441	4.7	0.44	(0.25, 0.63)
Soccer	1,374	4.5	0.42	(0.21, 0.63)
Ladders	1,263	4.1	0.39	(0.18, 0.59)
Volleyball	1,226	4.0	0.37	(0.18, 0.57)

\*Incidence rates are reported in 1 million person-years.

result of injuries during basketball (n = 4,766), stairs/steps (n = 2,134), football (n = 1,441), and soccer (n = 1,215) (**Figure 2**). In females, stairs/steps (n = 4,489) were the leading cause of ankle dislocations followed by floors/flooring materials (n = 1,494) (**Figure 3**). In males, basketball had the highest incidence rate of ankle dislocation at 3.14 per million person-years (95% CI: 2.31, 3.97) while stairs/steps had the highest incidence rate in females at 2.86 per million person-years (95% CI: 1.55, 4.17). Males sustained significantly more ankle dislocations than females with an incidence rate ratio (IRR) of 1.54 (95% CI: 1.22, 2.10) (p < 0.0001).

## Figure 2. Most Common Activities and Products Associated with Ankle Dislocation in Males, 2009–2018

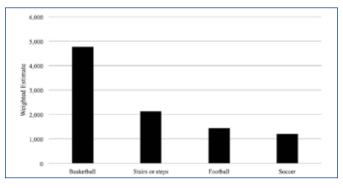


Figure 3. Most Common Activities and Products Associated with Ankle Dislocation in Females, 2009–2018

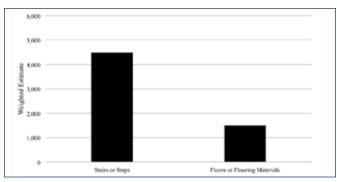
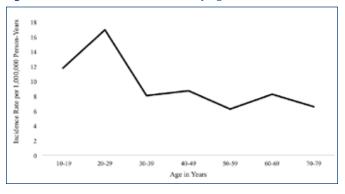


Figure 4. Incidence of Ankle Dislocations by Age, 2009–2018





#### Age and Sex

Individuals presenting with an ankle dislocation ranged in age from 8 to 95 years of age. Ankle dislocations peaked in the third decade of life at 16.94 per million person-years (**Figure 4**). The mean age of all patients was 33.97 years of age with a mode of 23. The age at which ankle dislocation peaked differed significantly by sex. In males, the mean age was 33.33 with a mode of 23 while in females, the mean age was 39.27 with a mode of 14 (p < 0.0001). For ages < 18 years of age, there was an incidence rate of 4.01 per million person-years (95% CI: 2.03, 6.00) while from 18–64 there was an incidence rate of 11.38 per million person-years (95% CI: 9.11, 13.64). Patients 65 years of age had an incidence rate of 8.79 per million person-years (95% CI: 5.71, 11.87).

#### Race

Only 66% of reported ankle dislocation had race data recorded. White patients contributed 71.69% of ankle dislocations with an incidence rate of 5.58 per million personyears (95% CI: 4.49, 6.67). Black patients contributed 16.76% with an incidence rate of 7.04 per million person-years (95% CI: 5.66, 8.42). Hispanic patients contributed 8.70% with an incidence rate of 2.92 per million person-years (95% CI: 2.35, 3.49). Asian patients accounted for 2.36% with an incidence rate of 2.45 per million person-years (95% CI: 1.97, 2.93). Native American patients accounted for 0.41% with an incidence rate of 1.97 per million person-years (95% CI: 1.59, 2.36). Native Hawaiian/Pacific Islander patients accounted for 0.08% with an incidence rate of 1.97 per million person-years (95% CI: 1.59, 2.36).

#### **Injury Locale and Disposition**

Among ankle dislocations identified with location data recorded, 42.05% of ankle dislocations occurred in a "place of sports/recreation", 38.61% occurred at "home", 8.71% occurred on "public property", 6.17% occurred at "school", 4.17% occurred on a "street/highway", and 0.19% occurred on a "farm/ranch." Location was recorded for 70.01% of NEISS ankle dislocation cases.

#### DISCUSSION

In this nationwide sample, stairs/steps were found to be associated with the greatest number of ankle dislocation events. The overall incidence of ankle dislocations presenting to U.S. EDs increased by 54% from 2009–2018 (p = 0.017). Males accounted for significantly more ED visits for ankle dislocations over the ten-year period.

Stairs have long been implicated in the epidemiology of ankle sprains.<sup>7</sup> There is little evidence available linking stairs and steps to ankle dislocation. However, it would follow that mechanisms that have been shown to lead to ligamentous sprain could precipitate dislocation of the joint with adequate force and appropriate vector. Faergemann and Larsen reported the ankle joint to be the most commonly sprained or contused joint in a retrospective study of 1462 patients with non-occupational fall injuries from ladders and scaffolds.<sup>10</sup> Furthermore, in the elderly population, falls are the leading cause of emergency department visits.<sup>11</sup> Many studies have shown formalized exercise programs and physical therapy regimens as effective strategies for fall reduction in the elderly population.<sup>12-14</sup> Given the association of ankle dislocation and stairs described here, fall prevention strategies could be of benefit, particularly in reducing rates of ankle injury in the elderly population.

It was not surprising to find high incidences of ankle dislocation in basketball and volleyball given the repetitive high-impact jumping in both sports. Much of the data regarding ankle injury in basketball and volleyball primarily describe ankle sprain. Bahr et al reported a relative risk of ankle inversion injuries in match play versus training amongst volleyball athletes.<sup>15</sup> The majority (63%) of the reported injuries were sustained after landing while blocking at the net.<sup>15</sup> A greater risk for ankle injury has been seen in athletes at a higher level of competition. Among both male and female basketball athletes, Hosea et al reported a doubling in the risk of ankle injury at the intercollegiate level compared with the interscholastic level.<sup>16</sup>

Several case reports have described isolated pure ankle dislocation in association with basketball and volleyball.<sup>17-20</sup> Ankle dislocations are more common in these sports because of the frequent jumping required in both sports.<sup>17</sup> However, there is a paucity of data regarding the epidemiology of ankle dislocation in these sports.

Ankle dislocations are most commonly complex ankle fracture-dislocations seen in the setting of concomitant ankle fracture.<sup>2-5</sup> Complex ankle fracture-dislocations have been shown to lead to worse functional outcomes.<sup>21</sup> Sculco et al reported a significant increase in pain upon 21-month follow-up as well as a significant decrease in both ankle and subtalar range of motion in patients with ankle fracture-dislocations.<sup>21</sup> Given the potential for adverse outcomes in patients with dislocation, the epidemiology of ankle dislocation is important to identify populations most likely to experience an ankle fracture dislocation in attempts to prevent new cases as well as to target existing cases for early, directed physical therapy.

Isolated ankle dislocations are far less common than other studied musculoskeletal injuries. Zacchilli and Owens reported a shoulder dislocation rate of 23.9 per 100,000 person-years also using the NEISS database.<sup>22</sup> Golan et al reported a finger dislocation rate of 11.11 per 100,000 person-years.<sup>23</sup> The study also reported the greatest incidence of finger dislocations to occur in Black males ages 15–19.<sup>23</sup> Our current study found that the greatest incidence of ankle dislocations occurs in males aged 20–29. Though ankle dislocations occur at a much less frequent rate than dislocation of other joints, the young male population remains the most affected demographic.



Furthermore, participation in outdoor organized exercise and recreational activities has increased in recent years.<sup>24</sup> This may account for a potential increase in ankle dislocations over the past 10 years.

#### Limitations

The NEISS database consists of a sampling of 100 hospitals' EDs nationwide and provides weighted estimates based on the sample. As such, this study is at risk for improper diagnosis coding and sampling bias. The sample in this study does not include individuals who did not seek treatment or those who sought treatment in a facility other than an ED. This database groups fracture-dislocations and isolated dislocations as a single diagnosis and did not identify specific mechanisms of injury implicated in ankle dislocation. Future studies should investigate the incidence of isolated ankle dislocations and assess the specific mechanisms associated with ankle dislocation in the identified products, sports, and activities.

Another potential limitation of this study lies in lack of details about patient's injury severity, associated injuries, hospital course and overall management. Because the NEISS database is comprised of data from emergency departments, there is often not much detailed information about the patient's injuries or management after they leave the ED. For example, there is no way to tell the incidence of open injuries, the time from injury to reduction, or the rates of neurovascular compromise or operative management. To better explore the post-ED care continuum for ankle dislocations, future studies should consider utilizing retrospective chart review to further explore the full hospital course of ankle dislocations that present to the ED.

#### CONCLUSION

This study demonstrates that there appears to be an increasing incidence of ankle dislocations occurring during the period 2009–2018. As participation in outdoor activities and sports increase, ankle dislocation events may follow suit. Individuals and providers should be aware of the potential for ankle dislocation in the adult population in those engaging in high-impact, jumping sports and recreational activities. Awareness should also exist about the potential for ankle dislocation particularly in those frequently interacting with stairs and steps. Further investigation may be warranted to help identify a reason for the increase in ankle dislocation cases and hopefully develop interventions to help reduce the incidence and morbidity of ankle dislocations.

#### References

- Rasmussen O. Stability of the ankle joint: Analysis of the function and traumatology of the ankle ligaments. vol. 56. 1985. https://doi.org/10.3109/17453678509154152.
- Shaik MM, Tandon T, Agrawal Y, Jadhav A, Taylor LJ. Medial and Lateral Rotatory Dislocations of the Ankle After Trivial Trauma-Pathomechanics and Management of Two Cases. J Foot Ankle Surg 2006. https://doi.org/10.1053/j.jfas.2006.05.002.
- Rivera F, Bertone C, De Martino M, Pietrobono D, Ghisellini F. Pure Dislocation of the Ankle: Three Case Reports. Clin Orthop Relat Res 2001;382:179–84.
- Mooney JF, Naylor PT, Poehling GG. Anterolateral ankle dislocation without fracture. South Med J 1991;84:244–7. https://doi. org/10.1097/00007611-199102000-00023.
- 5. Moehring HD, Tana RT, Marder RA, Lian G. Ankle Dislocation. J Orthop Trauma 1994;8:167–72.
- Wight L, Owen D, Goldbloom D, Knupp M. Pure Ankle Dislocation: A systematic review of the literature and estimation of incidence. Injury 2017. https://doi.org/10.1016/j.injury.2017.08.011.
- Waterman BR, Owens BD, Davey S, Zacchilli MA, Belmont PJ. The epidemiology of ankle sprains in the United States. J Bone Jt Surg - Ser A 2010;92:2279–84. https://doi.org/10.2106/ JBJS.I.01537.
- Durand WM, Goodman AD, Giglio P, Etzel C, Owens BD. Epidemiology of Upper Extremity Soccer Injuries Among High School- and College-Aged Players in the United States: An Analysis of the 1999-2016 NEISS Database. Sports Health 2018. https://doi.org/10.1177/1941738118795483.
- Van Tassel DC, Owens BD, Wolf JM. Incidence estimates and demographics of scaphoid fracture in the U.S. population. J Hand Surg Am 2010. https://doi.org/10.1016/j.jhsa.2010.05.017.
- Faergemann C, Larsen LB. Non-occupational ladder and scaffold fall injuries. Accid Anal Prev 2000;32:745–50. https://doi. org/10.1016/S0001-4575(99)00124-4.
- Shubert TE. Evidence-based exercise prescription for balance and falls prevention: A current review of the literature. J Geriatr Phys Ther 2011. https://doi.org/10.1519/JPT.0b013e31822938ac.
- Tinetti ME, Baker DI, Mcavay G, Claus EB, Garrett P, Gottschalk M, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. N Engl J Med 1994. https://doi.org/10.1056/NEJM199409293311301.
- Campbell AJ, Robertson MC, Gardner MM, Norton RN, Tilyard MW, Buchner DM. Randomised controlled trial of a general practice programme of home based exercise to prevent falls in elderly women. Br Med J 1997. https://doi.org/10.1136/ bmj.315.7115.1065.
- Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 2012. https://doi.org/10.1002/14651858.CD007146.pub3.
- Bahr R, Karlsen R, Lian O, Ovrebo R V. Incidence and Mechanisims af Acute Ankle Inversion Injuries in Volleyball. Am J Sports Med 1994;22:595–600.
- Hosea TM, Carey CM, Harrer MM. The Gender Issue: Epidemiology of Ankle Injuries in Athletes...: Clinical Orthopaedics and Related Research. Clin Orthop Relat Res 2000;372:45–9.
- Uyar M, Tan A, Işler M, Cetinus E. Closed posteromedial dislocation of the tibiotalar joint without fracture in a basketball player. Br J Sports Med 2004. https://doi.org/10.1136/ bjsm.2002.003954.
- Colville R, D M, Colville M. Posteromedial Dislocation of the Ankle without Fracture 1987:706–11.
- Lertwanich P, Santanapipatkul P, Harnroonroj T. Closed posteromedial dislocation of the ankle without fracture: A case report. J Med Assoc Thail 2008.
- Lazarettos I, Brilakis E, Efstathopoulos N. Open ankle dislocation without associated malleolar fracture. J Foot Ankle Surg 2013. https://doi.org/10.1053/j.jfas.2013.03.017.



- Sculco PK, Lazaro LE, Little MM, Berkes MB, Warner SJ, Helfet DL, et al. Dislocation is a risk factor for poor outcome after supination external rotation type ankle fractures. Arch Orthop Trauma Surg 2016;136:9–15. https://doi.org/10.1007/s00402-015-2353-0.
- Zacchilli MA, Owens BD. Epidemiology of shoulder dislocations presenting to emergency departments in the United States. J Bone Jt Surg - Ser A 2010;92:542–9. https://doi.org/10.2106/ JBJS.I.00450.
- Golan E, Kang KK, Culbertson M, Choueka J. The Epidemiology of Finger Dislocations Presenting for Emergency Care Within the United States. Hand 2016;11:192–6. https://doi. org/10.1177/1558944715627232.
- 24. Thapa B. The mediation effect of outdoor recreation participation on environmental attitude-behavior correspondence. J Environ Educ 2010;41:133–50. https://doi.org/10.1080/0095 8960903439989.

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## Anti-SARS-CoV-2 Monoclonal Antibodies in Pediatrics: Statewide Experience in Rhode Island

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#### ABSTRACT <sup>-</sup>

**BACKGROUND:** The pediatric population has suffered COVID-19 infections with measurable morbidity and mortality. Without oral options in those less than 12 years of age, practical treatment in this rapidly evolving disease is necessary. One treatment modality is monoclonal antibodies. Limited information describes the efficacy and safety of anti-SARS-CoV-2 monoclonal antibodies in pediatrics. This is the largest case series addressing efficacy and safety of monoclonal antibodies in this population.

**OBJECTIVE:** To report patient characteristics, side effects encountered, and hospital admissions or emergency department visits within 30 days following treatment.

**DESIGN:** This retrospective case series includes high-risk pediatric COVID-19 patients who received monoclonal antibody infusions in a tertiary care center as outpatients between January 2021 and January 2022.

**OUTCOMES:** There were 108 patients included with seven patients (6.5%) having infusion-related reactions with no other adverse events reported. Following the monoclonal treatment, three patients presented to the emergency department for worsening symptoms, and one patient was admitted to the pediatric ICU for worsening respiratory status. No other admissions or emergency department visits were reported in the one month following the infusion.

**CONCLUSIONS:** In this case series study, monoclonal antibody infusions were well tolerated.

**KEYWORDS:** COVID-19, monoclonal antibodies, pediatrics

#### INTRODUCTION

COVID-19 infection can manifest as a serious disease with severe consequences in pediatrics, especially those with certain high-risk medical conditions. Thirty percent of hospitalized unvaccinated children with COVID-19 require intensive care unit admission.<sup>1,2,3</sup> Of those who were hospitalized, more than 80% had at least one underlying medical condition.<sup>2</sup> A large portion of children and youth are not

vaccinated against COVID-19 in the United States.<sup>4</sup> Furthermore, immunosuppressed patients remain vulnerable to severe disease due to lower vaccine efficacy in this group.<sup>5</sup> This leaves a significant percentage of the pediatric population vulnerable to severe COVID-19 infections and subsequent multisystem inflammatory syndrome (MIS-C), thus the necessity for effective treatment measures, particularly as more transmissible strains of COVID-19 emerge. One such promising therapeutic agent to prevent severe illness and death has been the development of anti-SARS-CoV-2 monoclonal antibody therapies (mAbs). They target the receptor binding domain on the spike protein of the SARS-CoV-2 virus neutralizing the virus and minimizing the progression to the hyperinflammatory stage of COVID-19.<sup>6</sup>

The US Food and Drug Administration (FDA) reviewed and approved multiple Emergency Use Authorizations (EUA) for mAbs used in mild-to-moderate Covid-19 illness or as post-exposure prophylaxis in children with risk factors for progression to severe disease. These indicated risk factors included the following: BMI above 85th percentile, immunosuppressive disease or treatment, cardiovascular disease or hypertension, chronic lung diseases, sickle cell disease or thalassemia, neurodevelopmental disorders, having a dependence on medical technology, diabetes mellitus, chronic kidney disease, or pregnancy. However, due to the prevalence of the Omicron sub-variants, casirivimab/imdevimab, bamlanivimab/etesevimab, sotrovimab, bebtelovimab, tixagevimab/cilgavimab are no longer authorized in the United States.

Clinical trials have demonstrated decreasing viral loads and reductions in hospitalization and death in these highrisk COVID-19 patients after mAbs administration.<sup>7,8</sup> However, there were few pediatric patients in these trials, and there remains insufficient literature examining the effectiveness and tolerability of mAbs in clinical practice among the broader pediatric population. Available literature includes multiple case series of variable sizes and the largest study included 94 patients.<sup>9,10,11,12</sup> Overall, the administration was safe with a variable rate of side effects in adolescents and young adults. A recent European case series reported good tolerance in children younger than 12 years with no significant adverse events.<sup>13</sup>

This study reports a statewide experience with mAbs administration in eligible children of all age groups with



risk factors for severe COVID-19 disease, including transdisciplinary discussion of referral, administration, and clinical outcomes in Rhode Island, which has the highest documented rate of pediatric COVID-19 infection (38%) during the pandemic within the United States.<sup>14</sup>

#### **METHODS**

Patients with mild-to-moderate COVID-19 infection who had risk factors for developing severe disease and received monoclonal antibody infusion in the Tomorrow Fund Clinic at Hasbro Children's Hospital, the only tertiary pediatric hospital in RI, from January 2021 to January 2022 were included in the study. All patients had at least one underlying risk factor as per the FDA EUA. Patients were referred by community pediatricians and all of them were outpatients. Communications with referring pediatricians were by phone utilizing a standardized referral form. Communication between teams was done via HIPAA-compliant electronic methods. Pediatric Infectious Diseases specialists determined mAb eligibility. Patients were considered high risk if they had at least one of the following comorbidities: age less than one year, BMI above 85th percentile, immunosuppression, cardiovascular disease or hypertension, chronic lung diseases, sickle cell disease, neurodevelopmental disorders, liver disease, diabetes mellitus, chronic kidney disease, having a dependence on medical technology. All patients received one of the following: (1) bamlanivimab 700 mg, (2) casirivimab 600 mg and imdevimab 600 mg, (3) bamlanivimab 700 mg and etesevimab 1400 mg or (4) sotrovimab 500 mg over 30 minutes and all were observed for one hour afterward. After obtaining Lifespan's Institutional Review Board approval, relevant demographic and clinical data including sex, ethnicity, age, symptomatology, underlying disease, side effects, and outcome were abstracted retrospectively from the electronic health record. Quality checks were applied to the data to remove duplicates and errors. Descriptive statistics were reported using Microsoft Excel (2016).

#### RESULTS

Overall, 108 patients received mAb infusions for COVID-19, with 97 (89.8%) for treatment needs and 11 (10.2%) as post-exposure prophylaxis (**Table 1**). Of these, nine patients (8.3%) received bamlanivimab, 62 patients (57.4%) received bamlanivimab/etesevimab, 36 patients (33.3%) received casirivimab/imdevimab, and one patient (0.9%) received sotrovimab. Of the high-risk conditions, 65 patients (60.2%) had one comorbidity and 43 patients (39.8%) had two or more comorbidities. The most common comorbidities were obesity, chronic lung diseases, and immunosuppression. Patients ranged in age from 3 months to 26 years and the average age was 14.5 years. Fifty-one percent were females and 49% were males.

Table 1. Characteristics of patients –				
Age in years	Below 1: 6 (5.6) 1–11: 28 (25.9) 12–18: 66 (61.1) Above 18: 8 (7.4)			
Gender	Male 53 (49) Female 55 (51)			
Ethnicity	Hispanic 21 (19.4) Non-Hispanic 81 (75) Unknown 6 (5.6)			
Comorbidities Age<1 Obesity CKD DM Immunosuppression CHD/HTN Chronic lung diseases SCD Neurodevelopmental Liver disease Dependence on medical technology	168 6 48 1 5 33 13 37 4 15 3 3			
Number of comorbidities per patient	One comorbidity: 65 (60.2) Two comorbidities: 29 (26.8) Three comorbidities:11 (10.2) Four comorbidities: 3 (2.8)			
PCR timing in days	2 (median) 1–3 (25th and 75th quartiles)			
Duration of symptoms in days	4 (median) 2–6 (25th and 75th quartiles)			
Vaccination	Not vaccinated: 80 (74.1) Received 1 dose: 5 (4.6) Received 2 doses: 17 (15.7) Received 3 doses: 4 (3.7) Unknown: 2 (1.8)			
BMI	Below 85th percentile: 60 (55.6) Above 85th percentile: 48 (44.4)			
County	Providence: 61 (56.5) Newport: 6 (5.6) Washington: 7 (6.5) Kent: 13 (12) Bristol: 9 (8.3) Outside RI: 12 (11.1)			
Clinical outcomes	Infusion reactions: 7 (6.5) 30-d ED visit: 4 (3.7) 30-d admission: 3 (2.8)			

Nearly all patients tolerated the infusion. There were seven cases (6.5%) of infusion-related reactions that resolved in the observation area with the infusion discontinued in four patients (3.7%)[**Table 2**]. Of the cohort, 101 patients (93.5%) completed their recovery at home without emergency department visits or escalation of care (**Table 3**).

#### Table 1. Characteristics of patients – N 108 (%)



#### Table 2. Documentation of adverse events that occurred during infusion

Patient number	Side effect	Comorbidities	agent	Infusion completion
Patient 1	Chest tightness and desaturation down to 86%	B-ALL	Bamlanivimab/etesevimab	No
Patient 2	Dyspnea with desaturation to 70%, perioral cyanosis	Obesity	Bamlanivimab/etesevimab	No
Patient 3	Abdominal discomfort	Obesity	Casirivimab/imdevimab	Yes
Patient 4	Tingling lips and throat, cough, SOB, received solumedrol	HLH, obesity, HTN	Casirivimab/imdevimab	No
Patient 5	"Felt throat closing", fever, given solumedrol, acetaminophen, diphenhydramine	Obesity	Bamlanivimab/etesevimab	Yes
Patient 6	self-resolving itchiness, pain	DM, Asthma, Obesity	Casirivimab/imdevimab	Yes
Patient 7	Pain in legs and back, tightness	SCD, Asthma	Bamlanivimab/etesevimab	No

Table 3. Characteristics of patients with ED visits or hospital admissions

Patient number	Comorbidities	Initial symptoms	infusion	Duration of symptoms before infusion in days	Vaccination	Type of revisit		
COVID related								
Patient 1	Asthma, obesity	Rhinorrhea	Bamlanivimab/ etesevimab	8	Not vaccinated	PICU admission		
Patient 2	Asthma, obesity	Fever, rhinorrhea, cough	Bamlanivimab/ etesevimab	6	Not vaccinated	ED visit		
Patient 3	Obesity	Fever, cough, vomiting, diarrhea	Bamlanivimab/ etesevimab	8	Not vaccinated	ED visit		
Patient 4	Asthma, obesity, chronic liver disease, cardiovascular disease	Cough, dyspnea, aches, nausea/vomiting	Casirivimab/ imdevimab	8	2 doses	ED visit		
Non-Covid relate	ed							
Patient 1	Sickle cell disease, asthma	Post-exposure prophylaxis	Bamlanivimab/ etesevimab	NA	Not vaccinated	ED visit for SCD pain crisis		
Patient 2	Sickle cell disease	Fever, cough, dehydra- tion/vomiting/myalgia	Casirivimab/ imdevimab	2	2 doses	Floor admission for SCD pain crisis		
Patient 3	B cell ALL	Cough, diarrhea	Bamlanivimab	2	Not vaccinated	Floor admission for ALL relapse and sepsis		

Only one patient (0.9%) with obesity and asthma was admitted to the pediatric intensive care unit (PICU) 4 days after the infusion due to COVID-19 progression resulting in respiratory distress. The patient required continuous positive airway pressure and steroids and was discharged home after four days. Two patients (1.8%) were admitted to the hospital within 30 days due to other conditions, and of those, one patient with sickle cell disease was admitted for bilateral lower limb pain ischemic-occlusive crisis, while the other patient was admitted with leukemia relapse. Four total patients (3.7%) presented to the emergency department, three with worsening symptoms and one other with sickle cell-induced pain crisis, with all four treated symptomatically and discharged home. No cases with MIS-C were reported within two months post-infusion.

#### DISCUSSION

To date, there are few case series addressing the safety and tolerability of mAbs in pediatrics. In these studies, patients received different agents with good tolerability.<sup>9-12,15,16</sup> The clinical trials and adult data showed that side effects are usually mild. However, there remains a paucity of evidence for the safety, tolerability, efficacy, and indications for the usage of mAbs in the pediatric population. There is evidence in adults that early administration of mAbs decreases the burden on health systems by decreasing hospital admissions, emergency department visits, hospitalization, and duration of hospitalizations.<sup>17,18</sup> Data from one adult study assessing casirivimab/ imdevimab, showed decreased rates of hospital admissions in patients above 65 years of age, but the infusion was conversely associated with longer stays in the ED due to the mAb infusion process.<sup>19</sup> For this reason,



we gave the infusions in an outpatient center to prevent the overwhelming of emergency department resources.

There were four different regimens in our cohort. Bamlanivimab alone was infused in nine patients, and all of them recovered. While bamlanivimab demonstrated promising outcomes among high-risk populations including solid organ transplant recipients, it is no longer authorized due to emerging resistance among the SARS-CoV-2 variants.<sup>20,21</sup> Ninety-eight patients received bamlanivimab/etesevimab and casirivimab/imdevimab with good tolerance and promising efficacy but as the omicron variant became predominant, the FDA suspended authorization due to decreased activity and inability to neutralize the predominant subvariants.

The emergence of resistant variants that decrease the efficacy of vaccines and therapeutics is a major obstacle that needs collaborative efforts from governments, scientists, hospitals, and companies. Future surges of COVID-19 are a distinct threat, and physicians must be nimble to respond to emerging variants by streamlining supply chains for new treatments.

The route of parenteral administration can be a challenge, especially with overwhelmed health systems. A recent study showed that subcutaneous casirivimab and imdevimab had good efficacy compared with intravenous infusion.<sup>22</sup> Other obstacles to widespread mAb use among pediatric patients include cost, feasibility in community settings, and equity in delivery.<sup>23</sup> Multiple studies had shown Black and Hispanic patients with COVID-19 infection were less likely to receive mAbs.<sup>24,25</sup> This could be attributed to multiple factors including decreased awareness in some ethnic groups, inadequate insurance coverage, lack of health system access, and lack of transportation. The Rhode Island Department of Health did work with a home ambulance agency to administer mAbs in the community to those over 12 years of age. We were not able to report race in our study as our chart review process was able to identify ethnicity but not race.

There was an up-trending number of infusions per week in the last few months of the infusion period. This can be attributed to expanding EUA for bamlanivimab/etesevimab to include children of all ages but could also be attributed to improved community awareness and clinicians' understanding of mAbs safety and efficacy that supplanted the general lack of data and formal guidance among high-risk pediatric patients. Initially, some clinicians were not aware of the availability of mAbs for children, few were hesitant due to the absence of endorsement of routine use by the Pediatric Infectious Diseases Society during the study period.<sup>26</sup> As we are a large referring center, our pediatric infectious diseases fellows and faculty received phone calls from community physicians requesting guidance in managing children with comorbidities which helped to increase awareness. Our referral information, along with other community infusion resources were available on the state's Department of Health website.

Data regarding risk factors for severe COVID-19 in pediatrics is emerging; a case series of COVID-19 decedents showed that 86% of patients had at least one underlying comorbid condition including obesity (42%) and asthma (29%).<sup>27</sup> The evidence that conditions like obesity, immunosuppression, respiratory technology dependence, and chronic respiratory diseases can be independent risk factors for severe COVID-19 disease led the Pediatric Infectious Diseases Society to update its guidance on the use of mAbs.<sup>28</sup> However, there is a knowledge gap regarding how severe underlying conditions contribute to increased risk for COVID-19 severe disease. This can be important to ensure equity of treatment given the interruptions in supply. Data are still emerging regarding the other comorbidities listed in the FDA EUA. Most mAbs trials insufficiently enrolled pediatric populations inclusive of comorbidities like genetic disorders which can be absent in adult populations. As data emerge, indications for mAbs will continue to be modified. Partnering with our adult colleagues on clinical trials helped create the scaffolding to operationalize infusions once EUA approval occurred. In addition, key collaboration with pharmacy, information technology, and our infusion teams created the seamlessness necessary in our pathways to respond to changing environments concerning new/revoked authorizations, eligibility criteria, and emerging variants with resistance to mAbs.

Our 108-patient case series revealed that mAb infusions were well tolerated. The infusion was discontinued in 3.7 % of patients with all having complete resolutions of symptoms before leaving the infusion center. All patients recovered at home except for one patient who required PICU admission. He required respiratory support by BiPAP for 4 days before recovering completely, and three other patients presented to the emergency department. Another three patients required emergency department visits or admission for other reasons. It is worth mentioning that all the patients who represented to the hospital received the infusion between days 6 and 8 of symptoms. This, suggesting early infusion of mAbs, may indeed be more effective in preventing severe COVID-19 infection, death, and lower hospital services utilization among the high-risk pediatric population during COVID-19 surges. While we do not know the number needed to treat, we offer the largest pediatric mAbs case series to date during this pandemic. Ideally, a prospective study would provide strong evidence regarding the overall efficacy and tolerability of these treatments; however, this is not feasible due to inherent ethical concerns of withholding such a treatment to high-risk patients.

This study has several limitations as it is vulnerable to bias intrinsic to retrospective studies. There is no control arm to compare the mAbs cohort to an untreated population with the same characteristics to understand efficacy. The heterogeneity of the underlying comorbid conditions and mAb infusions is also a limitation that would prevent the generalizability of the results to the greater population,



especially among patients who do not have risk factors for severe COVID-19 infection. Another limitation is the convenience of the sample, as there was also limited availability for community infusions in those 12 years and older and whose outcomes we do not know. We can report there were no fatalities due to COVID-19 in children within the state during the study period.

#### CONCLUSION

In conclusion, we present the experience of a tertiary pediatric care facility with multiple regimens of monoclonal antibody infusion for COVID-19 in the high-risk pediatric population which demonstrates good tolerability and efficacy in preventing severe COVID-19 infection. The pediatric population cannot remain an afterthought with respect to therapeutics as this pandemic continues and further research is needed to support their therapeutics.

#### References

- Kompaniyets L, Agathis NT, Nelson JM, et al. Underlying Medical Conditions Associated with Severe COVID-19 Illness among Children. *JAMA Netw Open*. 2021;4(6):1-14. doi:10.1001/jamanetworkopen.2021.11182
- Wanga V, Gerdes ME, Shi DS, et al. Characteristics and Clinical Outcomes of Children and Adolescents Aged <18 Years Hospitalized with COVID-19 — Six Hospitals, United States, July–August 2021. MMWR Morb Mortal Wkly Rep. 2021;70(5152):1766-1772. doi:10.15585/mmwr.mm705152a3
- Swann O V., Holden KA, Turtle L, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: Prospective multicentre observational cohort study. *BMJ*. 2020;370. doi:10.1136/bmj.m3249
- 4. Analysis AAP, Posted D, Control D. Children and COVID-19 Vaccinations Trends. Published online 2022.
- Lee ARY Bin, Wong SY, Chai LYA, et al. Efficacy of covid-19 vaccines in immunocompromised patients: systematic review and meta-analysis. *Bmj*. 2022; (November 2021):e068632. doi: 10.1136/bmj-2021-068632
- Hurt AC, Wheatley AK. Neutralizing antibody therapeutics for covid-19. Viruses. 2021;13(4):1-15. doi:10.3390/v13040628
- Chen P, Nirula A, Heller B, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med. 2021;384(3):229-237. doi:10.1056/nejmoa2029849
- 8. Dougan M, Nirula A, Azizad M, et al. Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19. *N Engl J Med*. Published online 2021:1-11. doi:10.1056/nejmoa2102685
- Mak G, Dassner AM, Hammer BM, Hanisch BR. Safety and Tolerability of Monoclonal Antibody Therapies for Treatment of COVID-19 in Pediatric Patients. *Pediatr Infect Dis J.* 2021;40(12):e507-e509. doi:10.1097/INF.000000000003263
- Santos JDL, Bhisitkul D, Carman M, et al. The use of monoclonal antibody therapy in pediatric patients with COVID-19: a retrospective case series. 2022;8:1-7.
- Romani L, Carducci FIC, Chiurchiù S, et al. Safety of Monoclonal Antibodies in Children Affected by SARS-CoV-2 Infection. *Children*. 2022;9(3):10-15. doi:10.3390/children9030369
- 12. Bahakel H, Murphy C, Frenck RW, et al. Single Site Experience of the use of Monoclonal Antibodies for the Treatment

of COVID-19 in High-risk Pediatric and Young Adult Patients. *Pediatr Infect Dis J.* 2022;41(12):985-988. doi:10.1097/ inf.000000000003703

- Rau C, Auer-Hackenberg L, Deubzer HE, et al. Treatment of Infants and Children with SARS-CoV-2 Monoclonal Antibodies: A European Case Series. *Pediatr Infect Dis J.* 2023;42(2):125-129. doi:10.1097/INF.00000000003773
- 14. American Academy of Pediatrics and the Children's Hospital Association. Children and COVID-19: State Data Report Version: 6/24/21. Published online 2021. https://downloads.aap. org/AAP/PDF/AAP and CHA - Children and COVID-19 State Data Report 6.24 FINAL.pdf
- 15. Monoclonal antibody and antiviral therapy for treatment of mild-to-moderate COVID-19 in pediatric patients. Published online 2022.
- Sotrovimab W. Letters to the Editor. 2022;41(8):341-342. doi:10.1097/INF.00000000003552
- Piccicacco N, Zeitler K, Montero J, et al. Effectiveness of Severe Acute Respiratory Syndrome Coronavirus 2 Monoclonal Antibody Infusions in High-Risk Outpatients. Open Forum Infect Dis. 2021;8(7). doi:10.1093/ofid/ofab292
- Verderese JP, Stepanova M, Lam B, et al. Neutralizing Monoclonal Antibody Treatment Reduces Hospitalization for Mild and Moderate Coronavirus Disease 2019 (COVID-19): A Real-World Experience. *Clin Infect Dis.* 2022;74(6):1063-1069. doi:10.1093/ cid/ciab579
- Ash J, Leavitt R, Dietrich T, et al. Real world utilization of REGEN-COV2 at a community hospital. Am J Emerg Med. 2021;50:129-131. doi:10.1016/j.ajem.2021.07.050
- 20. Kumar RN, Wu E-L, Stosor V, et al. Real-World Experience of Bamlanivimab for Coronavirus Disease 2019 (COVID-19): A Case-Control Study. *Clin Infect Dis.* 2021;2019(Xx Xxxx):1-8. doi:10.1093/cid/ciab305
- Kutzler HL, Kuzaro HA, Serrano OK, Feingold A, Morgan G, Cheema F. Initial experience of bamlanivimab monotherapy use in solid organ transplant recipients. *Transpl Infect Dis.* 2021; [March]:1-7. doi:10.1111/tid.13662
- 22. McCreary EK, Bariola JR, Wadas RJ, et al. Association of subcutaneous or intravenous route of administration of casirivimab and imdevimab monoclonal antibodies with clinical outcomes in COVID-19. *medRxiv*. 2021;5(4):2021.11.30.21266756. doi:10.1001/jamanetworkopen.2022.6920
- Su J, Lu H. Opportunities and challenges to the use of neutralizing monoclonal antibody therapies for COVID-19. *Biosci Trends*. Published online 2021:1-6. doi:10.5582/bst.2021.01227
- 24. Wiltz JL, Feehan AK, Molinari NM, et al. Morbidity and Mortality Weekly Report Racial and Ethnic Disparities in Receipt of Medications for Treatment of COVID-19-United States. 2020;71(3):96-102. https://doi.org/10.1016/j.
- 25. Klein EJ, Hardesty A, Vieira K, Farmakiotis D. Use of anti-spike monoclonal antibodies in kidney transplant recipients with COVID-19: Efficacy, ethnic and racial disparities. *Am J Transplant*. 2022;22(2):640-645. doi:10.1111/ajt.16843
- 26. Wolf J, Abzug MJ, Wattier RL, et al. Initial guidance on use of monoclonal antibody therapy for treatment of coronavirus disease 2019 in children and adolescents. *J Pediatric Infect Dis Soc.* 2021;10(5):629-634. doi:10.1093/jpids/piaa175
- McCormick DW, Richardson LTC, Young PR, et al. Deaths in children and adolescents associated with covid-19 and mis-c in the united states. *Pediatrics*. 2021;148(5). doi:10.1542/ peds.2021-052273
- Wolf J, Abzug MJ, Anosike BI, et al. Updated Guidance on Use and Prioritization of Monoclonal Antibody Therapy for Treatment of COVID-19 in Adolescents. *J Pediatric Infect Dis Soc.* 2022;[Xx]:1-9. doi:10.1093/jpids/piab124



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The views expressed herein are those of the authors and do not necessarily reflect the views of the Warren Alpert Medical School of Brown University, Lifespan, or Hasbro Children's Hospital.

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## The Effect of Surgical Duration on Complications and Patient Reported Outcomes in Total Hip Replacement as Evaluated Through Multi-Surgeon Pooled FORCE Registry Data from a Tertiary Care Referral Total Joint Center

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## ABSTRACT <sup>-</sup>

**BACKGROUND:** The relationship between operative times and patient outcomes in total hip arthroplasty (THA) has not been well defined.

**METHODS:** From January 2016 to December 2019, data were prospectively collected for THA patients in the *FORCE-TJR* registry and hospital EMR of an academic total-joint center.

**RESULTS:** 1,123 patients were included. Operative times ranged from 36 to 366 minutes, with a mean operative time of 111.26+/-31.37 minutes. Unadjusted GLM showed HOOS pain, ADL, and QoL scores differed across operative times, with patients who had operative times between 106 and 120 minutes having significantly lower pain, higher function, and better quality of life at 12 months, especially compared to patients with operative times < 90 minutes. Patients who had operative times between 106 and 120 minutes had significantly better VR-12 PCS and MCS at 12 months. Although statistically significant, differences were small and did not persist after controlling for within-surgeon effects, patient socio-demographics and baseline patient-reported outcomes, suggesting that patient characteristics or within-surgeon effects may play a more significant role in these patient-reported outcomes than operative time.

**CONCLUSION:** This study showed that among THA patients, operative times were significantly associated with patient-reported outcomes at 12 months post-operatively, but is one of many surgeon and patient-related factors with effect on THA outcome.

**KEYWORDS:** Total Hip Arthroplasty, THA, Operative Time, PROM, FORCE-TJR

## INTRODUCTION

Shorter surgical times have been reported to be associated with a variety of better outcomes,<sup>1-4</sup> and could be assumed to decrease cost due to the high expense of operating room time.<sup>5</sup> It may appear that decreasing time of an operation will confer better result to the patient and be more cost effective, but this may be true only up to a point. We would propose that expert surgeons should be efficient and perform required steps of the operation in a timely manner while also avoiding rushing and errors, with the goal of the best long-term result for the patient. Furthermore, with the transition to shared-responsibility payer programs, including bundled care,<sup>6</sup> value is assigned to long-term successful outcomes and avoiding complication and reoperation. This idea of valuing quality over speed is a well-understood concept expressed commonly in familiar phrases such as *haste makes waste, and slow is smooth and smooth is fast.* 

The purpose of this study was to define the relationship between operative times and patient outcomes in total hip arthroplasty patients, drawing from the *Function and Outcomes Research for Comparative Effectiveness in Total Joint Replacement (FORCE-TJR) data registry of the Miriam Hospital Total Joint Center, Providence, RI.* The primary aim was to examine the relationship between operative times and patient-reported outcome measures 12 months postoperatively, and the secondary aim was to understand the relationship between operative time, length of hospital stay, and 90-day all-cause-readmissions.

## **METHODS**

This study was approved by the Lifespan Institutional Review Board.

## Data Source

Deidentified clinical data from patients undergoing total hip replacements were obtained from the Function and Outcomes Research for Comparative Effectiveness in Total *Joint Replacement (FORCE-TJR) data registry of the Miriam* Hospital Total Joint Center. This is a retrospective review of registry data from January 2016 to December 2019. The FORCE-TJR maintains outcome data on primary THR and TKR using validated patient reported outcome (PRO) instruments including, but not limited to, the hip disability and osteoarthritis outcome score (HOOS). This study uses the HOOS subscales of pain, activities of daily living (ADL), and quality of life (QOL), as well as the Veteran's Rand 12-item (VR-12) health survey instrument with 2 outcome domains (physical health and mental health). PROs were collected preoperatively and 12 months postoperatively. The FORCE-TJR also contains data on patient socio-demographics, including age, gender, race, educational level, marital status, insurance



status, body mass index, smoking status, diabetes, Charlson comorbidity index, and Oswestry low back score, all of which are included in this study. Additional data on length of hospital stay and 90-day-readmissions were obtained from the Miriam Hospital EPIC electronic medical record (EMR). Surgical time was defined as the difference between the timepoints logged in the EMR by the circulating nurse from "surgery start" to "surgery end." Clinically, these timepoints correspond to surgical incision to closure complete.

## **Outcomes Measures**

The primary study outcomes were the HOOS pain, ADL, and QoL outcome scores and secondary outcomes included the VR-12 physical component (PCS) and mental component (MCS) outcome scores. The HOOS is a validated patient-reported-outcome-measure (PROM)<sup>7</sup> with 2 domains relevant to THA (pain and ADL function), and a QoL subscale, with scores ranging from 1 to 100 with higher scores associated with better outcomes. The VR-12 is a validated PROM<sup>8</sup> with two domains (MCS and PCS), scores range from 0 to 80 where 50 is the general population mean, and higher scores are best. These measures were chosen as they represent different domains of recovery. Additional secondary study outcomes were length of hospital stay and 90-day all-cause readmissions.

## **Independent Variables**

The primary independent variable was operative time in minutes. For analysis purposes, operative time was examined as a categorical variable based on observed quintiles: <90 minutes, 90 to 105 minutes, 106 to 120 minutes, 121 to 135 minutes, and >135 minutes. The preoperative model covariates considered in this study were age, gender, race, educational level, marital status, insurance status, body mass index, smoking status, diabetes, Charlson comorbidity index, and Oswestry low back score.

## Power Analysis and Sample Size Justification

Power was estimated with intent to determine the difference between operative time quintiles that could be detected at 80% power with an estimated sample size of 1100 total hip arthroplasty cases, while accommodating the Bonferroni adjusted per-comparison alpha (p<0.005) necessary to maintain an overall two-tailed alpha of 0.05 across the hypotheses we tested. A Bonferroni adjustment was chosen for the purposes of power analysis because it is highly conservative and the Holm test, which was used in all analyses, is based on the empirical p-value attained at the time of data analysis which was unavailable. Given these parameters, a sample size of 1100 at the time of analysis maintained a power of approximately 80% to detect a difference of 3 points in the PROMS, a 0.22-day difference in hospital length of stay, and an 8% difference in 90-day all-cause readmission rates between operative time quintiles.

## **Statistical Methods**

Data was imported into SAS version 9.4 (SAS Institute Inc., Cary, NC) for data management and statistical analysis. Descriptive statistics for the sample socio-demographics and baseline patient reported outcomes were obtained for the overall sample and by operative time. Mean and standard deviation were reported for the continuous variables while frequency and percentage were reported for the categorical variables. Analysis of variance (continuous variables) and Chi-square test (categorical variables) were used to compare the patient socio-demographics and baseline patient reported outcomes across operative time. Generalized linear models (GLM) were used to assess the unadjusted association between study outcomes and operative times. Generalized estimating equations (GEE) were used to evaluate association between study outcomes and operative times, after accounting for study covariates and possible within-surgeon effects. Classical sandwich estimators were used to protect against possible model misspecification. Posthoc pairwise comparisons between operative time quintiles were conducted within the regression model via orthogonal contrasts. The Holm test was used to correct for multiple comparisons where appropriate in order to maintain a twotailed familywise alpha at 0.05. A p-value < 0.05 was used to determine statistical significance.

## RESULTS

## **Cohort Baseline Characteristics**

There were 1,123 total hip arthroplasty patients available for analysis between January 2016 and December 2019 (mean Age=65.5 years, 41% male). Operative times ranged from 36 minutes to 366 minutes, with a mean operative time of 111.26 minutes (SD=31.37). Table 1 presents the patient socio-demographics and baseline patient reported outcome measures. Several patient characteristics significantly differ across operative times, including age, gender, insurance status, education level, body mass index, Oswestry back pain score, baseline VR-12 mental component score, baseline HOOS pain score, and baseline HOOS activities of daily living score (p<0.05). (See Table 2: Comparisons of patient characteristics across time groups.) Patient age decreases across operative times, with a mean of 67.7 years for operative times <90 minutes and a mean of 64.1 years for operative times >135 minutes (p=0.006). The percentage of males, privately insured patients, and patients with a college degree increases with increasing operative times (p<0.0001, p=0.01, p=0.04 respectively). Similarly, body mass index and HOOS outcome scores increase with increasing operative times.

## **Outcome Assessments**

**Table 3** shows the distribution of patient reported outcome scores at 12 months postoperative, as well as the distribution of length of hospital and 90-day all-cause readmissions.



## 12-Months Patient-Reported Outcomes

Unadjusted GLM showed that HOOS pain scores 12-months post-operatively differed across operative times, with patients who had operative times of 106 to 120 minutes (M=89.04, p<0.0001 and p<0.0001 respectively), 121 to 135 minutes (M=88.75, p=0.0003 and p<0.0001 respectively), and >135 minutes (M=88.57, p=0.01 and p=0.002, respectively) having significantly lower pain at 3 months than patients with operative times <90 minutes (M=86.27) and between 90 and 105 minutes (M=87.35). Patients with operative times between 90 and 105 minutes had significantly lower pain than patients with operative times <90 minutes (M=80.01). There were no statistically significant differences in HOOS

Table 1. Sample Demographics and Baseline Patient Reported Outcomes

Characteristic	N	%
Male	459	41.28
BMI Category		
<25	230	21.12
25-30	398	36.55
30-35	293	26.91
35-40	137	12.58
>40	31	2.85
Race		
White	1042	94.73
Black or African American	27	2.45
Asian	4	0.36
Native American or Alaska Native	3	0.27
Native Hawaiian or Other Pacific Islander	1	0.09
Other	15	1.36
Refused	8	0.73
Married	712	64.26
Health Insurance Type		
Private	479	44.68
Medicaid	29	2.71
Medicare	520	48.51
Other	44	4.10
Cigarette smoker	65	5.88
Diabetes	108	9.91
Age, Mean ± SD	65.49 ±	± 10.04
BMI, Mean ± SD	29.39 ± 5.33	
OSWE Pain Intensity, Mean ± SD	2.00 ±	± 1.07
Charlson Comorbidity Index Count, Mean ± SD	0.40 ±	£ 0.78
Baseline VR12 PCS, Mean ± SD	31.30	± 9.59
Baseline VR12 MCS, Mean ± SD	54.89 ±	± 10.98
Baseline HOOS Pain, Mean ± SD	40.97 ±	± 17.56
Baseline HOOS ADL, Mean ± SD	46.47 ±	± 19.86
Baseline HOOS QoL, Mean ± SD	31.21 ±	± 17.97

pain scores at 12-months post-operatively between patients with operative times >105 minutes (all p>0.05) (**Table 4**).

HOOS ADL scores at 12-months post-surgery significantly differed across operative times in unadjusted GLM. Patients who had operative times between 106 and 120 minutes (M=89.36), between 121 and 135 minutes (M=88.83) and >135 minutes (M=89.40) had significantly fewer difficulties with activities of daily living than patients who had operative times <90 minutes (M=86.87, all p<0.0001) and between 90 and 105 minutes (M=87.87, p<0.0001, p=0.02, p<0.0001 respectively). Similarly, patients who had operative times between 90 and 105 minutes had significantly fewer difficulties with activities of daily living than patients who had operative times <90 minutes (p=0.02). There were no statistically significant differences in HOOS ADL scores among patients with operative times >105 minutes (all p>0.05) (**Table 4**).

HOOS QoL scores at 12-months post-surgery significantly differed across operative times in the unadjusted GLM. Patients with operative times between 106 and 120 minutes had significantly better quality of life at 12 months (i.e., higher QoL scores) (M=83.62) than patients with operative times <90 minutes (M=80.93, p<0.0001), between 90 and 105 minutes (M=80.61, p<0.0001), between 121 and 135 minutes (M=80.22, p<0.0001), and >135 minutes (M=80.93, p<0.0001). None of the other pairwise comparisons yielded statistically significant findings (**Table 4**).

VR-12 PCS at 12 months significantly differed across operative times in unadjusted GLM. Patients who had operative times between 106 and 120 minutes had significantly better physical functioning at 12 months (i.e., higher PCS scores) than patients who had operative times <90 minutes (M=47.53 vs. M=45.17, p<0.0001). Similarly, patients who had operative times >135 minutes had significantly better physical functioning at 12 months than patients who had operative times <90 minutes (M=45.17, p=0.001). There were no other statistically significant pairwise comparisons (**Table 4**).

VR-12 MCS scores at 12-months post-surgery significantly differed across operative times in the unadjusted GLM. Patients with operative times between 106 and 120 minutes had significantly better mental health at 12 months (i.e., higher MCS scores) (M=56.71) than patients with operative times <90 minutes (M=54.06, p<0.0001) and between 90 and 105 minutes (M=54.64, p=0.0003). Similarly, patients with operative times between 121 and 135 minutes (M=55.51) and >135 minutes (M=55.69) had significantly better mental health than patients with operative times <90 minutes (p=0.04 and p=0.01 respectively). Mental health at 12-months postoperative did not differ among patients who had operative times between 106 and 120 minutes and patients with operative times between 121 and 135 minutes (p=0.10) and >135 minutes (p=0.21). Similarly, mental health at 12-months postoperative did not significantly differ



Table 2. Comparisons of pat	ent characteristics acr	oss time groups
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	<90 min	91–105 min	106–120 min	121–135 min	>135 min	Р
Age	67.7 (10.2)	66.5 (10.8)	65.1 (9.7)	64.5 (9.2)	64.1 (10.1)	0.006
BMI	29.1 (5.4)	28.0 (4.8)	29.1 (5.1)	30.4 (5.7)	30.5 (5.3)	<0.0001
OWSE pain	2.3 (1.2)	2.0 (1.1)	1.8 (1.0)	2.0 (1.0)	1.9 (1.0)	<0.0001
CCI count	0.48 (0.90)	0.36 (0.62)	0.36 (0.85)	0.36 (0.85)	0.39 (0.71)	0.44
Pre PCS	31.2 (9.9)	30.7 (9.3)	31.6 (9.5)	31.6 (9.5)	31.2 (9.8)	0.78
Pre Pain	38.1 (18.2)	39.8 (17.2)	42.4 (18.1)	42.4 (18.1)	42.3 (16.3)	0.02
Pre MCS	52.7 (11.2)	55.1 (11.3)	56.6 (10.6)	56.6 (10.6)	55.5 (10.6)	0.002
Pre ADL	42.6 (20.5)	46.3 (19.1)	46.8 (20.3)	46.8 (20.3)	49.9 (18.9)	0.003
Male	71 (30.3%)	81 (39.1%)	109 (41.4%)	87 (43.1%)	110 (54.5%)	<0.0001
Race Asian Black Native Am. Native HI Other Refused White Married	0 (0%) 6 (2.6%) 2 (0.9%) 0 (0%) 3 (1.3%) 3 (1.3%) 219 (94%) 140 (60.1%)	1 (0.5%) 5 (2.5%) 0 (0%) 5 (2.5%) 0 (0%) 191 (94.6%) 138 (67.3%)	2 (0.8%) 2 (0.8%) 0 (0%) 1 (0.4%) 2 (0.8%) 3 (1.2%) 252 (96.2%) 175 (66.8%)	0 (0%) 3 (1.5%) 0 (0%) 0 (0%) 2 (1%) 1 (0.5%) 196 (97%) 124 (61.1%)	1 (0.5%) 10 (5.1%) 1 (0.5%) 0 (0%) 3 (1.5%) 1 (0.5%) 181 (91.9%) 133 (66.2%)	0.29
Insurance Medicaid Medicare Other Private	13 (5.7%) 130 (56.8%) 8 (3.5%) 78 (34.1%)	3 (1.5%) 95 (48.7%) 9 (4.6%) 88 (45.1%)	3 (1.2%) 117 (46.3%) 9 (3.6%) 124 (49%)	5 (2.5%) 93 (47%) 8 (4%) 92 (46.5%)	4 (2.1%) 83 (43%) 10 (5.3%) 96 (49.7%)	0.01
Smoker	17 (7.3%)	12 (5.9%)	18 (6.8%)	8 (4.0%)	10 (5.0%)	0.58
Diabetes	23 (10.2%)	20 (9.8%)	22 (8.4%)	23 (11.7%)	19 (9.6%)	0.85
School completed <hs ≥ College Grad HS/Some College Other</hs 	11 (4.7%) 81 (34.5%) 138 (58.7%) 5 (2.1%)	7 (3.4%) 100 (49.0%) 92 (45.1%) 5 (2.5%)	8 (3.1%) 127 (48.5%) 121 (46.2%) 6 (2.3%)	5 (2.5%) 97 (48.0%) 97 (48.0%) 3 (1.5%)	3 (1.5%) 106 (53.0%) 89 (44.5%) 2 (1.0%)	0.04

## Table 4. 12-month HOOS and VR-12 patient reported outcomes by operative times

Patient	Operative Time						
Reported Outcome	<90 minutes Mean (95% CI)	90–105 minutes Mean (95% CI)	106–120 minutes Mean (95% CI)	121–135 minutes Mean (95% CI)	>135 minutes Mean (95% CI)		
HOOS							
Pain	86.27	87.35	89.04	88.75	88.57		
	(85.78–86.74)	(86.85–87.83) †	(88.62–89.45) £†	(88.28–89.21) £†	(88.09–89.03) £†		
ADL	86.87	87.87	89.36	88.83	89.40		
	(86.39–87.34)	(87.38–88.34) †	(88.94–89.77) †£	(88.36–89.29) †£	(88.93–89.86) †£		
QoL	80.93	80.61	83.62	80.22	80.13		
	(80.26–81.58)	(89.90–81.29)	(83.07–84.16) †£	(79.53–80.89)*	(79.39–80.84)*		
VR-12							
PCS	46.26	47.53	46.34	47.16	45.17 (44.48–		
	(45.52–46.99)	(46.88–48.19)	(45.60–47.07) †	(46.43–47.89)	45.87) †		
MCS	54.06	54.64	56.71	55.51	55.69 (54.95–		
	(53.36–54.76)	(53.90–55.37)	(56.06–57.36) †£	(54.77–56.24) †	56.42) †		

 $\pm$  p<0.05 for comparisons to <90 minutes

 $\pm$  p<0.05 for comparisons to 90–105 minutes

\* p<0.05 for comparisons to 106-120 minutes



## **Table 3.** Descriptive Statisticsfor Study Outcome Measures

Measure	Mean	SD
12-month PROMS		
HOOS Pain	88.13	15.60
HOOS ADL	88.46	14.96
HOOS QoL	81.27	19.53
VR-12 PCS	46.59	10.09
VR-12 MCS	55.37	9.74
Length of Hospital Stay, in days	1.77	0.90
90-day All Cause Readmissions	366	32.59
90-day All Cause Inpatient Readmissions	51	4.54

among patients with operative times <90 minutes and between 90 and 105 minutes (p=0.54) or among patients with operative times between 90 and 105 minutes and between 121 and 135 minutes (p=0.30) or >135 minutes (p=0.21) (**Table 4**).

There were no statistically significant differences in patient-reported outcomes at 12 months after controlling for within-surgeon effects, patient socio-demographics and baseline patient reported outcomes in the GEE, suggesting that patient characteristics or withinsurgeon effects may play a more significant role in these patient-reported-outcomes than operative time.

## Length of Hospital Stay

There were no statistically significant differences in length of hospital stays between operative times.

## 90-Day All-Cause Readmissions

90-day-all-cause-readmissions significantly differed across operative times. (See **Table 5a,b**: Readmission rates by procedure time.) Patients who had

	<90 minutes	90–105 minutes	106–120 minutes	121–135 minutes	>135 minutes
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% Cl)
Readmission Rate	30% (24.5–36.1%)	34.3% (28.2–41.0%)	25.2% (20.3–30.8%)	33.0% (26.9–39.7%)	41.8% (24.5–36.1%)*

\* p<0.05 for comparisons to 106–120 minutes</p>

Table 5b. P-values for the above comparisons

Comparison	P-value
<90 minutes to	
90–105 minutes	0.99
106–120 minutes	0.91
121–135 minutes	0.99
> 135 minutes	0.09
90–105 minutes to	
106–120 minutes	0.25
121–135 minutes	0.99
> 135 minutes	0.59
106–120 minutes to	
121–135 minutes	0.44
> 135 minutes	0.002
121–135 minutes to	
>135 minutes	0.44

an operative time between 106 and 120 minutes had a significantly lower likelihood of 90-day all-cause readmission than patients who had an operative time >135 minutes (25.2% vs. 41.8%, p=0.002). There were no other statistically significant pairwise comparisons.

## DISCUSSION

This paper sought to determine the relationship between operative times and patient-reported outcomes, length of hospital stay, and 90-day all-cause readmissions among total hip arthroplasty patients. Analysis showed that among total hip arthroplasty patients, operative times were significantly associated with patient-reported outcomes 12 months post-operatively and 90-day all-cause readmissions but not with length of hospital stay. Further, the study indicated that this relationship between operative times and patient-reported outcomes and 90-day all-cause readmissions was not linear, suggesting an optimal operative time between 106 and 120 minutes.

Differences in the outcome measures, while statistically significant were very small, and the clinical significance of these small differences should be considered. The definition of a Minimal Clinically Important Change in HOOS score varies across publications,<sup>9-11</sup> but is reported at 6 to 33 depending on study and calculation methods.

Furthermore, these differences in patient-reported outcomes in relation to operative time, after controlling for within-surgeon effects, patient's socio-demographics and baseline patient reported outcomes became insignificant. This emphasizes that time in the operating room alone is not the only factor in the success of surgery, but instead this suggests that patient selection, and what is done in the operating room by the surgeon in the time they have may be more important factors influencing patient outcome.

It is important to note that the optimal operative time range we have determined in this study is slightly greater than a previous study using the ACS National Surgical Quality Improvement Program (NSQIP) database, which reported optimal THA operative time at approximately 80 minutes.<sup>12</sup> A THA operative time cutoff of greater than 150 minutes is suggested to prevent a significant but slight increase in revision rates using the Norwegian Arthroplasty Registry.<sup>13</sup> Historical average THA operative times reported in previous studies had been shown to decrease from 171.0 to 142.5 minutes from 1997–2004, using Medicare data,<sup>14</sup> but more recently, average THA operative times in NSQUIP patient sample has remained relatively uniform from 2008–2018<sup>15</sup> with median time reported as 87 minutes.

The current study has several limitations that warrant consideration. First, this study is a retrospective study of registry data; therefore, the findings cannot establish a causal relationship between operative times and patient outcomes. However, the study does suggest associations between operative times and several patient-related measures of outcome. A randomized controlled study of surgical times is very unlikely to be done for pragmatic and ethical reasons. Second, the clinical significances of the observed differences in patient-reported outcome measures are unknown. It may be postulated that, if these differences were of greater magnitude or the measured operative times were more extreme, clinical significances could be established. In this context, the study suggests a larger, prospective study of operative times on patient-reported outcomes.

Prolonged duration of surgery due to surgeon or operating room inefficiencies or errors should be avoided as this results in increased anesthesia time, cost, and risks associated with over-exposure of the surgical site without any benefit. Quick surgery resulting from skipped steps, less careful or rushed technique, similarly should be avoided as the slightly decreased cost of the diminished operative time could be outweighed by potential increased risk of



complication, re-operation, and worse long-term outcome for the patient. We propose that surgeons should operate efficiently and not waste time, but this should not come at the expense of rushing and compromising outcomes. Spending time to do the best job initially should be emphasized to prevent complications and revision surgery, which ultimately add more cost to the episode of care than what is saved by slightly decreased operative time.

Other stakeholders will also find this information useful. Defining surgery-time ranges resulting in optimal outcomes can help hospitals to provide adequate resources and block time, and payers to allocate appropriate value for the time of the team performing an operation. The results reported in this study help us understand surgical-time-outcome-quality relationship for total hip replacement in more quantitative terms.

#### References

- Bohl DD, Ondeck NT, Darrith B, Hannon CP, Fillingham YA, Della Valle CJ. Impact of Operative Time on Adverse Events Following Primary Total Joint Arthroplasty. J Arthroplasty. 2018 Jul;33(7):2256-2262.e4. doi: 10.1016/j.arth.2018.02.037. Epub 2018 Feb 17. PMID: 29551302.
- Duchman KR, Pugely AJ, Martin CT, Gao Y, Bedard NA, Callaghan JJ. Operative Time Affects Short-Term Complications in Total Joint Arthroplasty. J Arthroplasty. 2017 Apr;32(4):1285-1291. doi: 10.1016/j.arth.2016.12.003. Epub 2016 Dec 14. PMID: 28040399.
- Wills BW, Sheppard ED, Smith WR, Staggers JR, Li P, Shah A, Lee SR, Naranje SM. Impact of operative time on early joint infection and deep vein thrombosis in primary total hip arthroplasty. Orthop Traumatol Surg Res. 2018 Jun;104(4):445-448. doi: 10.1016/j.otsr.2018.02.008. Epub 2018 Mar 22. PMID: 29578104; PMCID: PMC6905075.
- Anis HK, Sodhi N, Klika AK, Mont MA, Barsoum WK, Higuera CA, Molloy RM. Is Operative Time a Predictor for Post-Operative Infection in Primary Total Knee Arthroplasty? J Arthroplasty. 2019 Jul;34(7S):S331-S336. doi: 10.1016/j.arth.2018.11.022. Epub 2018 Nov 22. PMID: 30545655.
- Lavernia CJ, Sierra RJ, Hernandez RA. The cost of teaching total knee arthroplasty surgery to orthopaedic surgery residents. Clin Orthop Relat Res. 2000 Nov;[380]:99-107. doi: 10.1097/ 00003086-200011000-00014. PMID: 11064979.
- Siddiqi A, White PB, Mistry JB, Gwam CU, Nace J, Mont MA, Delanois RE. Effect of Bundled Payments and Health Care Reform as Alternative Payment Models in Total Joint Arthroplasty: A Clinical Review. J Arthroplasty. 2017 Aug;32(8):2590-2597. doi: 10.1016/j.arth.2017.03.027. Epub 2017 Mar 20. PMID: 28438453.
- Goodman SM, Mehta BY, Mandl LA, Szymonifka JD, Finik J, Figgie MP, Navarro-Millán IY, Bostrom MP, Parks ML, Padgett DE, McLawhorn AS, Antao VC, Yates AJ, Springer BD, Lyman SL, Singh JA. Validation of the Hip Disability and Osteoarthritis Outcome Score and Knee Injury and Osteoarthritis Outcome Score Pain and Function Subscales for Use in Total Hip Replacement and Total Knee Replacement Clinical Trials. J Arthroplasty. 2020 May;35(5):1200-1207.e4. doi: 10.1016/j.arth. 2019.12.038. Epub 2019 Dec 27. PMID: 31952945; PMCID: PMC7193650.
- Kronzer VL, Jerry MR, Ben Abdallah A, Wildes TS, McKinnon SL, Sharma A, Avidan MS. Changes in quality of life after elective surgery: an observational study comparing two measures.

Qual Life Res. 2017 Aug;26(8):2093-2102. doi: 10.1007/s11136-017-1560-2. Epub 2017 Mar 29. PMID: 28357679; PMCID: PMC6309881.

- Deckey DG, Verhey JT, Christopher ZK, Gerhart CRB, Clarke HD, Spangehl MJ, Bingham JS. Discordance Abounds in Minimum Clinically Important Differences in THA: A Systematic Review. Clin Orthop Relat Res. 2022 Oct 19;481(4):702–14. doi: 10.1097/CORR.0000000002434. Epub ahead of print. PMID: 36398323; PMCID: PMC10013655.
- Lyman S, Lee YY, McLawhorn AS, Islam W, MacLean CH. What Are the Minimal and Substantial Improvements in the HOOS and KOOS and JR Versions After Total Joint Replacement? Clin Orthop Relat Res. 2018 Dec;476(12):2432-2441. doi: 10.1097/CORR.00000000000456. PMID: 30179951; PMCID: PMC6259893.
- Soh SE, Harris IA, Cashman K, Heath E, Lorimer M, Graves SE, Ackerman IN. Minimal Clinically Important Changes in HOOS-12 and KOOS-12 Scores Following Joint Replacement. J Bone Joint Surg Am. 2022 Jun 1;104(11):980-987. doi: 10.2106/ JBJS.21.00741. Epub 2022 Feb 22. PMID: 35648064.
- Surace P, Sultan AA, George J, Samuel LT, Khlopas A, Molloy RM, Stearns KL, Mont MA. The Association Between Operative Time and Short-Term Complications in Total Hip Arthroplasty: An Analysis of 89,802 Surgeries. J Arthroplasty. 2019 Mar;34(3):426-432. doi: 10.1016/j.arth.2018.11.015. Epub 2018 Nov 20. PMID: 30528133.
- Småbrekke A, Espehaug B, Havelin LI, Furnes O. Operating time and survival of primary total hip replacements: an analysis of 31,745 primary cemented and uncemented total hip replacements from local hospitals reported to the Norwegian Arthroplasty Register 1987-2001. Acta Orthop Scand. 2004 Oct;75(5): 524-32. doi: 10.1080/00016470410001376. PMID: 15513482.
- Ong K, Lau E, Manley M, Kurtz SM. Patient, hospital, and procedure characteristics influencing total hip and knee arthroplasty procedure duration. J Arthroplasty. 2009 Sep;24(6):925-31. doi: 10.1016/j.arth.2008.07.002. Epub 2008 Oct 5. PMID: 18835687.
- Acuña AJ, Samuel LT, Karnuta JM, Jella TK, Emara AK, Kamath AF. Have Total Hip Arthroplasty Operative Times Changed Over the Past Decade? An Analysis of 157,574 Procedures. J Arthroplasty. 2020 Aug;35(8):2101-2108.e8. doi: 10.1016/j. arth.2020.03.051. Epub 2020 Apr 6. PMID: 32340826.

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# Trends in Initiate Pediatric Opioid Prescriptions in Rhode Island: 2017–2021

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## ABSTRACT <sup>-</sup>

**OBJECTIVE:** To analyze recent trends in initiate pediatric opioid prescriptions dispensed in Rhode Island.

**METHODS:** All Rhode Island residents aged 0–17 years with an initiate opioid prescription dispensed between January 1, 2017 and December 31, 2021 were obtained from the Rhode Island Prescription Drug Monitoring Program. Analyses were conducted to investigate trends related to patient demographics, prescription characteristics, diagnosis codes, and prescriber type.

**RESULTS:** From 2017–2021, there was a decrease in the number of unique pediatric patients dispensed an initiate prescription, the number of initiate pediatric opioid prescriptions, and the initiate prescription dosage. Initiate opioid prescriptions were primarily related to dental-related diagnoses, and dentists and oral and maxillofacial (OMF) surgeons comprised the largest category of prescriber type.

**CONCLUSION:** Initiate pediatric opioid prescriptions have decreased in Rhode Island in recent years. However, there remain opportunities to educate prescribers on reducing opioid exposure to vulnerable populations, including the use of alternate analgesics.

**KEYWORDS:** opioids, prescription drugs, pediatrics, Rhode Island

## INTRODUCTION

A significant portion of the research and outreach programs addressing opioid misuse and overdose in the US primarily focus on adult populations; however, the deleterious impact of this epidemic on children and adolescents merits additional consideration. A study of national mortality data from the CDC for ages 0–19 reported approximately 9,000 pediatric opioid poisoning deaths between 1999 and 2016, representing a 286% mortality rate increase during that time.<sup>1</sup> The vast majority of these deaths were unintentional, and most involved prescription opioids. While mortality rates decreased in the following years, prescription opioids remained the top substances implicated in pediatric drug overdose deaths.<sup>2</sup>

Previous studies of pediatric opioid prescriptions have identified potential risk factors and patterns for this population. A study of children and young adults in the US in 2019 found that approximately 80% of opioid prescriptions were for opioid-naïve patients.3 Nearly half of these prescriptions were considered "high-risk", based on metrics including days-supply, drug type, morphine milligram equivalents (MMEs), and the presence of benzodiazepine prescriptions. This research group also found that increased daily dosage, co-prescriptions with benzodiazepines, and use of extended-release/long-acting drugs were associated with higher risk of subsequent opioid overdose.4 Risks presented by opioid prescriptions have also been identified in individual state analyses; 2016-2018 data from North Carolina Medicaid showed that nearly half of opioid-related adverse events in children were precipitated by a filled opioid prescription within the previous six months, often only days prior to the incident, and 1999-2014 data from Tennessee revealed that nearly 90% of reported opioid-related adverse events in children were related to their own prescription, and that approximately 70% of those events occurred when the patient was using the prescription properly.<sup>5-6</sup>

The source and purpose of opioid prescription is also an important point of consideration for pediatric populations. Some of the aforementioned studies reported that the highest percentage of pediatric opioid prescriptions analyzed were from dentists and surgeons, and furthermore that a small subset of providers were responsible for a significant volume of prescriptions, including those considered "highrisk" prescriptions.4,6 Another study of pediatric dental patients found that those who filled an opioid prescription had higher rates of subsequent opioid prescriptions as well as future events of opioid misuse.7 Use of opioids among family members may also be a risk factor for this group; a study of approximately 350,000 adolescents who were prescribed opioids found a higher rate of subsequent persistent use in patients who had a family member exhibiting long-term opioid use.8

Data from the Rhode Island Prescription Drug Monitoring Program (PDMP) have shown decreases in number of total opioid prescriptions, high-dose opioid prescriptions, and new opioid prescriptions across all age groups in recent years.<sup>9</sup> The purpose of this study was to conduct a more detailed analysis of initiate pediatric opioid prescription data



to investigate trends in patient demographics, prescription characteristics, diagnosis codes, and prescriber types. This could additionally help highlight any unique risks regarding opioid prescribing in pediatric patients compared to the general population, as well as identify potential patterns of overprescribing for particular diagnoses or within certain prescriber types.

## METHODS

## **Study Design and Population**

For this analysis, we utilized data from the RI PDMP from April 1, 2016 to December 31, 2021. Our study population included all RI residents that were dispensed their first opioid prescription by a retail pharmacy with a controlled substance registration, when they were a minor (aged 0–17 years) during the analysis period. Individuals were excluded from the analysis if they received an opioid prescription greater than 30 days prior to January 1st, 2017. Buprenorphine prescriptions prescribed for opioid use disorder treatment were excluded from this analysis.

An initial opioid prescription is defined in RI as either (1) the patient's first and only opioid prescription or (2) subsequent opioid prescriptions that started at least 30 days after the patient's previous opioid prescriptions. This was determined by using the prescription fill date and the days' supply of medication dispensed. A patient's first exposure to opioid prescriptions was flagged and for patients with more than one initial opioid prescription during the analysis period, one prescription per year was randomly selected for inclusion in the analysis of patient demographics to maintain independence of observations.

## Data Analysis

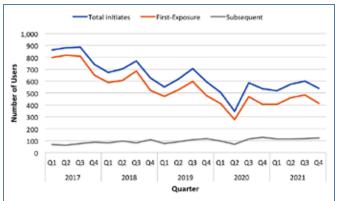
Patient demographic variables, including age and sex, were reported as recorded in the PDMP for all initiate pediatric opioid prescriptions, as well as characteristics of each initiate opioid prescription such as: opioid type and prescriber type. Prescriber type was also analyzed temporally across the 5-year time frame. Mean MME and days' supply were calculated, as well as their respective interquartile ranges, for all initiate pediatric opioid prescriptions. International Classification of Diseases-10 (ICD-10) codes were matched to their corresponding diagnoses. Prior to 2018, providers in RI were not required to indicate a diagnosis code on a patient's opioid prescription.9 This analysis is restricted to ICD-10 codes from 2020-2021, as years prior to this have counts of missing data. In addition to this, initial opioid prescriptions filled by pharmacies for which ICD-10 codes were missing for more than 80% of their dispensed opioid prescriptions were excluded from the analysis, as to avoid biased diagnostic entries. For brevity, only the top five diagnoses out of 102 were included in this analysis.

To determine if first exposure pediatric opioid prescriptions differ from overall initiate pediatric opioid prescriptions, we conducted a sensitivity analysis analyzing the above metrics on first exposure pediatric initiate prescriptions. Patient demographics, prescription characteristics and diagnostic codes were compared between first exposure initiate prescriptions and non-first exposure initiate prescriptions using Chi-Square test of association. In addition, differences in mean MME and days' supply across years within first exposure initiate prescriptions were compared. Based on the homogeneity of the samples, if samples were found to have unequal variances, then we performed a Welch's test. Otherwise, an Analysis of Variance (ANOVA) test was performed. If applicable, a Tukey-Kramer test was performed to assess differences between samples. For all tests, p-values less than .05 were statistically significant.

## RESULTS

The number of unique pediatric initiate users dropped from 3,368 in 2017 to 2,231 in 2021 (33.8%; Figure 1). When compared to RI pediatric population, the percent of minors being dispensed an initiate opioid prescription has dropped 40.5% between 2017 and 2021 (Table 1). Of these users, the distribution of binary sex remained equal, and 79.3% of users were between the ages of 12 and 17 years. All age categories have a downward trend from 2017 to 2020; however, ages 0-5 and 12-17 are showing increasing trends from 2020 to 2021 (Table 1). When comparing first exposure users and non-first exposure users, the relationship between binary sex and user type was significant,  $\chi^2$  (1, N=12,808) = 25.2, p < .0001). First exposure users were more likely to be male and non-first exposure users were more likely to be female. There was also a significant relationship between age category and user type,  $\chi^2$  (2, N=12,808) = 73.4, p <.0001). First exposure users were more likely to be between the ages of zero and 11-years-old when compared to non-first exposure users (Table 2).







	2017 N (%)	2018 N (%)	2019 N (%)	2020 N (%)	2021 N (%)	Total
Sex						
Female	1,621	1,351	1,241	1,023	1,082	6,316
	(48.1)	(48.8)	(50.3)	(51.9)	(48.5)	(49.3)
Male	1,747	1,418	1,226	949	1,149	6,489
	(51.9)	(51.2)	(49.7)	(48.1)	(51.5)	(50.7)
Age	Age					
0–5	241	187	138	87	127	780
	(7.2)	(6.8)	(5.6)	(4.4)	(5.7)	(6.1)
6–11	610	486	325	247	198	1,866
	(18.1)	(17.6)	(13.2)	(12.6)	(8.8)	(14.6)
12–17	2,517	2,096	2,005	1,638	1,906	10,162
	(74.7)	(75.7)	(81.2)	(83.1)	(85.4)	(79.3)
Proportion	Proportion of RI minors dispensed an initiate opioid prescription (%)					
	1.3	1.0	0.9	0.7	0.8	—

## **Table 1.** Demographics of initiate opioid prescription users aged 0–17years, 2017–2021.

**Table 2.** Demographics of initiate opioid prescription users aged 0–17years during their initial opioid prescription in RI, 2017–2021.

	First	Subsequent	Chi-sq		9
	Exposure		df	Value	р
Total	10,880	1,928			
Sex			1	25.2	<.0001*
Female	5,265 (48.4)	1,051 (54.6)			
Male	5,615 (51.6)	874 (45.4)			
Age Category			2	73.4	<.0001*
0–5	718 (6.6)	62 (3.2)			
6–11	1,667 (15.3)	199 (10.3)			
12–17	8,495 (78.1)	1,667 (86.5)			

\*Indicates a p-value that is statistically significant ( $\alpha = 0.05$ ).

## Table 3. Characteristics of pediatric initiate opioid prescriptions, 2017–2021.

	First	Subsequent	Total		Chi-s	q
	Exposure Rx	Rx		df	Value	р
Total	10,880	2,226	13,106			
Opioid Prescribed				9	1,051.9	<.0001*
Hydrocodone	4,928 (45.3)	561 (25.2)	5,489 (41.9)			
Oxycodone	4,063 (37.3)	1,072 (48.2)	5,135 (39.2)			
Codeine	1,569 (14.4)	246 (11.1)	1,815 (13.9)			
Tramadol	218 (2.0)	98 (4.4)	316 (2.4)			
Morphine	60 (0.6)	172 (7.7)	232 (1.8)			
Hydromorphone	23 (0.2)	56 (2.5)	79 (0.6)			
Buprenorphine†	10 (0.1)	14 (0.6)	24 (0.2)			
Methadone	<5	6 (0.3)	<5			
Fentanyl	8 (0.1)	0	8 (0.1)			
Prescriber Type				4	540.2	<.0001*
Dentist/OMF Surgeon	4,489 (41.3)	474 (21.3)	4,963 (37.9)			
Physician	1,853 (17.0)	746 (33.5)	2,599 (19.8)			
Adv Nurse	887 (8.2)	222 (10.0)	1,109 (8.5)			
PA	321 (3.0)	155 (7.0)	476 (3.6)			
Missing	3,330 (30.6)	269 (28.3)	3,959 (30.2)			
Diagnosis a, b, †, c				8	167.8	<.0001
Diseases of oral cavity and salivary glands	512 (18.4)	69 (8.4)	581 (16.1)			
Injuries to the knee and lower leg	142 (5.1)	65 (7.9)	20 (5.7)			
"Other" acute post-procedural pain	160 (5.8)	37 (4.5)	197 (5.5)			
Joint disorders (including dentofacial anomalies and disorders of the jaw)	78 (3.8)	69 (8.4)	147 (4.1)			
Injuries to shoulder and upper arm	93 (3.3)	30 (3.6)	123 (3.4)			

Note: Initiate prescriptions are defined as either the patient's first opioid prescription or an opioid prescription that started  $\geq$ 30 days after the patient's previous opioid prescription ended.

\*Indicates a p-value that is statistically significant ( $\alpha = 0.05$ ).

+ Excludes buprenorphine products that are only FDA-approved for medication-assisted treatment of opioid use disorder

a Excludes n=1,193 prescriptions (33.1%) missing a diagnosis code.

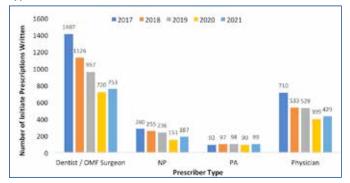
b Mandatory ICD-10 reporting by prescribers to pharmacies on opioid prescriptions was introduced in July 2018. The Prescription Drug Monitoring Program began collecting ICD-10 codes in April 2019; pharmacies are not required to report the ICD-10 codes.

c Data from 2020-2021, and pharmacies with >80% of ICD-10 codes missing were excluded from analysis.



Overall, the number of initiate pediatric opioid prescriptions dispensed dropped from 3,431 in 2017 to 2,300 in 2021 (33.0%). Within this, the number of first exposure initiate pediatric opioid prescriptions dropped from 3,076 in 2017 to 1,763 in 2021 (42.7%). The two most common initiate opioid prescriptions dispensed to minors were hydrocodone and oxycodone, making up 81.1% of all prescriptions. In addition, dentists and oral and maxillofacial (OMF) surgeons prescribed 37.9% of all pediatric initiate opioid prescriptions dispensed between 2017 and 2021 (Table 3). Pediatric initiate opioid prescriptions prescribe by dentists, OMF surgeons and physicians have decreased over the last 5 years, while prescriptions written by nurse practitioners (NPs) and physicians assistants have fluctuated (Figure 2). When comparing first exposure pediatric initiate opioid prescriptions and non-first exposure initiate opioid prescriptions, there was a significant relationship between opioid type and user type,  $\chi^2$  (9, N=13,106) = 1,051.9, p <.0001. First exposure prescriptions were more likely to include hydrocodone, codeine, and fentanyl. The relationship between prescriber type and user type was also significant,  $\chi^2$  (4, N=13,106) = 540.2, p <.0001. First exposure prescriptions were more likely to be prescribed by a dentist, or OMF surgeon when compared to non-first exposure prescriptions (Table 3).

## **Figure 2.** Number of Initiate Opioid Prescriptions Dispensed by Prescriber Type, 2017–2021 <sup>a</sup>



a Excludes n=3,959 prescriptions (30.2%) missing prescriber type.

Days' supply	MME
4.1	26.0
3.9	22.5
3.4	22.5
3.3	22.4
3.2	23.5
4.2	2.03
.0018	<.0001
	4.1 3.9 3.4 3.3 3.2 4.2

**Table 4.** ANOVA Comparing Mean MME and Days' Supply of First-Exposure Initiate Pediatric Opioid Prescriptions by year, 2017–2021.

Pediatric initiate opioid prescriptions dispensed between 2017 and 2021 had a mean days' supply of 3.6 days. When comparing mean days' supply of first exposure pediatric initiate opioid prescriptions across all 5 years, the variance across the samples was equal and so, a one-way ANOVA was used. We rejected the null hypothesis that days' supply was the same across all years (F=4.2, p=.0018, **Table 4**).

Pediatric initiate opioid prescriptions dispensed between 2017 and 2021 had a mean MME of 23.8 When comparing mean MME of first exposure pediatric initiate opioid prescriptions across all 5 years, the variance across the samples was unequal (p=.089). We rejected the null hypothesis that stated that mean MME was the same across all years (F=2.03, p<.0001, **Table 4**).

The most common diagnosis for a pediatric initiate opioid prescription was for "diseases of oral cavity and salivary glands", which accounted for 16.1% of prescriptions (Table 3). Diagnoses for oral cavity and salivary gland disease increased from 247 to 334 (35.4%) from 2020 to 2021. First exposure pediatric initiate opioid prescriptions are more likely to be prescribed with diagnosis codes for "diseases of oral cavity and salivary glands", "Other acute post-procedural pain", and "joint disorders (including dentofacial anomalies and disorders of the jaw)",  $\chi 2 (8, N=3,606) = 167.8$ , p < .0001 (Table 3). About 209 patients under the age of 12 years old were dispensed either Codeine or Tramadol as a first-exposure initial prescription and 196 (93.8%) of these patients were first-exposure users. Roughly 45.7% of these prescriptions were prescribed by physicians, and 39.1% by dentists or OMF surgeons.

## DISCUSSION

This analysis found an overall decline in initiate pediatric opioid prescribing patterns in Rhode Island between 2017 and 2021. Specifically, reductions were observed in number of unique pediatric initiate users, number of initiate pediatric opioid prescriptions, mean days' supply, and mean MMEs. These trends generally match those seen across all age groups within the state.<sup>10</sup>

First exposure users were more likely to be male and between the ages of 0–11 compared to non-first exposure users. Dentists and OMF surgeons comprised the leading group of initiate pediatric opioid prescriptions, followed by physicians, and first-exposure prescriptions were more likely to be prescribed by these practices compared to other prescriber types. Likewise, "diseases of oral cavity and salivary glands" was the most common diagnosis type for initiate prescriptions. Prescribing patterns for these groups followed the overall trend, with reductions in initiate prescriptions over the study period, whereas prescribing trends among NPs and physicians' assistants demonstrated more fluctuation.



When analyzing drug type, hydrocodone and oxycodone comprised the majority of dispensed initiate prescriptions. These were followed by codeine and tramadol. Of important note, approximately 200 patients under the years of 12 were dispensed codeine or tramadol, despite these drugs being contraindicated for this age group by the FDA.<sup>11</sup>

These findings generally complement pediatric opioid prescribing patterns observed in similar state and nationwide studies. A recent analysis of dispensing in South Carolina found a significant decline in opioid prescribing rates amongst children, although an observed reduction in MMEs was limited to ages 0–9.<sup>12</sup> Another study of an all-payer opioid prescription database noted a decrease in opioid prescription rates for ages 25 and younger between 2006–2018.<sup>13</sup> Higher rates of decline were seen in more recent years, which may be reflective of the rise of national initiatives designed to curb the opioid overdose epidemic.

When considering dental-related prescriptions specifically, an investigation using Medicaid claims database data for 2012-2019 reported an overall reduction in dental-related pediatric opioid prescriptions, although also noted that dental professions made up an increasingly higher percentage of pediatric opioid prescribers.<sup>14</sup> The findings from the current analysis also compliment recent all-ages data from Rhode Island, which showed substantial decreases in dental-related opioid prescriptions as well as number of dental providers actively prescribing opioids.<sup>15</sup> However, the US continues to be a significant dispenser of opioids for dental-related procedures; for example, a study of prescriptions by dentists in 2016 found that the proportion of those that were for opioids was 37 times greater among US dentists compared to their English counterparts.<sup>16</sup>

Although this analysis, along with similar studies, suggests an encouraging trend of reductions in pediatric opioid prescriptions, other investigations highlight lingering potential issues. One of the aforementioned studies of pediatric opioid prescribing in the US found that approximately 42% of prescriptions for opioid-naïve children exceeded a 3-day supply, and, similar to our findings, children were still being prescribed codeine and tramadol despite federal guidelines.<sup>3</sup> Many states have implemented cap-laws that place limits on dose and/or duration of opioid prescriptions, however a recent study found no association between implementation of these laws and changes in opioid dispensation patterns in children and adolescents, suggesting the need for additional measures.17 The consistent and proper use of Prescription Drug Monitoring Programs, as well as patient education on the risks of opioids, may also encourage safer prescribing patterns. One survey of dentists found that inconsistent PDMP implementation and lack of patient education was associated with higher rates of opioid prescribing, and another reported that, despite the comparable efficiency of non-opioid analgesics, many patients perceived opioids to be preferable for pain management.<sup>18-19</sup> In both studies, only approximately half of respondents reported consistent use of their state's PDMP.

In November 2022, the Centers for Disease Control and Prevention (CDC) published updated guidelines for prescribing opioid for pain management. These guidelines highlight that acute pain can often be managed with the use of nonopioid medications, and that prescribers should maximize the utility of these non-opioid pharmacologic treatments, including NSAIDs and acetaminophen when appropriate.<sup>20</sup> Although the intended target for the guidelines is adult patients, the authors recommend that treatment for minors also aligns with the guidelines to ensure safe and effective pain management.

In 2019, the Rhode Island Department of Health developed the PharmD academic detailing program to deliver educational sessions to Rhode Island prescribers about acute pain management best practices. RIDOH's trained pharmacist encourages prescribers to utilize non-opioid treatment options first. Additionally, prescribers are provided with guidance on prescribing opioids appropriately and safely for eligible patients where the benefits outweigh the risks. Regarding subsequent exposures, RIDOH has provided advice including the re-evaluation of patients after completion of a post-operation opioid prescription, as well as safely titrating patients off opioids. Guidance related to contraindicated substances for minors such as tramadol and codeine follow FDA and CDC recommendations.

The primary strength of this analysis is the robustness of the dataset. The RI PDMP functions as a centralized system for collecting data on all controlled substances dispensed by retail pharmacies with a Controlled Substance Regulation (CSR) within the state. Furthermore, in July 2016, all dispensers were automatically registered within the PDMP. Additionally, Schedule V substances and opioid agonists were added to reporting requirements, and reporting timeline was reduced to one business day.<sup>9</sup> Therefore, the vast majority of the data in this investigation fell within these regulations, contributing to completeness of the dataset.

One limitation of this study is that the RI PDMP only carries data on dispensed substances, and therefore does not capture prescriptions that are prescribed but not dispensed to the patient. Additionally, mandatory ICD-10 reporting by prescribers to pharmacies on opioid prescriptions was introduced in July 2018, and the PDMP did not begin collecting ICD-10 codes until April 2019, which limited the scope of the diagnostic analyses conducted.

Overall, there has a been a decline in initiate pediatric opioid prescribing in Rhode Island, including amongst "high-prescriber" professions. Despite this positive trend, there remain potential avenues for future reduction in pediatric opioid use. Additional consideration should be given to first-exposure patients, as these tend to be younger than opioid-exposed individuals. Prescribers should aim to avoid prescribing contraindicated opioid drugs in children, and further



consideration should be given to non-opioid analgesics including non-steroidal anti-inflammatory drugs (NSAIDs), as per CDC recommendations.<sup>20</sup> The Rhode Island PDMP continues to serve as a helpful tool to promote individual patient safety, as well as provides insight into prescribing patterns and behaviors that can help inform best practices.

#### References

- Gaither JR, Shabanova V, Leventhal JM. US national trends in pediatric deaths from prescription and illicit opioids, 1999-2016. JAMA Network Open. 2018;1(8): e186558. doi:10.1001/jamanetworkopen.2018.6558.
- 2. Renny MH, Cerda M. Addressing drug overdose deaths in pediatrics: Where do we go from here. Pediatric Research. 2021;90:1108-1109.
- Chua K, Brummett CM, Conti RM, Bohnert AS. Opioid prescribing to US children and young adults in 2019. Pediatrics. 2021;148(3): e2021051539.
- Chua K, Brummett CM, Conti RM, Bohnert AS. Association of opioid prescribing patterns with prescription opioid overdose in adolescents and young adults. JAMA Pediatr. 2020;174(2): 141-148. doi:10.1001/jamapediatrics.2019.4878.
- Brown KW, Carlisle K, Raman SR, Shrader P, Jiao M, Smith MJ, Einhorn LM, Wong CA. Children and the opioid epidemic: Age-stratified exposures and harms. Health Affairs. 2020;39(10): doi:10.1377/hlthaff.2020.00724.
- Chung CP, Callahan ST, Cooper WO, et al. Outpatient opioid prescriptions for children and opioid-related adverse events. Pediatrics. 2018;142(2): e20172156.
- Schroeder AR, Dehghan M, Newman TB, Bentley JP, Park KT. Association of opioid prescriptions from dental clinicians for US adolescents and young adults with subsequent opioid use and abuse. JAMA Intern Med. 2019;179(2):145-152.
- Harbaugh CM, Lee JS, Chua K, et al. Association between longterm opioid use in family members and persistent opioid use after surgery among adolescents and young adults. JAMA Surg. 2019;154(4):e185838.
- Paiva TJ, Nitenson AZ, Antinozzi D, et al. Dispensed Opioid, Buprenorphine, Benzodiazepine, and Stimulant Prescriptions among Rhode Island Residents, 2017-2021. In Press. 2023.
- 10. Opioid Prescribing Data. Rhode Island Department of Health. https://preventoverdoseri.org/prescribing-data/.
- FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. U.S. Food and Drug Administration. 20 Apr 2017. https://www.fda.gov/media/104268/ download.
- Basco WT, McCauley JL, Zhang J, et al. Trends in dispensed opioid analgesic prescriptions to children in South Carolina: 2010-2017. Pediatrics. 2021;147(3):e20200649.
- Renny MH, Yin HS, Jent V, Hadland SE, Cerda M. Temporal trends in opioid prescribing practices in children, adolescents, and younger adults in the US from 2006-2018. *JAMA Pediatrics*. 2021;175(10):1043-1052. doi:10.1001/jamapediatrics.2021.1832.
- Okunev I, Frantsve-Hawley J, Tranby E. Trends in national opioid prescribing for dental procedures among patients enrolled in Medicaid. *JADA*. 2021;152(8):622-630.
- Onyejekwe C, Chambers LC, Zwetchkenbaum S. Trends in opioid prescribing practices of Rhode Island dental professionals. 2020;4(1):14-18.
- Suda KJ, Durkin MJ, Calip GS, et al. Comparison of opioid prescribing by dentists in the United States and England. JAMA Network Open. 2019;2(5):e194303.

- 17. Stone EM, Tormohlen KN, McCourt AD, et al. Association between state opioid prescribing cap laws and receipt of opioid prescriptions among children and adolescents. *JAMA Health Forum*. 2022;3(8):e222461.
- McCauley JL, Leite RS, Gordan VV, et al. Opioid prescribing and risk mitigation implementation in the management of acute pain. *JADA*. 2018;149(5):353-362.
- Heron MJ, Nwokorie NA, O'Connor B, Brown RS, Fugh-Berman A. Survey of opioid prescribing among dentists indicates need for more effective education regarding pain management. *JADA*. 2022;153(2):110-119.
- Dowell D, Ragan K, Jones CM, Baldwin GT, Chou R. CDC clinical practice guideline for prescribing opioids for pain – United States, 2022. Morbidity and Mortality Weekly Report. 2022;71(3):1-95.

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#### **Ethics Statement**

This study was part of RIDOH's response to the opioid overdose epidemic in Rhode Island and did not require institutional review board approval. This analysis is limited to prescriptions dispensed vs. prescribed, and overlap was assumed based on the dispensed date and day supply, which may inaccurately represent prescribing practices. All authors approve this work, and we have no conflicts of interest to disclose.

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#### Disclaimer

The views expressed herein are those of the authors and do not necessarily reflect the views of the Bureau of Justice Assistance.

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## How All-Payer Claims Databases (APCDs) Can be Used to Examine Changes in Professional Spending: Experience from the Rhode Island APCD

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## ABSTRACT

States are increasingly the focus of health care spending reform efforts given political deadlock at the federal level. Using the Rhode Island All-Payer Claims Database (APCD) from 2016 to 2019, a modified National Uniform Claim Committee (NUCC) provider taxonomy, and the 2021 Restructured BETOS Classification System (RBCS), we evaluate professional spending trends in commercial and Medicaid populations, identify specialties and clinical service categories driving trends, and examine price and volume contributions to spending changes. We found that professional spending from 2016–2019 in Medicaid is increasing faster than professional spending in commercial (5.2% vs. 2.7% annually). We also found that nurse practitioner and physician assistant evaluation and management (E&M), behavioral health services E&M, anesthesia, diagnostic radiology imaging, and orthopedic procedures were among the largest areas of spending increase during the study period in Rhode Island. Threeyear trends showed heterogeneity in whether volume or price was primarily responsible for these spending increases.

**KEYWORDS:** health care costs, state health policy, health care financing, Medicaid, health economics

## INTRODUCTION

Trends in national health care spending growth<sup>1</sup> are of great concern for states as they seek to ensure affordability of health care for their residents. The opportunity cost of high health care spending and spending growth is substantial; rising health care costs hinder investment in social services such as education, housing, transportation, and infrastructure.<sup>2</sup> States have increasingly been the focus of attempts to evaluate and moderate health care spending growth.<sup>3,4</sup> Identifying factors that increase health care costs is an important step towards improving the value and efficiency of care delivery. State All-Payer Claims Databases (APCDs) are a potentially valuable source of information to facilitate understanding of overall cost trends and the drivers of those trends.<sup>5</sup>

Total health care spending can be divided into two components: professional spending and facility spending. Professional spending refers to reimbursement for health care personnel rendering care services. Facility spending refers to reimbursement for inpatient and outpatient centers where care is rendered. In recent years, national inpatient hospital spending has either been stable or declining as a result of care shifting to outpatient care settings (e.g., hospital outpatient departments, offices, and ambulatory surgical centers) where appropriate.6-10 Innovative methods to evaluate professional spending trends are needed. The growth of spending on specialty care is of particular interest, as a potential driver of both overall costs and cost increases.<sup>11,12</sup> A study of Medicare beneficiaries from 2000-2019 showed an increase in outpatient office visits to specialists, representing increased coordination burden for PCPs13 and likely proxies for increased use of specialty services. APCDs are uniquely suited to provide information on the growth of specialty care, and afford a systems-level perspective to consider trends across public and private insurance programs.

Rhode Island presents a unique opportunity to examine trends in specialty and primary care because prior policy efforts have been focused on increasing primary care spending as one mechanism to control total health care costs. Specifically, the Rhode Island Office of the Health Insurance Commissioner has implemented affordability standards in 2010 which emphasized primary care and established a hospital rate review process for commercial payers. Importantly, regulatory authority through hospital rate review restricts inpatient and outpatient facility rate increases, but does not apply to professional spending.<sup>14-16</sup> A 2018 HCCI report found RI professional spending among commercial payers exceeded the national average.<sup>17</sup> Primary care spending as a proportion of total spending in Rhode Island remains high relative to other states,<sup>18</sup> but little is known about the professional spending trends as they pertain to specific clinical areas.

In this study, we examine trends in professional spending for Rhode Island residents from 2016 to 2019 in commercial and Medicaid Managed Care (hereafter Medicaid) populations; these include individuals of all ages, who account for approximately 75% of the member months captured by the RI APCD and 50% of the total spending. To evaluate trends in professional spending, we use the Restructured Berenson-Eggers Types of Service Classification System (RBCS)<sup>19</sup> that we have enhanced to be more comprehensive



for service categories relevant for applications beyond Medicare populations (e.g., including obstetric and pediatric spending for younger insured populations). RBCS was developed to track changes in spending under the Medicare Physician Fee Schedule according to clinically meaningful categories. Using this approach, we compare changes in primary and specialty care professional spending in commercial and Medicaid populations, identify specialties and clinical service categories for which costs are increasing, and for those examine whether cost increases are explained by volume or price. This analytic approach serves as a model for other states seeking to turn robust claims data captured by APCDs into summary information that is actionable for health system performance monitoring and evaluation and policy development.

In this paper, we seek to answer three main research questions: first, how are broad professional spending trends similar and different across commercial and Medicaid populations? Second, which provider specialties and service categories are responsible for professional spending trends from 2016 to 2019? Finally, are professional spending trends attributable to changes in volume or price?

## **New Contribution**

All-Payer Claims Databases (APCDs) are a tool for studying health system performance monitoring and policy. This study further demonstrates (1) APCDs can be leveraged to study professional spending across payers, (2) professional spending can proxy for total health care spending, and (3) practical tools for studying professional spending generalizable to other payers/states.

## **Data and Methods**

We constructed an analytic dataset for the study period, 2016 to 2019, using the Rhode Island APCD which included all professional claims linked to provider elements to be able to identify provider specialty information for all Rhode Island residents enrolled in either commercial (fully and reported self-insured) or Medicaid MCO insurance plans. We excluded Medicaid FFS professional spending (approximately 9% of total Medicaid spending. In RI patients often spend a few months in Medicaid FFS before being enrolled in a managed care plan, so we did not believe that examining this in detail would produce valid systematic findings. We excluded approximately 16,000 (~5%) commercial members per year who lack pharmacy claims (due to prescription drug carveouts), and for whom total costs cannot be evaluated.

Each medical claim line includes information about the clinician who rendered the service and their corresponding National Uniform Claim Committee (NUCC) provider taxonomy code.<sup>20</sup> As the NUCC provider taxonomy was very granular, we used a more parsimonious approach to construct a clinically relevant provider classification system; a hybrid between the pure NUCC taxonomy and a BETOS-adapted

taxonomy used in a recent Urban Institute report.<sup>21</sup> The crosswalk between the NUCC taxonomy and our adapted taxonomy as well as a visual representation of our provider classification system is available for dissemination by the corresponding author. The main categories of clinicians are primary care, non-procedural medical, procedural internal medicine, surgical, other physicians, and other health professionals (e.g., nurse practitioners, physician assistants, social workers, physical therapists, etc.).

We then linked our claims dataset with the Restructured BETOS Classification System (RBCS) to identify clinically relevant service groupings for study. RBCS was developed to categorize healthcare services from the Medicare physician fee schedule (MPFS, Part B) into clinically meaningful groups and subcategories.<sup>19</sup> The first level of classification (hereafter, 'RBCS Level 1') includes anesthesia, durable medical equipment (DME), evaluation and management (E&M), imaging, other, procedures, tests, and treatments. The second level of classification (hereafter, 'RBCS Level 2') includes groups of Current Procedural Terminology (CPT)/Healthcare Common Procedures Coding System (HCPCS) codes of related services. For example, "CT scans" are a RBCS Level 2 subset of the "Imaging" RBCS Level 1 service category. Beyond applications in the Medicare program, the BETOS coding system has previously been used to study utilization among Veterans' Administration-Medicaid dual enrollees,<sup>22</sup> Medicaid primary care services in Oregon,<sup>23</sup> and a study of commercial patients insured by BCBSTX.24

Each professional claim was associated with a single provider specialty. Each claim was then assigned to a single RBCS Level 2 service category, nested within a Level 1 RBCS category. First, we calculated per-member-per-month (PMPM) spending across broad clinical categories and RBCS Level 1 service categories for commercial and Medicaid (see Table 2) members, separately. Next, we evaluated RBCS Level 1 service categories with the largest PMPM spending increases within specific provider specialties (see Table 3). Finally, we studied RBCS Level 2 service categories with the largest PMPM spending increases within specific provider specialties (see Table 4). In contrast to RBCS Level 1 service categories (e.g., Radiology Imaging), RBCS Level 2 service categories (e.g. Radiology CT Scans) offer the level of granularity necessary to meaningfully analyze changes in service price or volume over time. The largest RBCS Level 2 spending areas were evaluated to determine if trends in spending were driven primarily by volume or price (see Figure 1). This stepwise approach to health care cost analysis afforded a broad view of cost trends in addition to a granular view of the specific professional services responsible for those trends. Given stark differences across payers in age distribution, prices, and common population morbidities, analyses are conducted within each payer.

Our analyses have focused on professional spending given that the majority of health care spending has at least some



Dollar Amounts		Year			2016–2019	Average Annual
	2016	2017	2018	2019	% Increase	% Increase
Total Paid Claims	5.8B	6.1B	6.2B	5.5B		
Commercial						
Member Months	3.66M	3.51M	3.24M	3.01M		
Total Paid Claims	1.74B	1.73B	1.63B	1.61B		
Professional (% of Total Commercial)	521M (30%)	511M (30%)	483M (30%)	474M (29%)		
Professional PMPM	143	145	149	155	8.4%	2.7%
Professional Assignable to Specialty (% of Total Commercial)	441M (25%)	427M (25%)	410M (25%)	411M (26%)		
Medicaid Managed Care						
Member Months	2.70M	2.85M	2.85M	2.77M		
Total Paid Claims	1.10B	1.22B	1.26B	1.32B		
Professional (% of Total Medicaid MCO)	314M (29%)	338M (28%)	355M (28%)	373M (28%)		
Professional PMPM	116	119	124	135	16%	5.2%
Professional Assignable to Specialty (% of Total Medicaid MCO)	191M (17%)	214M (18%)	232M (18%)	223M (17%)		

Table 1. Trends in Spending by Commercial and Medicaid Managed Care Payers, 2016–2019

Notes: PMPM refers to "Per Member Per Month" spending. PMPM spending measures adjust for changes insurance enrollment in each study year and is therefore the primary metric of analysis used in the remainder of this paper. "Professional Assignable to Specialty" is the denominator used in the remainder of this paper for cost driver analyses.

	Spending Metrics					
	Total Spending 2019	PMPM 2019	PMPM Diff 2016–2019	PMPM Annual % Change 2016–2019		
Commercial	\$391,648,623	\$ 128.07	\$ 12.07	3%		
Other Health Professionals	\$112,308,264	\$ 36.72	\$ 6.51	7%		
Other Physicians	\$ 91,826,022	\$ 30.02	\$ 3.68	5%		
Nonprocedural Medical	\$ 42,301,959	\$ 13.85	\$ 1.40	4%		
Surgical Specialties	\$ 52,334,282	\$ 17.10	\$ 0.82	2%		
Primary Care	\$ 64,356,914	\$ 21.05	\$ (0.08)	0%		
Procedural Internal Medicine	\$ 28,521,182	\$ 9.33	\$ (0.26)	-1%		
Medicaid Managed Care	\$190,061,117	\$ 68.67	\$ 9.57	5%		
Other Health Professionals	\$ 62,812,461	\$ 22.69	\$ 4.47	8%		
Other Physicians	\$ 37,091,382	\$ 13.42	\$ 1.63	5%		
Nonprocedural Medical	\$ 23,167,284	\$ 8.34	\$ 1.33	6%		
Primary Care	\$ 38,616,401	\$ 13.96	\$ 1.17	3%		
Procedural Internal Medicine	\$ 9,378,785	\$ 3.39	\$ 0.56	7%		
Surgical Specialties	\$ 18,994,804	\$ 6.87	\$ 0.41	2%		

Table 2. PMPM Spending by Specialty Group in Commercial and Medicaid Managed Care Payers

Notes: PMPM = Per Member Per Month. E&M = Evaluation and Management. DME = Durable Medical Equipment. Percentages represent total spending in 2019. PMPM Difference 2016-19 is the difference of Spending PMPM 2019 subtracted by Spending PMPM 2016 (not shown). professional component, and we first confirmed a strong linear association between professional and facility spending at the procedure code encounter level. It is therefore reasonable to apply RBCS to professional spending alone as a tool for evaluating categories of spending, with the caveat that any services billed exclusively with facility claims or that are not classified by RBCS are beyond the scope of this study. Specifically, there are some CPT codes that are exclusively claims for children (for example, well-child visits, CPT 99381-99385) and would not be relevant for a Medicare population, so these codes would not be captured by RBCS; this represents approximately 7% of professional spending in Medicaid and 2% of professional spending in commercial. Professional claims submitted by organizations for which a single specialty could not be assigned were excluded from analysis (13% of the professional spending by commercial payers and 35% of professional spending in Medicaid). Finally, any professional spending for medical pharmacy (e.g., "J-codes") claims were also excluded from this analysis because APCDs lack information about drug rebates and therefore we cannot interpret data values as the true costs of these services.

## RESULTS

PMPM professional spending among commercially insured individuals increased by 8.4% from \$143 in 2016 to \$155 in 2019 (Table 1). Decreases in commercial covered lives included in the study population are a result declining reporting from self-insured commercial plans; PMPM calculations account for the change in the population over time. From 2016 to 2019, PMPM professional spending among individuals covered by Medicaid increased by 16% from \$116 in 2016 to \$135 in 2019. PMPM professional spending in Medicaid was 81% and 92% of professional spending in commercial in 2016 and 2019, respectively.



Table 3. Spending in Provider Specialties and RBCS Level 1 S	Specialty Service Categories, 2016–2019
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			Spending Metrics			
		PMPM 2019 (\$)	Total Spending 2019 (\$)	PMPM Difference 2016–2019 (\$)	PMPM Annual % Change 2016–2019	
Commercial			,			
Provider Specialty	RBCS Level	1				
Nurse Practitioner	E & M	5.18	15,832,051	2.02	21%	
Anesthesiology	Anesthesia	5.53	16,906,129	1.37	11%	
Diagnostic Radiology	Imaging	11.13	34,031,741	1.31	4%	
Counselor	E & M	2.91	8,886,012	0.91	15%	
Physician Assistant	E & M	2.61	7,987,615	0.78	14%	
Orthopedic Surgery	Procedure	4.6	14,053,745	0.64	5%	
Social Worker	E & M	3.4	10,380,540	0.6	7%	
CRNA/Anesthesiology Assistant	Anesthesia	1.68	5,121,845	0.51	15%	
Emergency Medicine	E & M	4.72	14,411,743	0.43	3%	
Radiation Oncology	Treatment	2.04	6,244,026	0.43	9%	
Medicaid Managed Care						
Provider Specialty	RBCS Level	1				
Nurse Practitioner	E & M	4.47	12,362,633	1.7	20%	
Diagnostic Radiology	Imaging	3.42	9,460,830	1.12	16%	
Psychiatry	E & M	2.01	5,573,085	0.91	27%	
Social Worker	E & M	2.63	7,267,784	0.61	10%	
Counselor	E & M	2.4	6,641,543	0.5	9%	
Physician Assistant	E & M	1.48	4,103,943	0.44	14%	
Pediatric Primary Care	E & M	5.13	14,192,776	0.42	3%	
Physical Therapist	Treatment	1.72	4,751,076	0.36	9%	
Primary Care Internal Medicine	E & M	3.84	10,623,670	0.36	3%	
Clinical Psychologist	E & M	1.12	3,099,830	0.34	15%	

Notes: PMPM = Per Member Per Month. Table 3 is sorted by highest PMPM spending difference from 2016–2019. PMPM Difference 2016-19 is the difference of Spending PMPM 2019 subtracted by Spending PMPM 2016 (not shown).

The annual percent increase in professional spending over the study period was higher in Medicaid than commercial (5.2% vs. 2.7%). Subsequent analyses show spending trends within specific provider specialties.

In 2019, PMPM spending levels were almost twice as large in commercial compared to Medicaid (Table 2) - while there is variation by clinician group, PMPM spending levels are larger in commercial across all clinician groups, reflecting higher levels of commercial payment compared to Medicaid. PMPM surgical specialty spending is 2.5 times that of Medicaid, and PMPM procedural internal medicine spending is 2.8 times that of Medicaid spending. Importantly, the ordering and relative magnitude of group spending by insurance program differs. For both commercial and Medicaid payers, other health professionals and other physician specialists represent high PMPM spending areas. However, in commercial, other health professionals and other physician specialists are similar in magnitude, whereas in Medicaid, other physician specialist spending is about 2/3 that of other health professionals. In commercial, other health professionals and other physician specialists saw the largest absolute growth in PMPM spending, while showing decreases in primary care and procedural internal medicine spending. In Medicaid, other health professionals saw the largest



Figure 1a. Radiology-Imaging-CT Commercial

Notes: Examples of price/volume analyses; figures represent yearly changes in price and volume of CT scans by diagnostic radiology in Commercial and Medicaid. Identical analyses were conducted for high spending areas from Table 4.



Figure 1b. Radiology-Imaging-CT Medicaid Managed Care

			Price and	Volume Analysis
			Annual % Change in Mean Price	Annual % Change in Per Capita Utilization
Commercial				
Provider Specialty	BETOS Lvl 1	BETOS Lvl 2		
Nurse Practitioner	E & M	Office/outpatient services	2.0%	7.0%
Anesthesiology	Anesthesia	Anesthesia	1.5%	-1.0%
Counselor	E & M	Behavioral health services	-0.2%	8.1%
Physician Assistant	E & M	Office/outpatient services	1.0%	3.6%
Orthopedic Surgery	Procedure	Musculoskeletal	6.8%	-1.6%
Diagnostic Radiology	Imaging	CT Scan	3.8%	3.0%
Social Worker	E & M	Behavioral health services	-0.4%	3.0%
CRNA/Anes. Assistant	Anesthesia	Anesthesia	0.6%	3.6%
Radiation Oncology	Treatment	Radiation oncology	2.5%	-0.4%
Diagnostic Radiology		Standard XRay	11.9%	0.8%
Medicaid Managed Ca	re	·		
Provider Specialty	BETOS Lvl 1	BETOS Lvl 2		
Nurse Practitioner	E & M	Office/outpatient services	1.3%	9.2%
Social Worker	E & M	Behavioral health services	1.2%	8.6%
Counselor	E & M	Behavioral health services	3.2%	7.3%
Primary Care Internal Medicine	E & M	Hospital inpatient services	8.5%	6.3%
Physician Assistant	E & M	Office/outpatient services	3.0%	2.3%
Psychiatry	E & M	Hospital inpatient services	-7.6%	56.9%
Diagnostic Radiology	Imaging	CT Scan	2.4%	5.1%
Pediatric Primary Care	E & M	Office/outpatient services	5.6%	0.2%
Physical Therapist	Treatment	Phys, occup, and speech therapy	1.5%	5.5%
Clinical Psychologist	E & M	Behavioral health services	-2.6%	20.9%

Table 4. Spending in Provider Specialties and RBCS Level 2 Specialty Service Categories, 2016–2019

Notes: PMPM = Per Member Per Month. Table 4 is sorted by highest PMPM spending increases from 2016–2019 (not shown).

absolute growth in PMPM spending.

Next, we evaluated the clinical service categories within provider specialties that had the largest absolute increases in PMPM spending between 2016 and 2019. Among specialty-specific RBCS Level 1 service categories that experienced a PMPM increase from 2016-2019 (about 33% in both payers), the median increase in PMPM spending was \$0.03 in both payers; among these service categories, the median PMPM annual percent increase was 9.5% in commercial and 10.4% in Medicaid. Across high spending areas in both payers from 2016 to 2019, E&M for nurse practitioners, counselors, physician assistants, and social workers and imaging for diagnostic radiology had notable increases in PMPM spending (Table 3). Additionally, anesthesia and orthopedic procedures had notable PMPM spending increases in commercial while E&M for psychiatry, internal medicine primary care, and pediatric primary care saw increases in Medicaid.

Finally, we evaluated the specific types of services, as relevant groupings of CPT/HCPCS codes (RBCS Level 2), driving overall spending trends. Among specialty-specific RBCS Level 2 service categories that experienced a PMPM increase from 2016 to 2019 (about 5-6% in both payers), the median increase was \$0.02 in both payers; among these service categories, the median PMPM annual percent increase was 22% in commercial and 15% in Medicaid. The median annual percent change in average service category prices was 4.9% in commercial and 3.8% in Medicaid. The median annual percent change in service category per capita utilization was 4.0% in commercial and 3.8% in Medicaid.

We further evaluated RCBS Level 2 categories with the largest PMPM spending differences; this final analysis is illustrative of potential cost drivers. Nurse practitioner (NP) and physician assistant (PA) office/outpatient services, counselor and social worker behavioral health services,



and diagnostic radiology CT were notable areas of spending increases in both payers. We disaggregated spending into utilization per capita and average price (see Figure 1) for one example of this analysis with Diagnostic Radiology CT) to evaluate the two determinants of health care spending. Three-year trends show spending increases across both payers in NP/PA office visits and most behavioral services were primarily driven by utilization; despite increased spending in these areas. Increased commercial spending on diagnostic radiology CT scans was driven by increases in price in commercial and increases in utilization in Medicaid. Rising spending for anesthesia services was driven by price in the commercial population. Commercial spending for orthopedic procedures increased by 5.4% annually between 2016 and 2019, driven by a 6.8% annual increase in price despite a 1.6% annual decrease in utilization. In Medicaid, primary care internal medicine hospital services and pediatric primary care office/outpatient services experienced price annual increases of 8.5% and 5.6% respectively. Medicaid spending for psychiatry hospital inpatient services increased substantially from 2016-2019, driven by a 56.9% annual increase in utilization despite a 7.6% annual decrease in price.

## DISCUSSION

This paper has three main findings. First, PMPM professional spending from 2016 to 2019 increased at a faster rate in Medicaid compared to increases in professional spending in commercial (5.2% in Medicaid vs. 2.7% in commercial, annually). Second, we observed that other health professionals and other physician specialties (primarily diagnostic radiology) exhibit high PMPM professional spending growth in both payers. Nurse practitioner and physician assistant E&M, diagnostic radiology imaging, behavioral health services E&M, anesthesia, and orthopedic procedures were the specific services areas of increasing spending. Finally, threeyear trends showed heterogeneity in whether changes in volume or price drove spending increases in these service categories.

We were not surprised to find that levels of commercial professional spending were considerably higher compared to Medicaid professional spending. Medicaid almost universally compensates providers less for similar services compared to commercial insurers or Medicare.<sup>25,26</sup> However, less is known about trends in professional costs across different insurance programs. In February of 2019, Governor Raimondo signed an Executive Order establishing a target growth rate of 3.2% for total health care spending in Rhode Island.<sup>27</sup> While this target growth rate applies to total costs, not professional spending in isolation, it is a useful reference point. We find that professional spending in commercial (2.7% annual growth) met this target, while Medicaid (5.3% annual growth) exceeded it. One potential interpretation of

these trends is that more attention to control cost growth is needed in the Medicaid MCO program (through additional oversight of MCO contracts), and that professional spending represents an actionable target for future efforts to reduce spending. A more nuanced interpretation, which we favor, is that persons with Medicaid coverage may have more complicated health needs and additionally face significant health-related social needs, which have the potential to increase both utilization and overall costs. It is essential to ensure appropriate provider reimbursement rates in the Medicaid program to avoid further disadvantaging providers who treat patient populations with complex medical and health-related social needs. While spending growth in the commercial population may be cause for concern and ripe for intervention given that prices are already higher and rising, we may instead seek to monitor spending growth in public payer programs to ensure sustainability. Importantly, primary care spending was relatively flat/decreasing in commercial but increasing for Medicaid over the study period. Increases in professional spending, if they represent appropriate evidence-based care, may improve quality and value, both for patients individually and the Medicaid program overall. For example, these increases may represent an appropriate response to the opioid epidemic. Studies that formally evaluate quality of care would be required to distinguish between these two alternatives; and elements of both may contribute.

Studies have shown that the employment of NPs and PAs in healthcare may decrease health care spending and improve efficiency of care.28 NPs have also been shown to provide high quality care<sup>29</sup> while being more likely to treat vulnerable populations.30 A move towards increased employment of other health professionals, especially in primary care evaluation and management settings, may improve value of care delivered. Other physician specialties were also shown to have large and increasing PMPM spending in both payers; diagnostic radiology and anesthesiology are large components of this specialty group. Since consumers tend not to choose the radiologists or anesthesiologists who render their care, spending growth in these areas may merit special attention, especially if it is resulting from considerable price increases. This has been an area of interest as it relates to the recently implemented and challenged No Surprises Act,<sup>31</sup> which limits reimbursement for out of network providers not selected by patients (emergency medicine, anesthesiology, pathology, radiology, etc.).32

Our results demonstrate that trends in volume and price are very sensitive to the service categories and payers being studied (See **Figure 1** for one example of the price/volume analyses carried out for high spending areas identified in **Table 4**). In addition, the year-to-year variation that we observe emphasizes the importance of examining multiyear trends. Understanding these trends is complicated; in most cases, ascertaining changes in volume and price could



only be meaningfully done via a granular view of specific professional services (i.e., analyzing RBCS Level 2 service categories within specific specialties). Increases in spending attributable to other health professionals (NPs, Counselors, PAs, etc.) were driven by increased volume of evaluation and management claims; the number of other health professionals and the number of patients served by other health professionals increased from 2016 to 2019, in line with national trends indicating greater reliance on other health professionals to meet population health needs.<sup>33</sup> We also identified notable increases in behavioral health professional spending (e.g. psychiatry, social workers, counselors), a likely response to increased population morbidity (namely, the ongoing opioid epidemic).

These approaches can inform efforts to identify spending drivers in other states. First, we show that APCDs can be leveraged to analyze multiple payers simultaneously while employing a consistent methodology. Second, we show that the RBCS classification system can be adapted to comprehensively evaluate professional spending for patients beyond the Medicare program. Further, our initial analyses confirmed that professional spending is a strong proxy for total spending, and may provide a more accessible avenue for analyses of health care spending using APCDs. Many states are developing infrastructure to evaluate and intervene on rising health care costs. The approach outlined by this study can support analyses of claims data to have actionable insights for policy and identify areas of further investigation in subsequent analyses. Third, our provider specialty crosswalk is generalizable across states for providers where a single specialty based on taxonomy is listed. Finally, spending for medical pharmacy (e.g., provider administered medications) is substantial, and increasing. Including professional and facility spending is essential to evaluating this category of services, and as such, they were out of the scope for this study. Additionally, the absence of high-quality data on rebates that would otherwise reduce the total spending on these services creates challenges for understanding the true spending growth of this service category. Further studies are needed to characterize the growth of spending on medical pharmacy and the impacts to overall spending.

This study has several limitations. First, APCDs only include information for claims billed to insurance; these data do not include additional information on non-claims payments, other incentive payments for high quality care, or health outcomes data, which may be advantageous to fully evaluate cost and value in the health system. Second, APCDs are likely to lack a significant portion of data for individuals enrolled in self-insured plans as a result of the Gobeille Supreme Court Decision;<sup>35</sup> the full story of professional spending trends in the commercial insurance market may not be represented. Third, we found that a substantial proportion of professional claims (13% in commercial and 35% in Medicaid) are billed with a specialty taxonomy that refers to a multispecialty organization, and therefore cannot be associated with a particular individual provider specialty classification. Fourth, our substantive findings may not be generalizable to other states. Finally, claims analyses generally cannot capture the experience of the uninsured.

Future studies can use this generalized provider taxonomy and stepwise approach for evaluating spending in RBCS categories to study drivers of cost in other states and populations. We would expect findings to potentially vary in line with each state's market structure and their particular regulatory context. Understanding trends and drivers of health care costs are one important step towards improving value in the U.S. health system; analyses of professional spending as proposed are one potentially valuable step forward in achieving this goal.

#### References

- Martin AB, Hartman M, Lassman D, Catlin A. National Health Care Spending In 2019: Steady Growth For The Fourth Consecutive Year. *Health Aff (Millwood)*. Published online December 16, 2020:10.1377/hlthaff.2020.02022. doi:10.1377/hlthaff. 2020.02022
- Bradley EH, Canavan M, Rogan E, et al. Variation In Health Outcomes: The Role Of Spending On Social Services, Public Health, And Health Care, 2000–09. *Health Aff (Millwood)*. 2016;35(5):760-768. doi:10.1377/hlthaff.2015.0814
- 3. Chernew ME, Cutler DA, Shah SA. Reducing Health Care Spending: What Tools Can States Leverage? doi:10.26099/dyp4-2t03
- Supporting States In Setting Health Care Cost Growth Targets To Improve Affordability | Health Affairs Blog. Accessed June 2, 2021. https://www.healthaffairs.org/do/10.1377/hblog 20210526.658347/full/
- 5. All-Payer Claims Databases. Agency for Healthcare Research and Quality. Published March 2018. Accessed January 20, 2020. http://www.ahrq.gov/data/apcd/index.html
- 2019 Health Care Cost and Utilization Report. Health Care Cost Institute; 2021. Accessed March 12, 2022. https://healthcostinstitute.org/images/pdfs/HCCI\_2019\_Health\_Care\_Cost\_ and\_Utilization\_Report.pdf
- Kumar P, Parthasarathy R. Walking Out of the Hospital. McKinsey & Company. Published September 18, 2020. Accessed November 27, 2021. https://www.mckinsey.com/industries/healthcaresystems-and-services/our-insights/walking-out-of-the-hospitalthe-continued-rise-of-ambulatory-care-and-how-to-take-advantage-of-it
- Hollenbeck BK, Dunn RL, Suskind AM, Zhang Y, Hollingsworth JM, Birkmeyer JD. Ambulatory Surgery Centers and Outpatient Procedure Use Among Medicare Beneficiaries. *Med Care*. 2014;52(10):926-931. doi:10.1097/MLR.000000000000213
- Hollenbeck BK, Dunn RL, Suskind AM, Strope SA, Zhang Y, Hollingsworth JM. Ambulatory Surgery Centers and Their Intended Effects on Outpatient Surgery. *Health Serv Res.* 2015;50(5):1491-1507. doi:10.1111/1475-6773.12278
- Hollingsworth JM, Ye Z, Strope SA, Krein SL, Hollenbeck AT, Hollenbeck BK. Physician-ownership of ambulatory surgery centers linked to higher volume of surgeries. *Health Aff Proj Hope*. 2010;29(4):683-689. doi:10.1377/hlthaff.2008.0567
- Barnett ML, Bitton A, Souza J, Landon BE. Trends in Outpatient Care for Medicare Beneficiaries and Implications for Primary Care, 2000 to 2019. Ann Intern Med. Published online November 2, 2021. doi:10.7326/M21-1523
- Bodenheimer T. High and Rising Health Care Costs. Part 3: The Role of Health Care Providers. Ann Intern Med. 2005;142(12\_ Part\_1):996. doi:10.7326/0003-4819-142-12\_Part\_1-200506210-00009



- Barnett ML, Bitton A, Souza J, Landon BE. Trends in Outpatient Care for Medicare Beneficiaries and Implications for Primary Care, 2000 to 2019. Ann Intern Med. 2021;174(12):1658-1665. doi:10.7326/M21-1523
- OHIC Affordability Standards Regulation.; 2010. Accessed March 16, 2022. http://www.ohic.ri.gov/documents/2020/July/31/230-RICR-20-30-4%20FINAL%20SOS.pdf
- Baum A, Song Z, Landon BE, Phillips RS, Bitton A, Basu S. Health Care Spending Slowed After Rhode Island Applied Affordability Standards To Commercial Insurers. *Health Aff (Millwood)*. 2019;38(2):237-245. doi:10.1377/hlthaff.2018.05164
- 16. Butler J. Insurance Rate Review as a Hospital Cost Containment Tool: Rhode Island's Experience. The National Academy for State Health Policy. Published February 1, 2021. Accessed March 16, 2022. https://www.nashp.org/insurance-rate-reviewas-a-hospital-cost-containment-tool-rhode-islands-experience/
- 2018 Health Care Cost and Utilization Report. Health Care Cost Institute; 2020. Accessed October 19, 2020. https://healthcostinstitute.org/annual-reports/2020-02-13-18-20-19
- Koller CF, Khullar D. Primary Care Spending Rate A Lever for Encouraging Investment in Primary Care. N Engl J Med. 2017;377(18):1709-1711. doi:10.1056/NEJMp1709538
- Restructured BETOS Classification System. Centers for Medicare & Medicaid Services Data. Published November 30, 2021. Accessed December 11, 2021. https://data.cms.gov/jsonapi/ node/dataset/65bdae77-6aee-42b6-9b78-e8c23a1d77c1
- 20. National Uniform Claim Committee Provider Taxonomy. National Uniform Claim Committee. Published 2021. Accessed November 26, 2021. https://www.nucc.org/index.php/codesets-mainmenu-41/provider-taxonomy-mainmenu-40
- 21. Berenson RA, Braid-Forbes MJ. Development and Structure of BETOS 2.0 with Illustrative Data. Urban Institute; 2020:51.
- 22. Yoon J, Vanneman ME, Dally SK, Trivedi AN, Phibbs CS. Veterans' Reliance on VA Care by Type of Service and Distance to VA for Nonelderly VA-Medicaid Dual Enrollees. *Med Care*. 2019;57(3):225-229. doi:10.1097/MLR.00000000001066
- Lindner S, Kaufman MR, Marino M, et al. A Medicaid Alternative Payment Model Program In Oregon Led To Reduced Volume Of Imaging Services. *Health Aff (Millwood)*. 2020;39(7):1194-1201. doi:10.1377/hlthaff.2019.01656
- 24. Ho V, Metcalfe L, Vu L, Short M, Morrow R. Annual Spending per Patient and Quality in Hospital-Owned Versus Physician-Owned Organizations: an Observational Study. *J Gen Intern Med.* 2020;35(3):649-655. doi:10.1007/s11606-019-05312-z
- 25. Hartman M, Martin AB, Washington B, Catlin A, The National Health Expenditure Accounts Team. National Health Care Spending In 2020: Growth Driven By Federal Spending In Response To The COVID-19 Pandemic: National Health Expenditures study examines US health care spending in 2020. *Health Aff (Millwood)*. 2022;41(1):13-25. doi:10.1377/hlthaff.2021.01763
- 26. Johnson B, Kennedy K, Kurowski D, et al. Comparing Commercial and Medicare Professional Service Prices. Health Care Cost Institute. Published June 2020. Accessed November 27, 2021. https://healthcostinstitute.org/hcci-research/comparing-commercial-and-medicare-professional-service-prices
- 27. Raimondo Signs Executive Order, Commits to Controlling Growth of Health Care Spending in Rhode Island- Press Release. Official Website for the State of Rhode Island. Published February 6, 2019. Accessed March 26, 2022. https://www.ri.gov/
- Roblin DW, Howard DH, Becker ER, Kathleen Adams E, Roberts MH. Use of Midlevel Practitioners to Achieve Labor Cost Savings in the Primary Care Practice of an MCO. *Health Serv Res.* 2004;39(3):607-626. doi:10.1111/j.1475-6773.2004.00247.x
- 29. Newhouse RP, Stanik-Hutt J, White KM, et al. Advanced practice nurse outcomes 1990-2008: a systematic review. *Nurs Econ*. 2011;29(5):230-250; quiz 251.

- Buerhaus PI, DesRoches CM, Dittus R, Donelan K. Practice characteristics of primary care nurse practitioners and physicians. *Nurs Outlook*. 2015;63(2):144-153. doi:10.1016/j.outlook.2014.08.008
- Keith K. The Six Provider Lawsuits Over The No Surprises Act: Latest Developments. Accessed March 17, 2022. https://www. healthaffairs.org/do/10.1377/forefront.20220216.824139/full/
- 32. Trish LA Matthew Fiedler, Paul Ginsburg, Mark Hall, Benedic Ippolito, and Erin. Understanding the No Surprises Act. Brookings. Published February 4, 2021. Accessed November 27, 2021. https://www.brookings.edu/blog/usc-brookings-schaeffer-onhealth-policy/2021/02/04/understanding-the-no-surprises-act/
- 33. Auerbach DI, Buerhaus PI, Staiger DO. Implications Of The Rapid Growth Of The Nurse Practitioner Workforce In The US: An examination of recent changes in demographic, employment, and earnings characteristics of nurse practitioners and the implications of those changes. *Health Aff (Millwood)*. 2020;39(2):273-279. doi:10.1377/hlthaff.2019.00686
- 34. 14-181 Gobeille v. Liberty Mut. Ins. Co.(Supreme Court 2016).
- 35. Brown E, King J. The Consequences Of Gobeille v. Liberty Mutual For Health Care Cost Control. Health Affairs. Published March 10, 2016. Accessed November 3, 2020. https://www. healthaffairs.org/do/10.1377/hblog20160310.053837/full/

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## Disclosures

The authors declare no conflict of interest.

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# Perceptions and Use of E-cigarettes among Young Adults with Cystic Fibrosis: An Observational Study

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## ABSTRACT

While smoking prevalence has decreased among the general population, the use of electronic cigarettes (Ecigarettes) has risen significantly and can cause significant lung injury. We sought to determine if persons with cystic fibrosis (PwCF) have similar rates of E-cigarette use as compared with age-matched peers, and to understand perceptions of E-cigarette safety through a survey-based study. A total of 29 PwCF and 26 age-matched control patients participated in this study. There was no significant difference between PwCF and control patients regarding perceptions of the negative impact of E-cigarette use on one's health. Overall, both PwCF and control patients reported a good quality of life. PwCF were equally likely to identify E-cigarettes as harmful to one's lung health as healthy controls but were significantly more likely to have heard of EVALI. While small, our study has demonstrated the need for further education of both PwCF and healthy young adults.

**KEYWORDS:** vaping, EVALI, Cystic Fibrosis, cigarettes

## BACKGROUND

In the last several decades, smoking prevalence has decreased among the general population.<sup>1</sup> However, new generations of tobacco and non-tobacco products are being increasingly used, particularly in the young adult population.<sup>2</sup> Since their introduction in 2007, the use of electronic cigarettes (E-cigarettes), battery-powered devices that vaporize nicotine and marijuana, has risen significantly.<sup>3</sup> According to the Surgeon General's office, E-cigarettes are the most common tobacco product used by U.S. youth for the past 5 years and in 2018, more than 3.6 million youth used E-cigarettes.<sup>3</sup>

Tobacco product use amongst adolescents has significant implications for long-term morbidity and mortality. Users of tobacco products are more likely to report poor health, have higher rates of hospitalizations, and greater healthcare expenditures than never smokers.<sup>4</sup> Given current smoking rates, 5.6 million youth will die prematurely of smoking-related illness.<sup>4</sup>

While conventionally thought to be less harmful than traditional cigarettes, E-cigarettes can cause significant

lung injury requiring hospitalization and even endotracheal intubation for respiratory failure. Between 2018 and February 2020, there were 2800 reported cases of E-cigarette or Vaping Associated Lung Injury (EVALI) with 68 deaths.<sup>3,5</sup> This new entity is currently the subject of an ongoing CDC investigation as well as multiple General Advisories from the Surgeon General's office resulting in bans of E-cigarettes in several states.<sup>4,5</sup> EVALI is associated with a spectrum of acute lung injury including eosinophilic pneumonia, interstitial lung disease, diffuse alveolar hemorrhage, lipoid pneumonia with pathology consistent with acute fibrinous pneumonitis, diffuse alveolar damage or organizing pneumonia, and bronchiolitis.6 While the etiology of lung injury remains unknown, there are several possible culprits including Vitamin E acetate (VEA), a condensing agent frequently used by manufacturers to alter the consistency of vaping liquids.7 VEA has been found in injured lung fluid samples from up to 94% of patients diagnosed with EVALI, and is thought to contribute to lung damage through multiple mechanisms, including disruption of surfactant membranes.7-10 In addition to Vitamin E acetate, flavor additives and nicotine use have been implicated in the development of airway hyperreactivity, decreased antimicrobial activity, and decreased alveolar development.11

While the prevalence of E-cigarette use, and the rise of EVALI has been studied in the general population, to our knowledge there is no existing data about the prevalence of E-cigarette use in a population of patients with childhood onset chronic lung disease. Individuals with Cystic Fibrosis (CF), an inherited disease which causes progressive decline in lung function, offer a unique perspective on the impact of E-cigarette use. The condition is typically diagnosed before the age of 2, and currently has a life expectancy of 44 years in the United States.<sup>12</sup> This young population is aware of their respiratory vulnerability at an early age and typically has close connection with the healthcare system and high health literacy.<sup>13, 14</sup>

The general decline of tobacco product use over the past several decades has been attributed in large part to increased educational efforts among the general population. Research on smoking cessation in populations with chronic illnesses is more limited, but prior studies among PwCF suggest that the prevalence of cigarette smoking is lower than the general population (8% vs 27% of adults).<sup>15-18</sup> There is limited



understanding of what prompts the use of tobacco products among adolescents and adults with chronic illness, particularly PwCF.

According to the results of the 2020 National Youth Tobacco Survey (NYTS), a bi-annual nationwide assessment of over 14,000 adolescents, 26.8% reported using E-cigarettes on at least one occasion.19 Of those who have tried E-cigarettes, 10% stated that the primary reason was that E-cigarettes were safer than other cigarette or tobacco products. For PwCF, E-cigarette use may be perceived as a safer alternative to cigarette use, and therefore less likely to cause deleterious effects on lung function. Despite growing awareness of the possible harms, several studies suggest that individuals who are not susceptible to cigarette smoking may be more likely to initiate E-cigarette use.<sup>20</sup> Tobacco product use in young adults is most frequently driven by social reasons such as peer pressure, as well as a desire for stress relief and the ready availability of tobacco products in their environment.21, 22

Given the compromised lung function of PwCF and the popularity of non-cigarette inhalation products, it is imperative to understand the prevalence of vaping in this population. While patients with worse lung function may be less likely to use traditional cigarettes, the lack of general awareness regarding the potential harms of E-cigarette use and the desire to fit in amongst peers may result in PwCF seeking out E-cigarettes as a less harmful alternative to traditional tobacco products. We hypothesized that PwCF have similar rates of E-cigarette use as compared with age-matched peers and were more likely to use E-cigarettes than conventional cigarettes.

## **METHODS**

We conducted a case-control observational study comparing PwCF and age matched patients from a Medicine-Pediatrics clinic (control).

**Case Definition:** PwCF seen at the Rhode Island Cystic Fibrosis Center between February 2020 and December 2020. PwCF who are on hospice or transplant waiting lists were not called.

**Control Definition:** Young adult patients of the Medicine-Pediatrics Primary Care Clinic that were age and sex matched +/- 2 years.

**Clinical Data:** The most recent spirometry data was collected from PwCF at the time of enrollment.

## Surveys used:

**E-cigarette use:** This survey was created from the CDC National Youth Tobacco Survey (NYTS) and National Adult Tobacco Survey (NATS).<sup>23, 24</sup>

**Social desirability:** The Marlowe-Crowne Social Desirability Scale (MC-SDS) was used to account for the effect of social desirability on respondents' answers.<sup>25</sup> The MC-SDS is a validated 33-item self-reporting tool designed to assess

respondents' concern with having social approval. A higher score indicates higher social desirability, and that a respondent may alter their response to provide a "good" answer.

**CF questionnaire revised (CFQR)**<sup>26</sup>: PwCF completed this questionnaire, a validated tool to assess overall and disease-specific quality of life.

**Quality of Life for Control:** This survey was completed by control participants. This survey was the MOS 36-item Short Form Health Survey (SF-36).<sup>27</sup>

Study design was approved by institutional IRB prior to data collection (IRB #1523061-5). Data was collected from February until December 2020 at Rhode Island Hospital. Study authors (SR, RA) administered the surveys in person and via telephone. These authors were physicians in training at time of survey administration and did not make clinical decisions regarding patient care to help mitigate participant hesitancy in reporting unhealthy behaviors. Participants were provided with a \$5 e-gift card following completion of the survey. Additional clinical data was collected on PwCF by chart review.

**Statistical Analysis:** Social desirability score category was compared between the group that reported using an E-cigarette and the group that reported no E-cigarette use using a Fishers exact test.

Using a generalized linear model, FEV1% predicted was modeled as a proportion of the total possible FEV1% predicted (100%: binomial distribution) and compared between the groups reporting E-cigarette use versus no E-cigarette use. Similarly, survey responses were modeled as binomial distributions and compared between the group that reported using E-cigarettes and the group that reported no E-cigarette use. From the models, estimated mean FEV1 and reported lung function were determined and compared between the two groups. P-values <0.05 were reported as significant.

As an additional check to survey responses, a generalized linear model was used to model survey responses (binomial distribution) to check the association between reported lung function and tested FEV1. P-values less than 0.05 were reported as a significant relationship between FEV1 and survey outcomes. Classic sandwich estimation was used to adjust for any model misspecification. All models were run using Proc Glimmix, allowing for modeling of generalized linear models and deriving p-values for model fixed effects and mean group comparisons (SAS: Version 9.2; SAS Institute Inc, Cary, NC)

## RESULTS

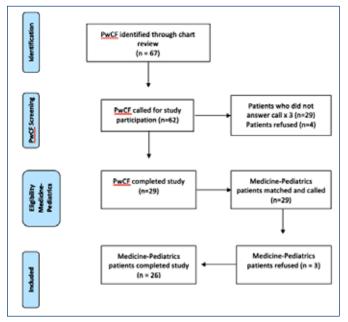
#### Demographics

A total of 29 PwCF and 26 age-matched control patients of the Medicine-Pediatrics clinic participated in this study. 62 adult patients (out of 67) of the Cystic Fibrosis Center were called up to three times or approached in clinic to complete the study. Twenty-nine PwCF did not return calls and four



declined participation. Twenty-nine Medicine-Pediatrics clinic patients were then identified, of whom three declined participation (Figure 1). Participants were predominantly male. The average age for study participants was 30 for PwCF and 28 for control subjects. Among PwCF, there was a mean FEV1% predicted of 63% (Table 1).

## Figure 1. Patient Participation Flow Diagram



Patient Characteristics	PwCF (n = 29)	Non-CF (control, n = 26)
Age (mean, range in years)	30.3 (18–49)	26.8 (18–40)
Sex, Female N (%)	13 (45)	10 (38)
BMI (mean)	22.9	27.0
FEV1 (% average, range)	63 (23–100)	
Modulator therapy (% taking)	89.7%	
Non-CF Lung Disease	4 (2 asthma, 1 MAC, 1 ABPA)	2 (mild intermittent asthma, 7.7%)
Pseudomonas aeruginosa sputum culture (%)	18 (62%)	
Lung transplant recipient (%)	2 (6.9%)	
CF Exacerbation Prior Year (%)	5 outpatient (17%), 16 inpatient (55%)	
Anxiety Diagnosis (%)	16 (55%)	15 (57.9%)

MAC = Mycobacterium avium complex.

ABPA = Allergic Bronchopulmonary aspergillosis

## Social desirability

Social desirability was categorized as low scorers (0–8: more willing than most people to respond truthfully), average scorers (9–19: average degree of conformity), and high scorers (20–33: highly concerned about social approval).

Three respondents among PwCF didn't answer all the social desirability questions. However, given their completed responses and assuming negative or positive responses to the questions they didn't answer, participants were categorized as average responders.

No significant difference was detected in social desirability responses between the PwCF participants who reported trying E-cigarettes and those who reported never trying E-cigarettes (p=0.2076). Approximately half of high scorers among PwCF reported never trying an E-cigarette (11/26) and there were no high scorers (0/3) among PwCF who reported having tried E-cigarettes (**Table 2**).

## **Perceptions of Health**

Both PwCF and patients of the Medicine-Pediatrics clinic were asked to rate their overall health on a scale of 1–4, with 4 being excellent. PwCF and control participants reported similar overall health (2.8 in PwCF vs 2.9 in control). There was a positive correlation between FEV1% predicted and participant-reported activity tolerance for PwCF (p = 0.0085) (**Figure 2**). FEV1% predicted correlated with self-perceived ability to breathe among all PwCF, irrespective of E-cigarette use (p=0.0498).



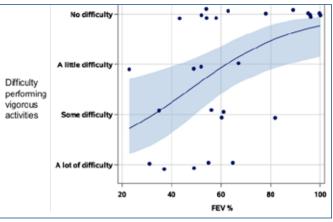


Table 2. Participant-Reported	Tobacco Product Use
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Tobacco Product Use	PwCF (n = 29)	Non-CF (control, n = 26)
Active smokers	0	0
Former use of conventional cigarette	6 (20.6%)	7 (27%)
Tried any E-cigarette product	3 (10.3%)	7 (27%)



## Conventional cigarette use vs E-cigarette use

Among control participants, an equal number have used conventional and electronic cigarettes (n=7, 27% each). For PwCF, however, twice as many individuals reported using conventional cigarettes as compared to E-cigarettes (n=6, 20.6% vs n=3, 10.3%). Among PwCF, 20% have tried conventional cigarettes at least once. There was no significant difference between PwCF and healthy controls' report of conventional cigarette use.

## FEV1% predicted and E-cigarette Use

FEV1% predicted for PwCF who reported trying E-cigarettes was higher than the group that reported never trying an E-cigarette (83.7% [54.4, 95.7] versus 60.4% [51.4, 68.7] FEV1% predicted). This difference did not reach significance (p=0.1088).

PwCF that used an E-cigarette reported a significantly better ability to breathe than those who had never tried an E-cigarette (mean 100 [100, 100] versus [76.8, 96.6], respectively, p<0.0001). The correlation between FEV1% predicted and question 44, 'Have you been wheezing?' approached significance but did not reach it (p=0.0566)

## Perceptions of E-cigarette use

There was no statistically significant difference between PwCF and Medicine-Pediatrics patients regarding perceptions of the negative impact of E-cigarette use on one's health. There was also high agreement between PwCF and the control population with regards to the increased impact of E-cigarettes on the health of individuals with existing chronic lung disease. The two groups differed, however, in their estimation of the time required to demonstrate evidence of lung damage from E-cigarette use, with the majority of PwCF identifying lung health as affected within one year of use (n = 25, 86%), compared with only 39% of healthy controls (n = 9). To date, there is no clear timeline for the development of EVALI, although frequent (>5 times daily) use of E-cigarettes has been associated with increased risk.5 Interestingly, the majority of PwCF indicated prior knowledge of EVALI (n = 21, 72.4%) but a significantly smaller number of healthy controls indicated that they had heard of EVALI prior to study enrollment (n = 5, 21.7%) (Table 3).

#### Table 3. Perceptions of E-Cigarette Use

## CONCLUSIONS

This single-center observational study helps to clarify the use and perceptions of E-cigarette use among young adults, both with CF and without this illness, as well as highlight general perceptions of health among these populations. Overall, both PwCF and our control population reported a generally good quality of life with regards to their physical health. This is consistent with national data for this age group, but our PwCF population had much higher quality of life metrics compared with many young adults with chronic diseases, who overwhelmingly tend towards lower reported quality of life.<sup>28,29</sup> The overall quality of life reported by PwCF correlated positively with the individuals' lung function as measured by FEV1% predicted, consistent with known data regarding lung function and quality of life, which supports the internal validity of our study.<sup>30</sup>

With regards to conventional cigarette use, the control population indicated cigarette use at a prevalence comparable to the national population.<sup>1</sup> PwCF were less likely to use cigarettes which is consistent with prior studies.<sup>17</sup> While the control population indicated E-cigarette use comparable with or slightly above national data, fewer PwCF reported E-cigarette use compared to conventional cigarettes. These findings demonstrate that PwCF are less likely than their counterparts without CF to use any inhalational products. This may be due to PwCF being acutely aware of their lung function and being engaged in the healthcare system from an early age. Counter to our hypothesis, PwCF were more likely to use conventional cigarettes than E-cigarettes. Further studies are needed to better understand why this might be the case.

PwCF were equally likely to identify E-cigarettes as harmful to one's lung health as healthy controls but were more likely to identify harm occurring within one year of E-cigarette use and were significantly more likely to have heard of EVALI than control peers. This discrepancy may be due to the newer development of E-cigarettes, and exposure among PwCF to more recent media coverage on the risks of EVALI, particularly compared with the anti-smoking campaigns of the early 2000s. EVALI is also promoted as affecting a younger population compared with conventional cigarettes, which may influence PwCF's choice on initiation of inhaled products.

Perceptions of E-Cigarette Use Impact	CF (n = 29)	Non-CF (control, n = 23*)
Impact of electronic cigarettes on individuals' health (0–100, 100 being significant negative impact)	86.6	80.3
Impact of electronic cigarettes on those with chronic lung disease (0-100, 100 significantly worse impact)	88.1	85.5
Length of time for electronic cigarettes to affect health	82.7% (24/29) said e-cigarette use would affect lung health within one year	39% (9/23) said e-cigarette use would affect lung health within one year
Heard about EVALI	72.4% (21/29)	21.7% (5/23)

\*3 individuals did not respond to these specific questions



While the low prevalence of E-cigarette use amongst PwCF may be reassuring to providers caring for this patient population, the use of conventional cigarettes amongst this group and the prevalence of use in the control population indicates a need for targeted assessment and education on inhalational product use.

Interestingly, PwCF expressed greater knowledge regarding EVALI. The lack of knowledge in the control population indicates that educational tools on the detrimental effects of E-cigarettes are also needed for healthy adolescents and young adults.

Limitations of this study include its small sample size, single-center and retrospective design. We did not have coincident FEV1% predicted data and E-cigarette or conventional cigarette use, nor was chronicity of use assessed. Participants willing to engage in a telephone-based survey may have self-selected and thus may not be truly representative of the population. While the state of Rhode Island has had <10 cases of EVALI according to CDC data, the rates of EVALI may be variable between different states and thus may limit generalizability.

This is the first study to our knowledge to look at the use and perceptions of E-cigarette use amongst young adults with CF, a progressive lung disease in which the mainstay of care is the preservation of lung function. While small, our study has demonstrated the need for further education of both PwCF and healthy young adults regarding E-cigarette use and conventional cigarette use and the potential impact on their health.

#### References

- U.S. Department of Health and Human Services. Smoking and Tobacco Use. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. 2021.
- National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General. National Centers for Disease Control and Prevention. 2012.
- U.S. Department of Health and Human Services. E-cigarette Use Among Youth and Young Adults. A Report of the Surgeon General. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. 2016.
- Office of the Surgeon General. Surgeon General's Advisory on E-cigarette Use Among Youth. Washington, DC: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. 2019.
- National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. Outbreak of Lung Injury Associated with the Use of E-cigarette, or Vaping, Products. Centers for Disease Control and Prevention. 2021.
- Butt YM, Smith ML, Tazelaar HD, Vaszar LT, Swanson KL, Cecchini MJ, Boland JM, Bois MC, Boyum JH, Froemming AT, Khoor A, Mira-Avendano I, Patel A, Larsen BT. Pathology of Vaping-Associated Lung Injury. N Engl J Med. 2019 Oct 31;381(18):1780-1781.

- Lee H. Vitamin E acetate as linactant in the pathophysiology of EVALI. *Med Hypotheses*. 2020 Nov;144:110182.
- Boudi FB, Patel S, Boudi A, Chan C. Vitamin E Acetate as a Plausible Cause of Acute Vaping-related Illness. *Cureus*. 2019;11(12):e6350.
- Blount BC, Karwowski MP, Shields PG, et al. Vitamin E Acetate in Bronchoalveolar-Lavage Fluid Associated with EVALI. N Engl J Med. 2020;382(8):697-705.
- Muthumalage T, Friedman MR, McGraw MD, Ginsberg G, Friedman AE, Rahman I. Chemical Constituents Involved in E-cigarette, or Vaping Product Use-Associated Lung Injury (EVALI). Toxics. 2020; 8(2):25.
- Chun LF, Moazed F, Calfee CS, Matthay MA, Gotts JE. Pulmonary toxicity of E-cigarettes. *Am J Physiol Lung Cell Mol Physi*ol. 2017;313(2):L193-L206.
- 12. 2016 Patient Registry Annual Data Report. Cystic Fibrosis Foundation Patient Registry. 2016:94.
- Conway SP, Pond MN, Watson A, Hamnett T. Knowledge of adult patients with cystic fibrosis about their illness. *Thorax*. 1996 Jan;51(1):34-8.
- Nolan T, Desmond K, Herlich R, Hardy S. Knowledge of cystic fibrosis in patients and their parents. *Pediatrics*. 1986 Feb;77(2):229-35.
- 15. Ssewanyana D, Nyongesa MK, van Baar A, Newton CR, Abubakar A. Health risk behavior among chronically ill adolescents: a systematic review of assessment tools. *Child Adolesc Psychiatry Ment Health*. 2017;11:32.
- Ortega-García JA, López-Fernández MT, Llano R, et al. Smoking prevention and cessation programme in cystic fibrosis: integrating an environmental health approach. J Cyst Fibros. 2012;11(1):34-39.
- Britto MT, Garrett JM, Dugliss MAJ, et al. Risky Behavior in Teens With Cystic Fibrosis or Sickle Cell Disease: A Multicenter Study. *Pediatrics*. 1998;101(2):250-256.
- Verma A, Clough D, McKenna D, Dodd M, Webb AK. Smoking and cystic fibrosis. J R Soc Med. 2001;94 Suppl 40:29-34.
- Gentzke AS, Wang TW, Jamal A, et al. Tobacco Product Use Among Middle and High School Students — United States, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1881–1888.
- Kowitt SD, Osman A, Ranney LM, Heck C, Goldstein AO. E-cigarette Use Among Adolescents Not Susceptible to Using Cigarettes. *Prev Chronic Dis.* 2018;15:170368.
- Kong G, Bold KW, Cavallo DA, Davis DR, Jackson A, Krishnan-Sarin S. Informing the development of adolescent E-cigarette cessation interventions: A qualitative study. *Addict Behav.* 2021 Mar;114:106720.
- 22. Wadsworth E, Neale J, McNeill A, Hitchman SC. How and Why Do Smokers Start Using E-cigarettes? Qualitative Study of Vapers in London, UK. *Int J Environ Res Public Health*. 2016;13(7):661.
- CDC, Office on Smoking and Health. Smoking and Tobacco Use; Data and Statistics; Surveys; National Youth Tobacco Survey (NYTS). Smoking and Tobacco Use. December 21, 2020.
- Creamer MR. Tobacco Product Use and Cessation Indicators Among Adults — United States, 2018. MMWR Morb Mortal Wkly Rep. 2019;68.
- 25. Crowne DP, Marlowe D. A new scale of social desirability independent of psychopathology. *J Consult Psychol*. 1960 Aug;24:349-54.
- 26. Henry B, Aussage P, Grosskopf C, Goehrs JM. Development of the Cystic Fibrosis Questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. *Qual Life Res.* 2003 Feb;12(1):63-76.
- 27. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-483.



- Soubelet A, Salthouse TA. Influence of social desirability on age differences in self-reports of mood and personality. J Pers. 2011;79(4):741-762.
- 29. Bronner, M.B., Peeters, M.A.C., Sattoe, J.N.T., et al. The impact of type 1 diabetes on young adults' health-related quality of life. *Health Qual Life Outcomes*. 2020;18(137).
- Riekert KA, Bartlett SJ, Boyle MP, Krishnan JA, Rand CS. The association between depression, lung function, and health-related quality of life among adults with cystic fibrosis. *Chest.* 2007 Jul;132(1):231-7.

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## Disclosures

We confirm that there are no Conflicts of Interest or disclosures to report for all authors of this study.

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## Rhode Island Monthly Vital Statistics Report Provisional Occurrence Data from the Division of Vital Records

	REPORTING PERIOD				
VITAL EVENTS	DECEMBER 2022	12 MONTHS ENDI	DING WITH DECEMBER 2022		
VITAL EVENTS	Number	Number	Rates		
Live Births	904	11,182	10.6*		
Deaths	1005	11,063	10.4*		
Infant Deaths	1	39	3.5#		
Neonatal Deaths	1	30	2.7#		
Marriages	365	6,986	6.6*		
Divorces	229	2,614	2.5*		

\* Rates per 1,000 estimated population

# Rates per 1,000 live births

	REPORTING PERIOD				
	JUNE 2022	12	MONTHS ENDING	WITH JUNE 2022	
Underlying Cause of Death Category	Number (a) Number (a) Rates (b)		YPLL (c)		
Diseases of the Heart	173	2,390	217.8	3,487.0	
Malignant Neoplasms	153	2,187	199.3	4,129.5	
Cerebrovascular Disease	44	513	46.7	672.0	
Injuries (Accident/Suicide/Homicide)	98	1,107	100.9	15,621.0	
COPD	34	457	41.6	400.0	

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,097,379 for 2020 (www.census.gov)

(c) Years of Potential Life Lost (YPLL).

NOTE: Totals represent vital events, which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.



## Troglodyte

JOSEPH H. FRIEDMAN, MD

do a lot of peer reviewing. I probably average about two papers each week, which forces me to closely read and constructively critique a small number of papers rather than review, less critically, a large number to keep up in my field. Perhaps I've been falling behind as I seek to learn more and more about less and less. If so, the various journal editors haven't picked up on it. However, I have a persistent anxiety, which I think I share with the majority, if not the vast majority of older people, that I am declining in both my memory and my cognition. When my patients, mostly

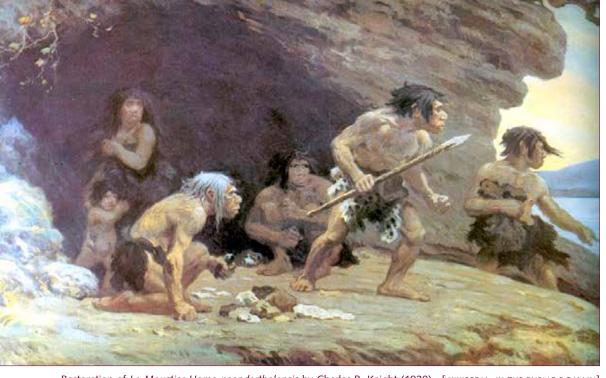
older people with Parkinson's disease (PD), tell me they can't remember names and can't plan things as well, I ask them if this is worse than it is for their friends. Usually it isn't and we move on.

## Subjective Cognitive Impairment

Currently I'm reviewing a paper on Subjective Cognitive Impairment (SCI, as it's known in the trade). There's been a lot written about it in recent years. I only chanced upon the topic a year or two ago, at which time it had firmly planted a seed in the dementia literature, but had not yet risen to the kudzu stage. I thought two things: on the one hand, it was a silly pursuit of a non-problem, on the other, it was a great way for researchers with time on their hands to write some peer-reviewed articles to advance their career. Like the Golem, in James Thurber's classic children's tale, *The Thirteen Clocks*, when asked why he had joined a gold rush in a distant place, having taken responsibility for starting the rumor in the first place that there was gold there, he remarked that so many people were going that there must be something to it. I comfort my patients by relating an

> observation I read many years ago, "The older I get, the better I was."

I now have to opine on a research study of the purported problem, which I am unsure exists. So, I am no longer an uninterested party on the sidelines in this SCI business. I have, however, reflected on what I consider an important and persistent problem that seems analogous, which is the memory impairment that a small percentage of patients treated with electroconvulsive therapy report, even when their depression remits. It may be



Restoration of Le Moustier Homo neanderthalensis by Charles R. Knight (1920). [WIKIPEDIA, IN THE PUBLIC DOMAIN]



permanent, and is not associated with tangible abnormalities on formal testing. It does not, so far as is currently known, lead to dementia. No one knows what this memory deficit means. Is it physiological, or is it simply a matter of, "the older I get the better I was," or a nocebo (negative placebo) effect?

When I used to see general neurology patients, 20 years ago, not just those with movement disorders, I often saw patients whose primary complaint was their memory loss, and most had normal exams. They suffered, I thought, from anxiety. Now they would be suffering from SCI.

Many years ago, I attended a small meeting to discuss apathy, a very important issue in psychiatry, particularly in schizophrenia, but also in dementing disorders, particularly Alzheimer's disease and, to a lesser extent, PD. When the dementia doctors discussed the negative consequences of apathy, I noted that in PD it was a cloud with a silver lining. The absence of emotions softened the blows inflicted by the disease as it robbed people of their dexterity, speech, gait, balance, and even their cognitive skills. When patients were asked how they felt, the usual answer was "fine." And they meant it. The non-apathetic said, "I'm frustrated. I'm angry." "I'm depressed." "I can't do anything I enjoy. I'm trapped. My life is terrible. I'm a burden." And on and on. I point out to the families, who are

distraught, that they are suffering more than the patient. They see my point and act as if I've lightened their burden to a small degree. When I said this to the group of clinicians, their jaws dropped. What I believed was a thoughtful insight they took as an assault on the received modern psychiatric interface cannon. I was a Neanderthal, apparently invited to the meeting by mistake.

I mention this only to put my thoughts on SCI in perspective. And that perspective is, I fear that my thoughts may be somewhere between those of a troglodyte and a Luddite. I had never thought of myself as an opinionated person until I was in college, when some friends noted that I was, in fact, very opinionated. I thought I wasn't because I was usually able to see both sides of an argument, which, I perceived, made me sort of "wishy washy." My friends thought not. I've had wrong opinions, of course, and like to think that I've corrected them, and I may have wrong opinions about SCI, and I'll be ready to correct them, too, but right now, I've found that every one of my older friends (over 70) has SCI. I'll bet that almost every reader of this column over age 70, and many a good deal younger, have SCI, too. We used to call them "the worried well." It is common in people with anxiety, depression, whiplash, chronic fatigue, etc.

The manuscript I reviewed, like many, but not all articles on SCI, has

a long-term follow-up showing that people with this diagnosis are more likely to become demented than those who didn't complain, or apparently notice, their developing memory impairment. I would have thought that it would have been the opposite, as with driving. Bad drivers don't worry about their driving because they don't recognize their deficits, while good drivers track their every mistake.

I'm willing to acknowledge my mistakes, I think. The paper I reviewed is flawed, but acknowledges its flaws. Few papers are perfect and the better papers acknowledge the limitations of their observations, as this one did. However, unless the investigators set out to debunk a theory, they can't report that they spent their time investigating a silly idea. This puts me in the position of helping decide whether a good investigation of a worthless concept is worth publishing. Although I'm opinionated, I do realize that I'm wrong sometimes, so I voted to help clog up the journals with another contribution of little value. \*

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## BLED, SLOVENIA

**Marianne Migliori**, RIMJ graphic designer, views the journal from the shore of **Lake Bled** in northern Slovenia, about 10 miles form the Austrian border. Its shores were settled by 7th-century Slavs. **Bled Castle**, built in the 11th century, stands on the edge of a 200foot precipice overlooking the lake. On tiny **Bled Island**, the 17th-century Church of the Assumption sits atop a 99-step staircase on the site of a former sacred site that dates to the 9th century. The lake's natural blue-green waters are fed by warm springs, and in the mid 19th century, baths were opened, making this a favorite resort destination. Bled was the summer residence of the Yugoslav royal family, and later of Marshall Josip Tito, who controlled Yugoslavia from 1956 until his death in 1980. In 1990, Slovenia was the first Yugoslav republic to hold free elections and declare its independence.

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RHODE ISLAND MEDICAL SOCIETY

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211<sup>TH</sup> ANNUAL MEETING and AWARDS DINNER 6:00 pm Reception, 7:00 pm Dinner The Squantum Association, East Providence

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## Working for You: RIMS advocacy activities

## July 3, Monday

Warren Alpert Medical School Resident Orientation: Rita Towers, MSW, LCSW, Clinical Associate, Physician Health Program, and Stacy Paterno, staff

## July 10, Monday

RIMS Board meeting:

Thomas Bledsoe, MD, President

Protect our Health Care Policy Group: Stacy Paterno, staff

## May 5, Friday

American Association of Medical Society Executives meeting: Stacy Paterno, staff

## July 12, Wednesday

Rhode Island Department of Health (RIDOH) Board of Medical Licensure and Discipline (BMLD): Stacy Paterno, staff

Governor's Overdose Intervention and Prevention Task Force: **Sarah Fessler, MD**, Past President

#### July 13, Thursday

CTC-RI Prior Authorization Steering Committee: **Peter Hollmann**, **MD**, Chair; **Elizabeth Lange**, **MD**, Past President; Stacy Paterno, staff

## July 14, Friday

Medical Society Consortium on Climate & Health Webinar: Stacy Paterno, staff

## July 17, Monday

AMA Washington Update: Stacy Paterno, staff

#### July 19, Wednesday

Rhode Island Foundation Long-term Health Committee meeting: Stacy Paterno, staff

#### July 20, Thursday

Health Information Technology Steering Committee meeting: Stacy Paterno, staff

RIMS Climate Change and Health Committee: Katelyn Moretti, MD, Co-Chair; Alison Hayward, MD, Co-Chair

## July 24, Monday

Protect our Health Care Policy Group: Stacy Paterno, staff

Nursing and Direct Care Career Ladders combined meeting: Stacy Paterno, staff

RIMS Public Laws Committee Meeting: **Michael Migliori, MD**, Chair

#### July 27, Thursday

Rhode Island Quality Institute meeting: Thomas Bledsoe, MD, President; Heather Smith, MD, MPH, Incoming President; and Stacy Paterno, staff

RIMS Finance Committee meeting: **Matthew Smith, MD, MHL**, Treasurer and Chair





## RIMS gratefully acknowledges the practices who participate in our discounted Group Membership Program





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## URI neuroscientist part of \$8M consortium grant on translational approach towards understanding brain waste clearance in Cerebral Amyloid Angiopathy



William Van Nostrand, PhD [PHOTO: URI]

KINGSTON, RI – **WILLIAM VAN NOSTRAND, PhD**, co-executive director of the George & Anne Ryan Institute for Neuroscience at the University of Rhode Island, is part of a team awarded a five-year, \$8 million grant from the Leducq Foundation that will establish a transatlantic consortium on the study of the brain's waste-clearing system as a contributor to cerebral amyloid angiopathy.

The consortium will work with innovative transgenic and gene-edited rodent models developed by Van Nostrand, who has studied cerebral amyloid angiopathy (CAA) for nearly 30 years.

According to a statement from the Leducq Foundation, CAA is a highly prevalent and currently untreatable condition, affecting the brains of >50% of individuals over 80 and ~80–100% of patients with Alzheimer's disease. The specific goals of our consortium are to:

- 1. Establish a data-driven, integrated multi-scale understanding of perivascular brain clearance in health and CAA
- 2. Translate experimental findings from rodent models to the human brain
- 3. Identify relevant driving forces to be tested in future clinical trials to enhance brain clearance.

The consortium is expected to officially start work Jan. 1, 2024, and includes:

## Coordinators

- Matthias Van Osch, Leiden University Medical Center (Netherlands)
- Susanne Van Veluw, Massachusetts General Hospital

## Members

- Erik Bakker, Amsterdam University Medical Center (Netherlands)
- Helene Benveniste, Yale University
- Roxana Carare, University of Southampton (UK)
- Steven Greenberg, Massachusetts General Hospital
- Jeffrey Iliff, University of Washington
- Sylvie Lorthois, Institut De Mécanique Des Fluides De Toulouse (France)
- Gabor Petzold, German Center For Neurodegenerative Diseases (Germany)
- · Andy Shih, University of Washington
- William Van Nostrand, University of Rhode Island

Van Nostrand joined URI in 2017. He is Herrmann Professor of Neuroscience and a professor of biomedical and pharmaceutical sciences in URI's College of Pharmacy.

The Leducq Foundation is an international grant-making organization with a mission to improve human health through international efforts to combat cardiovascular disease and stroke. By forging scientific alliances that transcend national borders, it promotes long-term collaborative relationships to foster innovations in cardiovascular and stroke research and change the way that patients with cardiovascular and neurovascular disease are diagnosed and treated. For more information, visit https://www.fondationleducq.org/  $\diamond$ 

## Rhode Island Enacts Nurse Licensure Compact (NLC)

CHICAGO – Gov. **DANIEL J. MCKEE** signed the NLC into law on June 24, 2023, making Rhode Island the 41st jurisdiction to enact the NLC. The compact allows registered nurses (RNs) and licensed practical/vocational nurses (LPN/VNs) to have one multistate license, with the ability to practice in person or via telehealth, in both their home territory/state and other NLC states.

Sen. Joshua Miller, one of the NLC bill sponsors remarked, "Our state is grappling with a severe shortage of nurses. Returning to the compact is a way we can make it easier and more appealing for nurses to come here for a job, making it easier for our hospitals and health facilities to fill their staffing needs. Rejoining the compact is good for our public health and safety."

Licensure requirements are aligned in NLC states, so all nurses applying for a multistate license are required to meet those same standards, including submission to a federal and state fingerprintbased criminal background check.

Although the NLC has been enacted in Rhode Island, an implementation process must be completed before its residents will be able to apply for a multistate license, and before nurses in other NLC states who hold a multistate license will be able to practice there. The implementation date has not been set.

With the multistate license, nurses are able to provide telehealth nursing services to patients located in NLC states without having to obtain additional licenses. A multistate license facilitates cross-border practice for many types of nurses who routinely practice with patients in other states, including primary care nurses, case managers, transport nurses, school and hospice nurses and many others. Further, military spouses who experience moves every few years also benefit greatly from the multistate license. **\*** 



## New RI law reduces cost of HIV-prevention medications

PROVIDENCE – Governor **DAN MCKEE** on June 28th signed into law legislation sponsored by Senator **MELISSA MURRAY** that will help reduce the spread of HIV transmission by making HIV-prevention and post-exposure medications accessible and covered by insurance, including newer injectable formulations. The Governor signed the legislation at Open Door Health and was joined by Senator Murray, state and local officials and community advocates.

"PReP and PEP are key tools to prevent the spread and help us work towards the eradication of HIV," said Governor Dan McKee. "However, this will only happen if we continue to break down barriers to access these critical medications. Thank you to all the advocates for raising their voices on this important issue."

There are two commonly used HIVprevention medications: pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP). PrEP is taken before an exposure to prevent HIV, whereas PEP is taken after a potential or known exposure. Together, the treatments have contributed to a dramatic reduction in HIV transmission rates [hiv.gov] [r20.rs6.net] in recent years. But only about 25 percent of individuals at risk of HIV transmission are using these treatments, according to the US Centers for Disease Control (CDC) [cdc.gov] [r20.rs6.net]. Advocates point to both out-of-pocket costs and lack of access as barriers.

The legislation (2023-S 0563Aaa [webserver.rilegislature.gov] [r20.rs6.net]) requires the coverage of PrEP and PEP drugs by health insurance plans at no out-ofpocket costs to patients. The bill would also enable pharmacists to prescribe them to eligible patients. The bill outlines clear guidelines for which patients would be eligible.

"The use of PrEP can substantially reduce the risk of HIV transmission, and PEP is an equally remarkable intervention for people who may have been exposed to HIV. However, these medications are underused, especially amongst people in groups with higher rates of HIV," said Interim Director of Health **UTPALA BANDY, MD, MPH**. "This legislation is an important step toward ensuring equitable access to these critical medications, and consistent with our goal of giving Rhode Islanders in every community the tools and resources they need to stay healthy and safe."

"By mandating insurance coverage, limiting prior authorizations and reducing out-of-pocket costs for PrEP and PEP treatments, this law will expand access to these critical treatments and play a direct, significant role in helping Rhode Islanders proactively protect themselves against HIV," said **DR. AMY NUNN**, executive director, Rhode Island Public Health Institute. "This is one of the most progressive public health policies in the country, and we applaud Governor McKee and the General Assembly for their leadership in getting it across the finish line."

"I've been prescribing PrEP for over 10 years. This bill overcomes a significant obstacle that many of my patients have mentioned including high out-of-pocket costs for the medication, " said **PHILIP A. CHAN, MD**, an infectious diseases specialist and the Chief Medical Offer at Open Door Health. "Additionally, this bill covers injectable PrEP which is an important option for some people. The HIV epidemic is still impacting many people including cisgender gay and bisexual men. People should be aware of PrEP and talk to their medical provider about their potential HIV risk and whether PrEP may be an option for them."

CDC recommends that all adults test at least once for HIV in their lifetime and more frequently if engaging in behaviors that may place a person at ongoing risk of infection.

For people that may be at risk of HIV, PrEP is initiated before and continued throughout periods of potential exposure to HIV. It was first approved by the U.S. Food and Drug Administration in 2012 and is safe and highly effective when taken as prescribed. PEP is taken after a potential exposure, such as a broken condom, shared needle or sexual assault. If taken within 72 hours of a possible HIV exposure, the drug is highly effective at preventing transmission.

Both treatments are considered preventative, and free coverage had been required under the Affordable Care Act. But on March 30, in a case called Braidwood Management Inc. v. Becerra, U.S. District Judge Reed O'Connor ruled, among other things, that this requirement violated the religious freedom of employers. The case is expected to head to the U.S. Supreme Court.

A growing list of states including Maine, Nevada and Virginia have passed similar legislation.

RIDOH has additional information online about HIV prevention, including PrEP and PEP: https://health.ri.gov/diseases/ hivaids/about/prevention/. \*



## Alzheimer's International Conference covers new treatments, early diagnosis options, risk factors

AMSTERDAM, JULY 20, 2023 – New research reported at the Alzheimer's Association International Conference<sup>®</sup> (AAIC<sup>®</sup>) 2023 covered the breadth of Alzheimer's disease and dementia research, including advancements in treatment, early and accurate diagnosis, and our understanding of risk factors for Alzheimer's and other dementias.

AAIC is the premier annual forum for presentation and discussion of the latest Alzheimer's and dementia research. This year's conference took place both virtually and in-person in Amsterdam, Netherlands, and attracted over 10,000 attendees and more than 3,000 scientific presentations.

## Advances in Treatments, Clinical Trial Results

The Alzheimer's Association highlighted results from trials of drug and non-drug interventions for Alzheimer's disease at AAIC 2023.

New, more complete data were reported at AAIC 2023 by Eli Lilly from the TRAILBLAZER-ALZ 2 Phase 3 clinical trial of donanemab in early symptomatic Alzheimer's disease. With this fuller picture of the donanemab Phase 3 results, we see additional convincing scientific evidence that thoroughly removing beta amyloid from the brain is associated with significant slowing of disease progression in people living with early Alzheimer's. The results of this trial also further illustrate that initiating treatment as early as possible in the course of the disease enables the possibility of a bigger beneficial effect, but also that there is potential for slowing of disease progression even when treatment is started later. The progress we've seen in this class of treatments, as well as the diversification of potential new therapies over the past few years, provides hope to those impacted by this devastating disease.

Two new therapeutic approaches for Alzheimer's based on CRISPR gene editing were reported at AAIC. One aims to reduce the impact of the strongest known Alzheimer's risk gene, APOE-e4. The other strives to reduce production of a toxic protein in the brain, beta amyloid, which is a hallmark of Alzheimer's and the target of recently-approved treatments. CRISPR technology is making drug target identification faster with the goal of speeding up the drug discovery process, and building platforms for the development of next-generation treatments.

Non-drug interventions were also highlighted at AAIC, including results from the Aging and Cognitive Health Evaluation in Elders (ACHIEVE) study, the largest randomized, controlled clinical trial of hearing aids for reducing long-term cognitive decline in older adults. While the results were negative in the total study population, the hearing intervention slowed cognitive decline in older adults with mild to moderate hearing loss by 48% in a pre-specified segment of the study population consisting of 238 people participating in an ongoing observational study of heart health. The three-year intervention included use of hearing aids, a hearing "toolkit," and ongoing instruction and counseling with an audiologist.

## Blood Tests: The Next Frontier in Alzheimer's Diagnosis

Advancements in technology and practice reported for the first time at AAIC 2023 demonstrate the simplicity, transportability and diagnostic value of blood-based biomarkers for Alzheimer's.

Researchers from University of Gothenburg, Sweden reported results from a simple, finger prick blood test that shows promise in the ability to detect markers of Alzheimer's using a single drop of blood dried on spot cards and shipped overnight between two countries, without temperature control or cooling. If validated through additional research, this test could offer a quick, noninvasive and cost-effective option that is simple enough to be performed independently, or by caregivers. It may be particularly valuable for use in rural districts or other lower resourced areas.

A research group with Lund University, Sweden conducted the first study to examine the use of blood-based biomarkers for Alzheimer's in primary care and compare them to the diagnostic accuracy of primary care physicians. A blood test was more than 80% accurate in identifying Alzheimer's-related changes – significantly better than doctors in the study who did not have access to the test. Blood tests for Alzheimer's have great potential for improving early diagnosis, diagnostic accuracy and proper treatment of people with Alzheimer's.

## New Use of Opioids and Mortality Among Older Adults With Dementia

New opioid use in older adults with dementia is associated with a significantly increased risk of death, including an eleven-fold increase in the first two weeks, according to research presented at AAIC 2023. Researchers from the Danish Dementia Research Centre used data from everyone in Denmark aged 65 and older diagnosed with dementia between 2008 and 2018, including both home-living and nursing home residents. Of that group, 42% of those diagnosed with dementia redeemed a prescription for an opioid at a pharmacy.

They found 33.1% of study participants died within 180 days after initiating their first opioid prescription, compared with 6.4% of those unexposed to opioids. After adjusting for potential differences between groups, researchers found a four-fold increase in excess mortality risk. The risk was greatest in the first 14 days, where mortality for all opioids was increased eleven fold. These initial findings emphasize the need for discussion between the patient, family and physician about pain medication.

## **Chronic Constipation Associated With Cognitive Decline**

New research demonstrating the relationship between gut health and the brain were revealed at AAIC. A researcher from University of Massachusetts, Amherst found individuals with chronic constipation (bowel movements every three days or more) had significantly worse cognition, equivalent to three years more of chronological cognitive aging, than those with healthy bowel movement patterns.



Plus, researchers from University of Texas San Antonio found specific gut bacteria that are associated with increased dementia risk, as well as gut bacteria that may be neuroprotective. Previous research has connected the health and makeup of the gut microbiome, which is the community of microorganisms that live in our digestive tracts, with a number of other vital body functions.

## First-ever Nationwide Estimates of U.S. County-Level Alzheimer's Prevalence

The first-ever nationwide estimates of the county-level prevalence of people with Alzheimer's dementia – in all 3,142 United States counties – were revealed at AAIC 2023. Researchers from Rush University Medical Center in Chicago found that the eastern and southeastern U.S. have the highest prevalence of Alzheimer's dementia. Higher percentages of older people and Black and Hispanic, all groups at higher risk for the disease, may explain the elevated prevalence in those regions. The findings can help guide the allocation of resources to public health programs for individuals and families affected by Alzheimer's in those regions.

## Volunteering Later in Life May Promote a Healthy Brain

Reported for the first time at AAIC 2023, researchers from University of California, Davis examined volunteering habits among an ethnic and racially diverse population of older adults and found that volunteering was associated with better baseline scores on tests of memory, thinking and planning. The researchers stated volunteering may be important for better cognition in late life and could serve as a simple intervention in older adults to protect against Alzheimer's and other dementias.  $\diamondsuit$ 

## Blue Cross & Blue Shield of RI announces nonprofits to benefit from its 2023 day of service, Blue across Rhode Island

Organized teams of BCBSRI employees will spend the workday volunteering for 14 nonprofits across the state in support of a wide range of community projects

PROVIDENCE – Blue Cross & Blue Shield of Rhode Island (BCBSRI) has announced the nonprofit organizations that will benefit from Blue across Rhode Island, the company's signature day of service in which hundreds of employees spend the workday volunteering at community and social service agencies.

On Sept. 15, Blue Cross associates will have the opportunity to volunteer for one of 14 nonprofits that applied for support with their efforts to help Rhode Islanders. This is the 12th consecutive year for Blue across Rhode Island, one of the largest annual volunteer events of its kind in the state.

The 2023 beneficiaries were revealed recently at a spirited kickoff for Blue across Rhode Island during which associates learn about this year's volunteer opportunities from team leaders and prepare to begin signing up the next day.

"We look forward to Blue across Rhode Island so much that the theme of our 2023 day of service is 'Best. Day. Ever,'" said BCBSRI Managing Director of Corporate Social Responsibility **CAROLYN BELISLE**. "The kickoff generates real excitement for our day of service and that excitement builds throughout the summer as we prepare to lend a hand to our community-based partners, who work tirelessly year-round to make a difference in the lives of Rhode Islanders. It's an honor to support their efforts through Blue across RI."

The BCBSRI volunteers will support a variety of community-based organizations and their projects, including ones that address food, housing, dental care, mental health, community recreation, and LGBTQIA+ youth.

The following are the 14 participating organizations that BCBSRI employees will support:

- Amenity Aid
- Bike Newport
- Crossroads Rhode Island
- Gotta Have Sole Foundation
- Habitat for Humanity of Rhode Island – Greater Providence
- Habitat for Humanity of Rhode Island
   South County
- Happy Hope Foundation

- Hope Alzheimer's Center
- NeighborWorks Blackstone River Valley
- Playworks New England
- Rhode Island Oral Health Foundation
- The Elisha Project
- YMCA of Pawtucket
- Youth Pride

In addition to the time and effort of volunteers, BCBSRI awards each partner organization \$5,000 in grant funding.

Since the launch of Blue across Rhode Island in 2012, \$749,000 in BCBSRI funding has been distributed to 78 organizations across the state and employees have logged more than 34,000 volunteer hours. These projects have had an impact on the lives of more than 162,000 Rhode Islanders.

Since its founding, BCBSRI has partnered with community organizations across the state through philanthropy, partnership, and service. BCBSRI's multifaceted corporate social responsibility program, Blue-Angel Community Investment, has enabled associates to serve our community for more than 20 years, with efforts such as Blue across Rhode Island.

## FDA converts novel Alzheimer's Disease treatment to traditional approval

## Action follows confirmatory trial to verify clinical benefit

WASHINGTON, DC – On July 6th, the U.S. Food and Drug Administration (FDA) converted Leqembi (lecanemab-irmb), indicated to treat adult patients with Alzheimer's Disease, to traditional approval following a determination that a confirmatory trial verified clinical benefit. Leqembi is the first amyloid betadirected antibody to be converted from an accelerated approval to a traditional approval for the treatment of Alzheimer's disease. The drug works by reducing amyloid plaques that form in the brain, a defining pathophysiological feature of the disease.

Leqembi was approved in January under the Accelerated Approval pathway. This pathway allows the FDA to approve drugs for serious conditions where there is an unmet medical need, based on clinical data demonstrating the drug's effect on a surrogate endpoint – in the case of Leqembi, reducing amyloid plaques in the brain – that is reasonably likely to predict a clinical benefit to patients. As a postmarketing requirement of the accelerated approval, the FDA required the applicant to conduct a clinical trial, often referred to as a confirmatory study, to verify the anticipated clinical benefit of Leqembi. Efficacy of Leqembi was evaluated using the results of Study 301 (CLARITY AD), a Phase 3 randomized, controlled clinical trial.

"Today's action is the first verification that a drug targeting the underlying disease process of Alzheimer's disease has shown clinical benefit in this devastating disease," said **TERESA BURACCHIO**, acting director of the Office of Neuroscience in the FDA's Center for Drug Evaluation and Research. "This confirmatory study verified that it is a safe and effective treatment for patients with Alzheimer's disease."

Study 301 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study that enrolled 1,795 patients with Alzheimer's disease. Treatment was initiated in patients with mild cognitive impairment or mild dementia stage of disease and confirmed presence of amyloid beta pathology. Patients were randomized in a 1:1 ratio to receive placebo or Leqembi at a dose of 10 milligrams (mg)/kilograms (kg), once every two weeks. Leqembi demonstrated a statistically significant and clinically meaningful reduction of decline from baseline to 18 months on the primary endpoint, the Clinical Dementia Rating Scale Sum of Boxes score, compared to placebo. Statistically significant differences between treatment groups were also demonstrated on all secondary endpoints, which included the Alzheimer's Disease Assessment Scale Cognitive Subscale 14, and the Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment.

On June 9, the FDA convened the Peripheral and Central

Nervous System Drugs Advisory Committee to discuss whether Study 301 provided evidence of clinical benefit of Leqembi for the treatment of Alzheimer's disease. All committee members voted affirmatively that the results of the study verified the clinical benefit of Leqembi for the indicated use.

The most common side effects of Leqembi were headache, infusion-related reactions and amyloid-related imaging abnormalities (ARIA), a side effect known to occur with the class of antibodies targeting amyloid. ARIA most commonly presents as temporary swelling in areas of the brain seen on imaging studies that usually resolves over time and may be accompanied by small spots of bleeding in or on the surface of the brain. Although ARIA is often not associated with any symptoms, symptoms can occur and include headache, confusion, dizziness, vision changes and nausea. ARIA can also infrequently present with serious and life-threatening brain edema that can be associated with seizures and other severe neurological symptoms. Intracerebral hemorrhages can occur in patients treated with this class of medications and can be fatal. A boxed warning is included in the prescribing information to alert patients and caregivers to the potential risks associated with ARIA.

Patients treated with Leqembi who are homozygous for the ApoE  $\varepsilon$ 4 allele have a higher incidence of ARIA, including symptomatic, serious and severe ARIA, compared to heterozygotes and noncarriers. The prescribing information states that testing for ApoE  $\varepsilon$ 4 status should be performed before starting treatment with Leqembi to inform the risk of developing ARIA.

Use of anticoagulant medication was associated with an increased number of intracerebral hemorrhages in patients taking Leqembi compared to placebo. The prescribing information recommends caution when considering use of Leqembi in patients taking anticoagulants or with other risk factors for intracerebral hemorrhage.

Leqembi is contraindicated in patients with serious hypersensitivity to lecanemab-irmb or to any of its inactive ingredients. Adverse reactions may include angioedema (swelling) and anaphylaxis (allergic reaction).

Leqembi should be initiated in patients with mild cognitive impairment or mild dementia stage of Alzheimer's disease, the population in which treatment was studied in clinical trials. The labeling states that there are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied.

The approval of Leqembi was granted to Eisai Inc. 💠



## FDA approves new drug to prevent RSV in babies and toddlers

WASHINGTON, DC – On July 17th, the U.S. Food and Drug Administration (FDA) approved Beyfortus (nirsevimab-alip) for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants born during or entering their first RSV season, and in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

Approximately 1% to 3% of children under 12 months of age in the United States are hospitalized each year due to RSV, according to the American Academy of Pediatrics. In most parts of the US, RSV circulation is seasonal, typically starting during the fall and peaking in the winter; it is transmitted from person to person through close contact with someone who is infected.

Beyfortus is a monoclonal antibody with activity against RSV. One dose of Beyfortus, administered as a single intramuscular injection prior to or during RSV season, may provide protection during the RSV season.

The safety and efficacy of Beyfortus were supported by three clinical trials (Trials 03, 04 and 05). The key measure of efficacy was the incidence of medically attended RSV lower respiratory tract infection (MA RSV LRTI), evaluated during the 150 days after Beyfortus administration. MA RSV LRTI included all health care provider visits (physician office, urgent care, emergency room visits and hospitalization) for lower respiratory tract disease with worsening clinical severity and a positive RSV test. Trials 03 and 04 were randomized, double-blind, placebo-controlled, multicenter clinical trials.

Trial 03 included 1,453 preterm infants (born at greater than or equal to 29 weeks of gestational age up to less than 35 weeks of gestation) who were born during or entering their first RSV season. Of the 1,453 preterm infants in the trial, 969 received a single dose of Beyfortus and 484 received placebo. Among infants who were treated with Beyfortus, 25 (2.6%) experienced MA RSV LRTI compared with 46 (9.5%) infants who received placebo. Beyfortus reduced the risk of MA RSV LRTI by approximately 70% relative to placebo.

For Trial 04, the primary analysis group within the trial included 1,490 term and late preterm infants (born at greater than or equal to 35 weeks in gestational age), 994 of whom received a single dose of Beyfortus and 496 of whom received placebo. Among infants who were treated with Beyfortus, 12 (1.2%) experienced MA RSV LRTI compared with 25 (5.0%) infants who received placebo. Beyfortus reduced the risk of MA RSV LRTI by approximately 75% relative to placebo. Trial 05, a randomized, double-blind, active (palivizumab)-controlled, multicenter trial, supported the use of Beyfortus in in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. The trial enrolled 925 preterm infants and infants with chronic lung disease of prematurity or congenital heart disease. The safety and pharmacokinetic data from Trial 05 provided evidence for the use of Beyfortus to prevent MA RSV LRTI in this population.

Possible side effects of Beyfortus include rash and injection site reactions. Beyfortus should not be given to infants and children with a history of serious hypersensitivity reactions to Beyfortus' active ingredients or any of its excipients.

Beyfortus comes with warnings and precautions about serious hypersensitivity reactions, including anaphylaxis, which have been observed with other human IgG1 monoclonal antibodies. Beyfortus should be given with caution to infants and children with clinically significant bleeding disorders.

Beyfortus received a Fast Track designation for this indication.

The FDA granted this approval to AstraZeneca. ♦

## FDA approves first nonprescription daily oral contraceptive

WASHINGTON, DC – On July 16th, the U.S. Food and Drug Administration (FDA) approved Opill (norgestrel) tablet for nonprescription use to prevent pregnancy – the first daily oral contraceptive approved for use in the U.S. without a prescription. Approval of this progestin-only oral contraceptive pill provides an option for consumers to purchase oral contraceptive medicine without a prescription at drug stores, convenience stores and grocery stores, as well as online.

The timeline for availability and price of this nonprescription product is determined by the manufacturer. Other approved formulations and dosages of other oral contraceptives will remain available by prescription only.

"Today's approval marks the first time a nonprescription daily oral contraceptive will be an available option for millions of people in the United States," said **PATRIZIA CAVAZZONI, MD**, director of the FDA's Center for Drug Evaluation and Research. "When used as directed, daily oral contraception is safe and is expected to be more effective than currently available nonprescription contraceptive methods in preventing unintended pregnancy."

Nonprescription availability of Opill may reduce barriers to access by allowing individuals to obtain an oral contraceptive without the need to first see a health care provider. Almost half of the 6.1 million pregnancies in the U.S. each year are unintended. Unintended pregnancies have been linked to negative maternal and perinatal outcomes, including reduced likelihood of receiving early prenatal care and increased risk of preterm delivery, with associated adverse neonatal, developmental and child health outcomes. Availability of nonprescription Opill may help reduce the number of unintended pregnancies and their potential negative impacts.



The contraceptive efficacy of norgestrel was established with the original approval for prescription use in 1973. HRA Pharma applied to switch norgestrel from a prescription to an over-the-counter product. For approval of a product for use in the nonprescription setting, the FDA requires that the applicant demonstrate that the product can be used by consumers safely and effectively, relying only on the nonprescription drug labeling without any assistance from a health care professional. Studies showed that consumer understanding of information on the Opill Drug Facts label was high overall and that a high proportion of consumers understood the label instructions, supporting their ability to properly use the drug when it is available as an over-the-counter product. When properly used, Opill is safe and effective.

Opill should be taken at the same time every day; adherence to daily use at the same time of day is important for the effectiveness of Opill. Using medications that interact with Opill can result in decreased efficacy of Opill or the other medication, or both, potentially resulting in unintended pregnancy.

The most common side effects of Opill include irregular bleeding, headaches, dizziness, nausea, increased appetite, abdominal pain, cramps or bloating.

The FDA granted the approval to Laboratoire HRA Pharma, recently acquired by Perrigo Company plc. ◆

# Application period now open for Blue Cross & Blue Shield of Rhode Island's LGBTQ Safe Zone Program

## Safe Zone designation identifies sites providing safe and inclusive care to the LGBTQ community

PROVIDENCE – Blue Cross & Blue Shield of Rhode Island (BCBSRI) is now accepting applications for its newest cohort of LGBTQ Safe Zone facilities. Healthcare facilities designated as Safe Zones will join more than 80 sites statewide that have demonstrated they are providing safe, affirming, and inclusive care to Rhode Island's LGBTQ community. Applications are due by Tuesday, August 15, 2023, at 5 p.m.

"We recognize that getting quality care can be more difficult for certain communities than it is for others and that the LGBTQ community has historically experienced discrimination in healthcare," said **JENNY BAUTISTA-RAVREBY**, BCBSRI diversity, equity and inclusion manager. "We're committed to furthering health equity however we can, and the LGBTQ Safe Zone program provides a way for Rhode Islanders to find inclusive, affirming care with confidence."

BCBSRI LGBTQ Safe Zones are certified based on a variety of factors. Certified facilities must train staff members in LGBTQ cultural competency, be committed to protecting staff and patients from discrimination, provide gender-neutral bathrooms, utilize inclusive forms and intake procedures, and display a commitment to working with the LGBTQ community.

Since launching its LGBTQ Safe Zone program in 2015, BCBSRI has certified more than 80 Safe Zone providers in over 25 towns and cities across Rhode Island. These providers span a range of specialties that include primary care, dental and mental health practices, pediatric care, assisted living facilities for older adults, and more. Visit bcbsri.com/ safezones to view the complete list of Safe Zone facilities.

Providers that meet certification requirements will be given a window cling so that visiting patients recognize it as a place that offers safe and affirming care to the LGBTQ community. Certified Safe Zones will also be added to a list that members can use to seek inclusive care settings. There is no cost to apply or obtain certification.

To learn more or apply for certification, visit bcbsri.com/providers/safezone-program. BCBSRI will notify newly certified facilities by October. ◆



## Appointments



## Elizabeth Burke Bryant joins faculty at the Brown School of Public Health

PROVIDENCE – **ELIZABETH BURKE BRYANT, JD**, has been appointed professor of the practice of health services, policy and practice at the Brown University School of Public Health, effective July 1, 2023.

In her new role at Brown Uni-

versity, Burke Bryant will share her wealth of knowledge and experience by teaching a policy and advocacy course within the School of Public Health. Simultaneously, she will continue her influential policy and advocacy work at both the national and state levels through the Hassenfeld Child Health Innovation Institute.

She is a child advocate with over 30 years of experience in advancing equitable policies and programs to improve the well-being of children, youth, and families. She served as Executive Director of Rhode Island KIDS COUNT, a children's policy and advocacy organization, for 28 years – from its establishment in 1994 to 2022.

A graduate of the University of Vermont and the George Washington University Law School, Burke Bryant has actively contributed to the field of child advocacy on a national scale. She served as co-chair of the board of the Partnership for America's Children, a prominent network of state and local child advocacy organizations striving to improve policies affecting children.  $\diamondsuit$ 



## John A. Stoukides, MD, named chairman of RWMC Department of Medicine

PROVIDENCE – JOHN A. STOU-KIDES, MD, ScD, has been named Chairman of Medicine at Roger Williams Medical Center. His appointment was effective in June and he becomes the fifth chair in the history of the department.

Dr. Stoukides was the unanimous recommendation of the search committee, co-chaired by Dr. Ponnandai Somasundar and Dr. Rita Peter-Faherty. The process began last year following the passing of Dr. Vincent Armenio.

Dr. Stoukides has been practicing medicine for 33 years, exclusively at RWMC, where he completed his residency. He is a graduate of the University of Rhode Island College of Pharmacy and Tufts University School of Medicine. Board-certified in Internal Medicine and Hospice and Palliative Medicine, he also received an honorary doctor of science degree in Geriatrics from URI.

He has been Vice Chairman of the Department of Medicine but has served as Interim Chair since last year. He is the longtime Chief of the Division of Geriatrics and Palliative Medicine at Roger Williams and was instrumental in developing the senior care practice group at the hospital, the state's largest. Dr. Stoukides also serves as Medical Director of Utilization Management for CharterCARE. He is a Clinical Assistant Professor at Boston University School of Medicine and the Warren Alpert School of Medicine at Brown University, as well as Associate Professor of Nursing and Adjunct Professor of Pharmacy at URI. He also has a private practice in East Providence.

In addition to serving on numerous hospital committees and local boards, Dr. Stoukides was a key member of the Governor's COVID-19 Task Force and was actively involved in our own COVID vaccination program at CharterCARE. ◆



## Appointments



## Yale New Haven Health System names Richard Lisitano president of Lawrence + Memorial Healthcare

NEW LONDON, CT/WESTERLY, RI – Yale New Haven Health System (YNHHS) has named **RICHARD LISITANO** as the new president of Lawrence +

Memorial Healthcare (Lawrence + Memorial Hospital, Westerly Hospital and VNA of Southeastern Connecticut) and executive vice president of Yale New Haven Health effective July 17. He replaces Patrick Green who accepted a position at UF Health Jacksonville.

Lisitano has been senior vice president of Operations at Yale New Haven Hospital (YNHH) since 2021 and has been employed at YNHH since 1996 when he started as director of Pharmacy. He holds a Master of Science from Ohio State University and a Bachelor of Science in Pharmacy from the University of Connecticut.

Lisitano, who has ascended the leadership ranks, has a record of contributions with Yale New Haven Health including the growth of various service lines for Urology, Neurosciences, Oncology, Orthopedics and Digestive Health; and developing/executing/integrating system-wide Epic EMR across five separate campuses.

"Rich's institutional knowledge across our system will be an asset as he leads Lawrence + Memorial and Westerly hospitals on the journey to greater operational excellence and strategic growth," said Pamela Sutton-Wallace, MPS, executive vice president and chief operating officer, Yale New Haven Health. "L+M and Westerly hospitals have experienced tremendous growth over the past six years as more patients are seeking specialized, high quality care in these communities, closer to where they live, work and play." "I'm honored to have been selected to lead and work alongside the staff at Lawrence + Memorial and Westerly hospitals," said Lisitano. "I look forward to partnering with employees, the physicians and our community partners to enhance the health of the communities we serve." 💠



## Blue Cross & Blue Shield of Rhode Island (BCBSRI) following a national search. Dr.

Blue Cross & Blue Shield of RI appoints Farah Shafi, MD, chief medical officer

PROVIDENCE – **FARAH SHAFI, MD, MBA**, has been appointed chief medical officer of

Shafi, who began her new position in June,

brings demonstrated leadership and results

in key areas of community and member health including maternal health, health equity, and behavioral health.

Dr. Shafi comes to BCBSRI from Mass General Brigham Health Plan where she worked for seven years, most recently as deputy chief medical officer. She is an obstetrician-gynecologist, who has served as an attending physician at Columbia University Medical Center in New York and Atrius Health in Massachusetts and was on staff at Mount Auburn Hospital, Newton-Wellesley Hospital, and Beth Israel Deaconess Medical Center.

Dr. Shafi was born in Providence at the former Lying-in Hospital and completed her residency at its successor, Women & Infants Hospital. She was elected to serve as a chief resident and also was an assistant instructor in obstetrics and gynecology at Brown University Medical School.

"We are thrilled to have Dr. Shafi join BCBSRI. She brings extensive experience as a clinician and a physician leader, which equip her to both lead our clinical team and to partner with providers throughout Rhode Island," said BCBSRI President and CEO Martha L. Wofford. "We specifically sought a hands-on physician leader with expertise in two key areas of focus: health equity and behavioral health. We are ecstatic to have found Dr. Shafi, whose deep experience is matched only by her passion for addressing disparities."

As chief medical officer at BCBSRI, Dr. Shafi will take the helm of clinical affairs, overseeing BCBSRI's proactive efforts to help members manage their health, prevent disease, and better navigate the healthcare system to access critical services. Among her areas of focus will be youth behavioral health and initiatives to address healthcare disparities such as colorectal cancer screening and maternal health outcomes.

"I'm excited to join this wonderful organization and to return to my personal and professional roots in Rhode Island," said Dr. Shafi, whose family lived in Newport and Providence. "I'm eager to lead BCBSRI's outstanding clinical services on behalf of members, which have contributed to the organization winning best-in-class service recognition. Given my clinical background, I am also passionate about advancing BCBSRI's critically important work to respond to the nationwide adolescent behavioral health crisis and to end persistent health inequities."

Following her birth in Rhode Island, Dr. Shafi was raised in Chicago and Kentucky. She received her medical degree from the University of Louisville School of Medicine and, completed her residency at Women & Infants Hospital. She received her MBA from the Heller School of Social Policy and Management at Brandeis University. \*



## Appointments

## David McCready, MBA, MHA, named CEO at Southcoast



FALL RIVER, MA - The Southcoast Health Board of Trustees announced July 21 that **DAVID McCREADY**, MBA, MHA, will join the system as president and chief executive officer of the Southcoast Hospitals Group on October 1, 2023, and succeed Rayford Kruger, MD, FACS as the next Southcoast Health System president and chief executive officer effective January 3, 2024.

McCready joins Southcoast from Brigham and Women's Faulkner Hospital where he has served as president for the past 5 years. In addition to his role as President of the Faulkner, he served for 18 years as a member of the leadership team at Brigham and Women's Hospital leadership team.

As Southcoast Health's president and CEO, McCready will be responsible for the overall strategy and operations of the system and all subsidiary organizations. McCready will ensure organizational integrity, the provision of high-quality and integrated patient care, efficient operations, financial sustainability, and exceptional patient experience and outcomes across the entire Southcoast enterprise.

Beginning in November of 2022, Southcoast Health engaged in a comprehensive and wide-ranging search, attracting interest from over 70 candidates nationwide.

Before joining BWH, McCready worked for several years as an administrative leader at Boston Medical Center and at Highmark Health in Pittsburgh, and as a management consultant with PricewaterhouseCoopers. McCready earned a master's degree in business administration and a master's in healthcare administration from the University of Pittsburgh.

## RHODE (IN) ISLAND MEDICAL OURNAL

## RIMJ seeks social-media-savvy Board member

The Rhode Island Medical Journal (RIMJ) is seeking a social-media-savvy applicant to join its Editorial Board. Responsibilities include assisting in expanding RIMJ's reach and visibility on social media platforms, reporting site analytics, and researching and reporting on other medical social media platforms to inform the Board.

Expected time commitment is flexible, at several hours a month, and attendance at guarterly board meetings held via Zoom. A volunteer position, it is open to health care professionals in the RI medical community, and students, residents, or fellows,

Interested candidates can contact William Binder, MD, editor-in-chief, and Mary Korr, managing editor, at: william\_binder@brown.edu mkorr@rimed.org

## Help your Patients Keep their Medicaid Coverage

Medicaid members will need to renew their eligibility with the State of Rhode Island to keep their health insurance.

You can help now by reminding your Medicaid patients to update their account information with their current address and phone number. Medicaid members can update their information by:

- Logging into their HealthSource RI account: https://healthyrhode.ri.gov/
- Calling HealthSource RI at 1-855-840-4774 (TTY 711)

Thank you from all of us at Neighborh for your commitment and partnership nsuring Rhode Island families keep ir health care coverage!

www.nhpri.org 1-800-459-6019 (TTY 711)

Neighborhood Heaith Plan



## Recognition

## Butler Hospital awarded Joint Commission's Gold Seal of Approval

PROVIDENCE – Butler Hospital has earned The Joint Commission's Gold Seal of Approval® for its Partial Hospital and Intensive Outpatient Programs in its Providence and South County locations by demonstrating continuous compliance with its performance standards. Butler Hospital also notably received The Joint Commission's accreditation for its inpatient units, including the Opioid Treatment Program. The Gold Seal is a symbol of quality that reflects a healthcare organization's commitment to providing safe and quality care to the individuals it serves.



The certification recognizes healthcare organizations that integrate and coordinate an individual's behavioral health and primary physical health care services to facilitate access to a broad array of behavioral health care, medical care, and community-based social services and supports. These organizations focus on key concepts of individual-centered, comprehensive, and coordinated care and services that support recovery and resilience philosophies.

Butler Hospital underwent a rigorous, unannounced onsite review on April 14th, 2023. During the visit, a team of Joint Commission reviewers evaluated compliance with related certification standards including those covering the care, treatment, or services provided; environment of care; leadership; human resources; outcomes measurement; and rights and responsibilities of the individual served. Joint Commission standards are developed in consultation with healthcare experts and providers, measurement experts, and patients. The reviewers also conducted onsite observations and interviews.

"I am proud of the hard work done by our staff to maintain this important accreditation. The few findings we had were minimal in scope and presented a low risk to patient safety. These findings have since been mitigated. We commit to maintaining the high bar set by The Joint Commission Accreditation for high-quality care and patient safety," said **MARY MARRAN, MS, OT, MBA**, president and COO, Butler Hospital.

Maintaining this certification involves close collaboration between Butler Hospital's Pharmacy Department, the Rhode Island Department of Health, and the US Drug Enforcement Agency. Additionally, the leadership of the Opioid Treatment Program works closely with community agencies to ensure individuals can continue the evidence-based treatment initiated in the hospital.  $\diamond$ 

## VA Providence has achieved the Pathway To Excellence<sup>®</sup> designation

PROVIDENCE, RI – The VA Providence Healthcare System joins a premier group of organizations that have received Pathway to Excellence<sup>®</sup> designation from the American Nurses Credentialing Center (ANCC) for the third consecutive time.

The Pathway designation is a global credential that highlights VA Providence's commitment to creating a healthy work environment where nurses feel empowered and valued. VA Providence's nurses are an integral part of the healthcare team, with a voice in policy and practice. Pathway nurses are engaged, resulting in higher job satisfaction, reduced turnover, improved safety, and better patient outcomes.

As a Pathway organization, VA Providence leads the effort to enhance quality of care, patient and nursing safety, and the future of healthcare delivery. \*



## Obituaries

**SAMIR MOUBAYED, MD**, 98, a longtime obstetrician and gynecologist with OBGYN Associates, Inc., died peacefully at HopeHealth Hospice July 1. Born in Alexandria, Egypt, he was a graduate of Victoria College and Alexandria University Medical School. After practicing medicine in Egypt for 10 years, he spent one



year working for the United Nations in the Congo. He immigrated to the United States in 1963 on a political refugee visa.

In Rhode Island he was on the staffs of Women & Infants and Miriam hospitals. He was a Life Fellow of the American College of Obstetricians and Gynecologists, a Diplomat of the American Board of OBGYN, a member of the Rhode Island Medical Society, and Clinical Associate Professor Emeritus at Brown University.

He is survived by his wife, Susan Moubayed; three sons, Shereen Moubayed of Wilton, CT, John Moubayed of Falmouth, MA, and Peter Moubayed of Swansea, MA; a step daughter, Leslie Eimas of Fabius, NY; a brother, Remy Moubayed of Montreal, Canada, and nine grandchildren.

A Celebration of Life will be held at a future date. Memorial contributions may be made to HopeHealth Hospice, 1085 North Main St., Providence, RI 02904 or Rhode Island Philharmonic Orchestra & Music School, 667 Waterman St., East Providence, RI 02914. Condolences may be made at www. monahandrabblesherman.com **\*** 



JACK R. WANDS, MD, 80, passed away peacefully and surrounded by loved ones on Wednesday, July 19th, 2023 at Rhode Island Hospital. Dr. Wands was revered for his academic and scientific achievements as the Director of the Liver Research Center at Brown University and as the Chief of the Division of Gastroenterology at

Rhode Island Hospital and the Brown Alpert Medical School.

He was a giant in his field of hepatology marked by a seemingly endless list of peer-reviewed publications, hundreds of patents and guest lectures. As the tenured Jeffrey and Kimberly Greenberg–Artemis and Martha Joukowsky Professor in Gastroenterology and Professor of Medical Sciences of Brown University he trained future generations of physicians and scientists whose impacts will be felt across the globe for decades to come.

He was a loving father and grandpa who, even with his endless list of professional obligations, made it a mission to always be present for his family. He was the beloved father of Gregory D. Wands and Raymie A. Black, and her husband, Robert E. Black, and the loving grandfather of Amanda N. Black and Robert D. Black. He was the brother of James Dixson and Chester Dixson.

Most of all, he was a generous, selfless, kind man who touched many lives with a warm smile, a shoulder to lean on, and an ever-present calm voice that will be profoundly missed. In his memory, memorial contributions may be made to: Jack Wands, MD, Liver Research Fund at Rhode Island Hospital, Attn: Development Office, 139 Point St., Providence, RI 02903.

To donate online go to: https://giving.lifespan.org/RIH/Support-RIH and in the comment box please indicate Jack Wands MD Liver Research Fund.

For information and condolences, visit www.theQuinn FuneralHome.com.

