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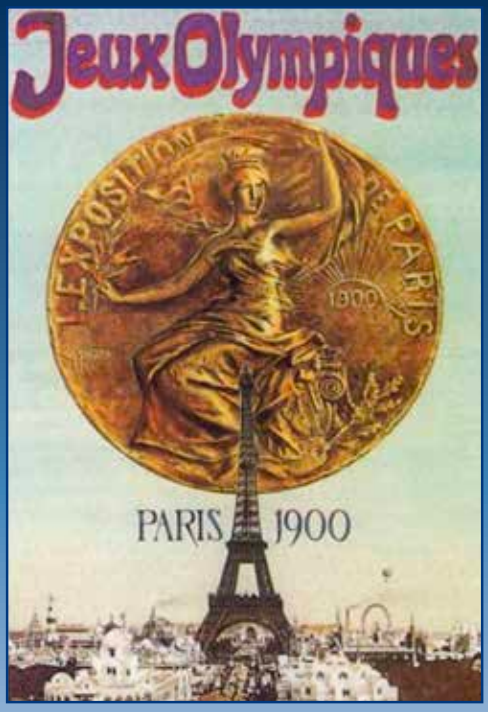



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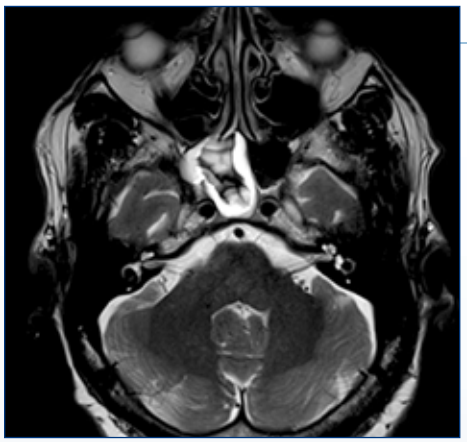

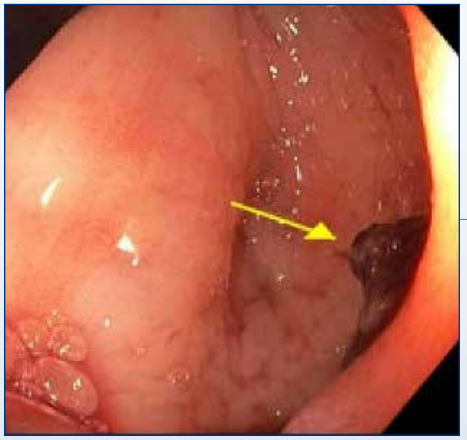

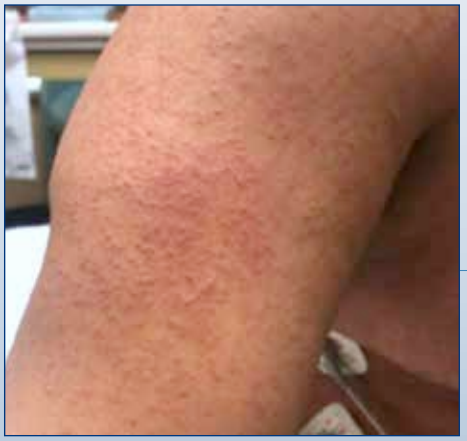

## CASE REPORTS



## IMAGES IN MEDICINE

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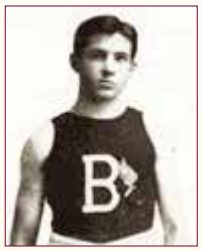

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# A Case of Pituitary Apoplexy Following Leuprolide Injection for Prostate Cancer

KANG WOO KIM, BA; SORA CHEE, MD; NAVEENA SUNKARA, MD; MARGARET HAYES BAKER, MD


## ABSTRACT

Pituitary apoplexy is a rare but potentially life-threatening complication of androgen deprivation therapy for prostate cancer. We present a case of a 70-year-old African American male with prostate cancer who developed symptoms of pituitary apoplexy, including hot flashes, nausea, vomiting, and cranial nerve III palsy, following the initiation of leuprolide therapy. Imaging revealed a pituitary adenoma with hemorrhage, and prompt multidisciplinary management was initiated. The patient was managed conservatively with improvement in symptoms. This case highlights the importance of recognizing the potential for pituitary apoplexy in patients receiving GnRH agonist therapy. We discuss the clinical presentation of GnRH agonist induced pituitary apoplexy, emphasizing that clinicians should maintain a high index of suspicion and promptly investigate any new neuro-ophthalmic symptoms in this group of patients. Ultimately, prompt diagnosis and treatment are crucial to mitigate the severity of this complication in patients with prostate cancer undergoing androgen deprivation therapy.


**KEYWORDS:** Prostate cancer, Pituitary apoplexy, Androgen deprivation therapy, Leuprolide, Pituitary adenoma

## INTRODUCTION

In 2019, prostate cancer was the second leading cancer related mortality in America and the cancer with the highest incidence, with 112 new cases per 100,000 men.[1] Worldwide estimates report approximately 190,000 new cases with 80,000 deaths each year. About 60% of diagnoses occur in men over the age of 65, with African American men having the highest incidence globally.[2-4] Among medical castration methods used to achieve androgen deprivation, GnRH agonists have been widely accepted across guidelines for initial systemic therapy for regional and advanced prostate cancer. GnRH agonists (GnRHa) have well documented side effects such as fatigue, hot flashes, EKG changes, and a rare association with pituitary apoplexy (PA) in male patients with a pituitary adenoma.[5,6] To date, only 22 cases of induced PA have been described, but it is crucial for healthcare professionals to remain alert to this potentially fatal association for early detection and treatment.

## CASE REPORT

A 70-year-old African American male with past medical history significant for hypertension, gout, osteoarthritis, and recently diagnosed prostate cancer presented to the ED with nausea and vomiting. He had been recently diagnosed with metastatic prostate cancer (Gleason 4+5, with pelvic LN involvement on finasteride), and was administered a GnRHa (Leuprolide 7.5 mg subcutaneous 1-month depot injection). Within 3–4 hours after the first injection, the patient began experiencing hot flashes, night sweats, chills, nausea, vomiting, and myalgia. On day 5, he developed diplopia, intermittent headaches, and right eye ptosis. Physical exam findings were significant for isolated cranial nerve 3 palsy. CT Brain and CTA of the head and neck were negative for acute intracranial processes. MRI Brain with contrast revealed a heterogeneous lesion arising from the pituitary fossa and extending into the suprasellar cistern measuring approximately 2.4 cm in the greatest transverse dimension, suggestive of an atypical pituitary adenoma (**Figures 1,2**). Repeat MRI brain with dedicated pituitary protocol was performed

**Figure 1.** [**A**] Sagittal and [**B**] coronal T1-weighted gadolinium-enhanced MRI.

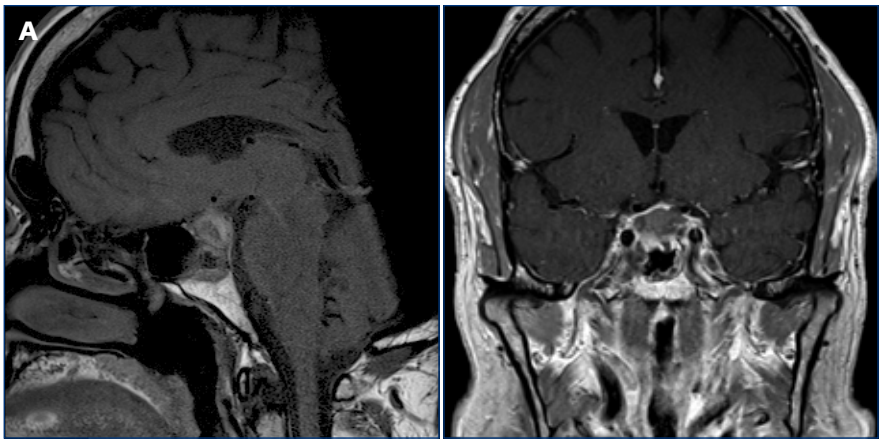

**Figure 2.** Transverse T2-weighted gadolinium-enhanced MRI.

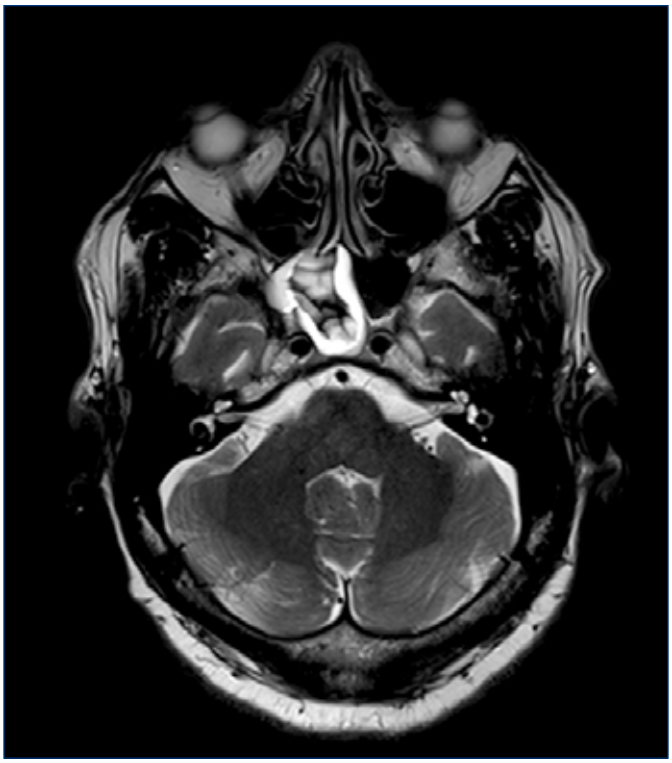

**Table 1.** Pan-hormone studies relative to post-GnRHa injection date.

| | Normal Range | Day 8 | Day 27 | Day 50 |
|---|---|---|---|---|
| Prolactin | 3–20 | <0.60 | <0.60 | 0.80 |
| FSH | 1–19 | 1.77 | - | 0.44 |
| LH | 1–9 | 0.45 | <0.07 | < 0.07 |
| Cortisol AM | 6–28 | 2.6 | 3.8 | < 1.0 |
| TSH 3rd generation | 0.35–5 | 0.19 | 0.22 | 0.36 |
| Free T4 | 0.6–1.6 | 1.15 | 0.78 | 0.8 |
| ACTH | 6–50 | <5 | <5 | <5 |
| T Total | 250–1110 | 8.14 | 3 | 3 |
| Sex hormone binding globulin | 22–77 | — | 35 | 51 |
| Albumin | 3.6–5.1 | — | 4 | 3.9 |
| T bioavailable | 15–150 | | 0.6 | 0.4 |
| T free | 6–73 | — | 0.3 | 0.3 |
| PSA | 0–4 | — | 1.43 | 0.23 |
| Human Growth Hormone | <=7.1 | 0.1 | 0.1 | — |

on day 6 for further clarification, which revealed a new hemorrhage within the pituitary adenoma suggesting pituitary apoplexy. A multidisciplinary team including endocrinology, ophthalmology, neurology, radiology, and neurosurgery was promptly consulted. Further laboratory work up was significant for low ACTH, LH, FSH, prolactin, AM cortisol, and testosterone (**Table 1**). Per the endocrinology team, the patient's AM cortisol was presumed low due to HPA axis suppression from 20 mg prednisone administered a day prior to lab collection and the patient's daily physiologic prednisone dosing as an outpatient regimen for his prostate cancer. Given the absence of clinical signs of adrenal crisis and mineralocorticoid deficiencies alongside stable neurologic exams, the patient was managed conservatively with 5 mg daily prednisone and without indication for urgent surgical management. Within 48 hours of steroid initiation, he had a significant improvement of right eye ptosis, and complete resolution of diplopia with intact extraocular movements. The patient was discharged with endocrinology and surgery follow up for pan-pituitary hormone monitoring and further apoplexy management. Regarding his prostate cancer therapy, leuprolide was discontinued and the patient was scheduled to continue androgen deprivation therapy with degarelix given its GnRH antagonistic effects.

## DISCUSSION

Pituitary apoplexy is a rare but potentially life-threatening syndrome encompassing a constellation of symptoms associated with hemorrhage into the gland and surrounding space. Several mechanisms of GnRHa induced pituitary apoplexy have been proposed, including compromised tumor vascularity, increased metabolic activity resulting in perfusion mismatch and mass effect from expanding pituitary hemorrhage leading to pituitary infarct.[7–9]

GnRHa induced PA can present through a wide range of symptoms, most commonly including headache (100%), followed by cranial nerve III/IV/VI palsy (85.7%), and nausea/vomiting (71.4%).[6] Previous reviews have reported that the majority of cases (63%) developed symptoms within 24 hours of receiving a GnRH agonist; however, there has been a case report of symptoms developing as late as 12 months post GnRHa exposure.[6,10] Consistent with previously reported cases, our patient began exhibiting constitutional symptoms including hot flashes, chills, nausea, vomiting within 4 hours after his first leuprolide injection. However, it is important to highlight that he did not develop symptoms more concerning for PA such as cranial nerve III palsy or headache until 5 days following leuprolide administration. This suggests that patients who develop constitutional symptoms several hours after GnRHa injection should be closely examined for neuro-ophthalmic symptoms and be given a higher index of suspicion for PA.

TSH deficiency and decreased prolactin level found in our patient were also consistent with most common central hormone derangements reported in previous literature. Of note, our patient had free T4 levels within normal limits, though there were no values reported in the literature for comparison. Review of prior cases of PA following GNRHa injection demonstrated that levels of LH and FSH can vary widely amongst patients with similar presentations (N=6 normal, N=4 deficient, N=6 elevated, N=5 unknown). Interestingly, our patient had depressed LH and FSH levels

(LH 0.45, FSH 1.77). Our imaging findings demonstrated suprasellar extension which was also consistent with 52.4% of incidence reported.[6]

During his hospital stay, our patient's condition was managed conservatively with a non-stress physiologic dose of daily prednisone, with significant improvement in ptosis and extraocular movements within 48 hours of steroid administration. While there is no gold standard of care for PAs following GNRHa therapy, it is worth noting that two recent cases in the literature treated medically using stress doses of steroids, in contrast to our physiologic dosing.[11,12] Despite this difference, our patient's low AM cortisol was presumed to be due to his daily outpatient steroid dosing for his prostate cancer, thus he was continued on physiologic dosing and his condition improved and was stable for discharge with follow up for surgical planning.

While routine screening MRI prior to ADT initiation is not always practical in the clinical setting, this should serve as a reminder that patients who develop constitutional symptoms after GnRHa injection should be closely followed for further work up including pituitary hormone monitoring and brain imaging. Of note, the presence of a known pituitary microadenoma in patients with prostate cancer is not an absolute contraindication, however requires close evaluation by multidisciplinary team prior to proceeding with GnRHa therapy.[13] It has also been suggested that those who are at risk of developing PA with GnRH agonist use be considered for GnRH antagonist therapy, such as degarelix as part of ADT.[6]

## CONCLUSION

While a rare consequence of GnRH agonist treatment, pituitary apoplexy has a major potential for severity and most patients are known to end up with associated hormonal deficiencies with a necessity for long-term replacement therapy.[6,14] Clinicians should be aware of this complication in the management of patients with prostate cancer. With regards to our patient, prior to his onset of ptosis and diplopia, his presenting symptoms were thought to be attributable to the well documented side effect profile of leuprolide injections, and further workup would likely not have been initiated otherwise. It is critical that symptoms such as hot flashes and sweats not be dismissed as common side effects of androgen deprivation therapy and that appropriate workup and treatment be conducted promptly in patients with suspicion for possible GnRH agonist associated pituitary apoplexy.

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# Malignancy Associated Type B Lactic Acidosis: A Rare, yet Fascinating Oncological Emergency

YASHVIN ONKARAPPA MANGALA, MD; NANCY J. FREEMAN, MD


## ABSTRACT

Type B lactic acidosis has been described infrequently in hematologic malignancies, but even less often in solid tumors. Since 1978, there have been only 58 cases of solid tumor associated Type B lactic acidosis described in the literature. Lung cancer (neuroendocrine) is the most common tumor; others frequently have a poorly/undifferentiated histology. The prognosis is dismal. Malignancy associated type B lactic acidosis is not associated with hypoxemia. The most highlighted pathogenetic mechanism is the Warburg effect (aerobic glycolysis of tumor cells causing excess lactate). We describe a patient with metastatic GI neuroendocrine carcinoma with profound lactic acidosis, who died within 24 hours. When extremely ill cancer patients present with lactic acidosis, sepsis is usually a primary concern. This case highlights the need for providers to consider malignancy associated lactic acidosis (MA-LA) in the differential diagnosis, particularly in patients with advanced malignancies, of lung origin, of neuroendocrine or poorly/undifferentiated histologic subtypes. The implications and approach are distinct from Type A/D lactic acidosis, and would involve treatment of the underlying malignancy at the earliest.


**KEYWORDS:** Lactic Acidosis, Type B Lactic Acidosis, Solid Tumor Malignancy, Warburg Effect, Neuroendocrine Tumors

## INTRODUCTION

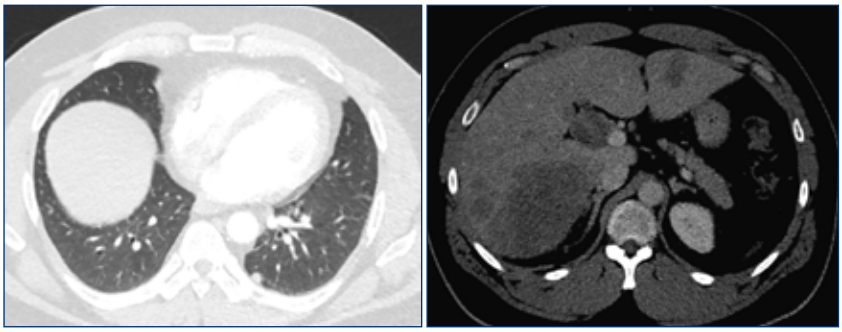
Lactic acidosis is a common occurrence in critically ill patients and stands as the most prevalent cause of metabolic acidosis. It is characterized by a pH of ≤7.35 and a serum lactate level of ≥5 mEq/L.[1] The condition is categorized into three subtypes based on its underlying pathophysiology. Type A lactic acidosis is associated with sepsis, tissue hypoperfusion, and hypoxemia. Type B lactic acidosis occurs in oxygen-rich conditions, the causes of which may involve exposure to toxins, medications (e.g., metformin, HIV antiretroviral therapy), diabetic ketoacidosis, thiamine deficiency, liver disease, and, though rare, malignancies (hematologic, and even less commonly, solid tumors).[2] Type D lactic acidosis is characterized by excessive D-lactic acid production stemming from the proliferation of intestinal bacteria.

We present a patient who developed Type B lactic acidosis in the context of a widely metastatic aggressive neuroendocrine carcinoma of GI origin.

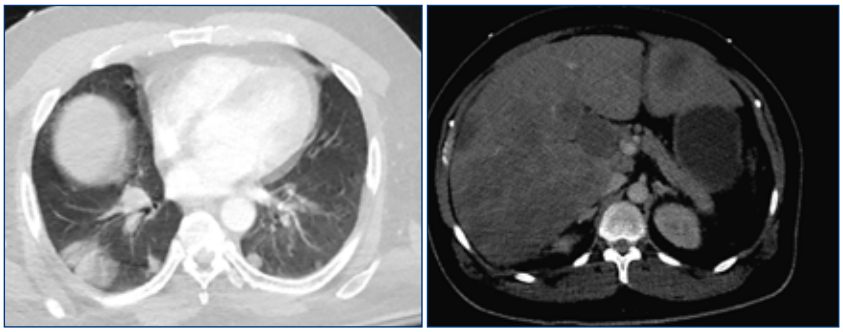
## CASE PRESENTATION

A 51-year-old African American male, previously healthy, presented with right shoulder pain. Imaging studies revealed a 3.4cm soft tissue mass within the common bile duct area, multiple liver hypodensities, bilateral lung nodules measuring up to 7 mm, and a 1.7cm lymph node near the right hilum; brain imaging was negative. The right shoulder pain was attributed to referred pain from the liver. Laboratory findings revealed a markedly elevated lactate dehydrogenase (LDH) of 1440 Units/L (125–243), an INR of 1.5, and liver enzymes which were mildly/minimally elevated. A liver biopsy was done and the immunohistochemical statins were positive for synaptophysin, equivocal for chromogranin and CD56, negative for keratin 7, keratin 20, TTF-1, p40, CA19-9 and GATA-3. Overall, the findings were consistent with large cell neuroendocrine carcinoma, likely originating from the gastrointestinal tract. He was started on treatment with etoposide (VP-16) and carboplatin. Next generation sequencing testing was unremarkable; PDL1 was 0, and tumor mutational burden (TMB) was 4. Following two cycles of chemotherapy, the patient developed a cough, dyspnea, diffuse pain, and weakness. A chest CT scan confirmed the presence of a pulmonary embolus and demonstrated disease progression in the periportal and aortocaval nodes, along with the emergence of a new pulmonary nodule in the left lung. Notably, hepatic metastases and the lymph nodes near the right hilum remained stable **(Figures 1,2)**. He was treated for possible pneumonia with outpatient antibiotics. However, his condition continued to deteriorate over the next 10 days, resulting in confusion, anorexia, a persistent cough with clear sputum, and increased dyspnea. On exam, vital signs revealed tachycardia (129 bpm), tachypnea (respiratory rate 28), and an oxygen saturation level of 95% on room air. Physical examination was notable for a significantly enlarged liver, at least five fingerbreadths below the margin. Laboratory studies displayed a white blood cell count of 44.7 K/cmm (4.5–11), platelet count 447 K/cmm

**Figures 1 and 2.** Cross sectional images of CT chest and abdomen showing left lower lobe pulmonary nodule and multiple hypodensities in the liver.



**Figures 3 and 4.** Cross sectional images of CT chest and abdomen showing mass like consolidation in the right lower lobe, increased size of left lower lung nodule, increased hepatic metastases at the time of presentation with lactic acidosis.



(140-360), serum creatinine 1.3 mg/dL (0.5–1.5), potassium 5.8 mMOL/L (3.5–5.0), anion gap 33 (8–12), CO2 7 mMOL/L (20-30), Bilirubin 4.1mg/dL (0.2–1.2) mostly direct, gamma glutamyl transferase 555 (10–65), aspartate transferase 351 Units/L (5–34), alanine transferase 132 Units/L (7–52), and glucose 80mg/dL (65–100). Lactate levels were alarmingly high at >11.95 (0.5–1.8). A urinalysis detected the presence of blood, but was negative for leukocyte esterase, nitrite or pyuria. Blood cultures were negative. Peripheral blood smear, which revealed dacrocytes, nucleated red blood cells, and early white cells, was consistent with a leucoerythroblastic picture, suggestive of bone marrow involvement by tumor. While a CT of the head was unremarkable, CT scans of the chest, abdomen, and pelvis confirmed further disease progression, particularly in the liver and chest, without evidence of ductal dilatation **(Figures 3,4)**. Reevaluation of the previously suspected "pneumonia" was more consistent with disease progression, based on the appearance of an enlarging consolidative mass. In the absence of any apparent infection, the possibility of MA-LA was considered the most likely diagnosis. The patient's family opted against hospital admission, and he was discharged home with hospice services. Unfortunately, the patient died 24 later.

## DISCUSSION

Lactic acidosis can arise due to an increased production of lactate, decreased metabolism, or a combination of both factors. Type A lactic acidosis is primarily associated with tissue hypoperfusion, while Type D lactic acidosis is attributed to the excessive production of D-lactic acid resulting from small intestinal bacterial overgrowth. In contrast, Type B lactic acidosis occurs in the absence of tissue hypoperfusion.

Malignancy associated type B lactic acidosis is a rare but life-threatening oncological emergency. It was first documented in 1963 in a patient with leukemia[3] and has since been reported in both hematological malignancies and, much less commonly, in solid tumors.[4] Upon literature review on PubMed from the year 1978 (first case associated with a solid tumor) to 2023, we identified 58 reported cases of Type B lactic acidosis in patients with solid tumors.

The exact pathophysiology of MA-LA remains unclear; however, there are several proposed mechanisms. One prominent hypothesis, known as the Warburg effect, is a phenomenon in which tumor cells switch their metabolic machinery towards a glycolytic state even in the presence of normal oxygen concentration, leading to excess lactate production.[5] Another hypothesis suggests that altered lactate metabolism due to liver and kidney dysfunction plays a role; the liver metabolizes 80% of lactic acid through gluconeogenesis to produce glucose, while the kidneys are responsible for metabolizing the remainder. This observation corresponds to the fact that most solid tumor cases associated with lactic acidosis have liver metastases. However, this relationship is not vice versa, and the presence of liver metastasis does not suggest the patient will develop lactic acidosis. Thirdly, severe thiamine depletion has been linked to lactic acidosis especially in the context of rapidly proliferating tumors, and patients who get total parenteral nutrition. Thiamine acts as a cofactor for pyruvate dehydrogenase, an enzyme critical for the conversion of pyruvate to acetyl CoA. In the absence of thiamine, excess pyruvate is converted to lactic acid by lactate dehydrogenase.[6] Finally, the role of tumor necrosis factor alpha (TNF-alpha) in inhibiting pyruvate dehydrogenase and increasing lactic acid production has also been proposed, but remains unclear in solid tumors. Some solid tumors express other growth factors such as insulin-like growth factor that induces overexpression of the enzyme type II hexokinase, which is responsible for catalyzing the first step in glycolysis which can lead to increased glycolysis and pyruvate production.[7]

Effective management strategies for lactic acidosis in the context of solid tumors have not been definitively established. Thiamine supplementation is often employed (but is not a standard of care, and the benefit unclear), as thiamine serves as a cofactor in the conversion of pyruvate to acetyl CoA, potentially diverting pyruvate away from lactic acid production. Intravenous bicarbonate and renal replacement therapy have been utilized as temporary measures, although their efficacy is limited as they do not directly target the mechanisms driving lactic acid overproduction.[4] In general, chemotherapy is considered the most effective treatment as it reduces tumor burden and addresses malignant liver involvement. However, many patients at this stage have aggressive disease and poor performance status which may preclude them from getting prompt antineoplastic therapy.

To date, there have been a total of 59 cases of MA-LA reported in solid tumors (including our present case). Twenty-five (42%) of the cases were of neuroendocrine origin, and the majority of the other cases appeared to be undifferentiated or poorly differentiated. Most patients had lung cancer (30%), followed by gastrointestinal (24%), and breast (18%) malignancies. Of the 59 cases, 66% cases had liver metastases. Most patients died within 10 weeks (80%), with 55% died within a week.

A comprehensive workup for lactic acidosis is imperative in critically ill patients who have cancer; given the severity of MA-LA, lack of good treatment options, and dismal prognosis overall, this phenomenon should be considered particularly in cancer patients who have a high tumor burden, extensive liver metastases, and a neuroendocrine or poorly/undifferentiated histology. The implications and approach are different from that of other forms of lactic acidosis. The overall prognosis for MA-LA is exceedingly poor, with survival typically measured in days to weeks.[8]

## CONCLUSION

This case underscores the critical role that malignancy can play in Type B lactic acidosis, and emphasizes the importance of considering it as a potential cause of lactic acidosis in patients who do not exhibit clear signs of tissue hypoperfusion, sepsis, and hypoxemia. MA-LA is associated with few effective treatment options, and an extremely grim prognosis.

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# Not a Laughing Matter: When Nitrous Oxide Causes Functional Vitamin B12 Deficiency

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## ABSTRACT

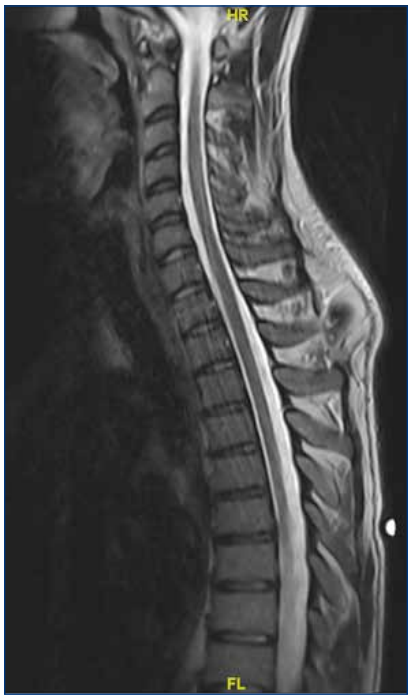
Subacute combined degeneration (SCD) is an acquired neurologic complication from prolonged vitamin B12 deficiency. As a result of dorsal and lateral spinal cord column degeneration, patients present with a range of neurological symptoms, including paresthesias, ataxia, and muscle weakness. Without prompt treatment, irreversible nerve damage occurs. Here we present a young man who developed progressive ascending paresthesias and lower extremity weakness after escalated nitrous oxide use. This case highlights the importance of considering SCD from nitrous oxide toxicity when patients present with progressive ataxia, paresthesia, and lower extremity weakness.


**KEYWORDS:** Nitrous oxide use, functional cobalamin deficiency, subacute combined degeneration

## INTRODUCTION

Nitrous oxide ($N_2O$), or "laughing gas," is a commonly used anesthetic and analgesic in medical and dental procedures. It is also widely used as a mixing and foaming agent in the culinary arts and as a fuel booster in the motor industry.[1] Due to its euphoric effects, easy accessibility for nonmedical purposes, and relatively cheap cost, it has become a popular recreational drug. The U.S. Department of Health and Human Services' National Survey on Drug Use and Health found a 4.5–5.1% lifetime prevalence of recreational $N_2O$ use in the United States among individuals aged 12 and older.[2] $N_2O$ exposure can lead to many symptoms due to its impact on the metabolism of vitamin B12 (cobalamin), specifically by inactivating vitamin B12 through irreversible oxidation. In this report, a 23-year-old male developed progressive disabling neurologic symptoms following heavy $N_2O$ use with spinal imaging consistent with SCD, but biochemical findings suggestive of only functional cobalamin deficiency.

**Figure 1.** T2-weighted sagittal MRI view demonstrating abnormal signal in the dorsal columns of the cervical spine.




## CASE PRESENTATION

A 23-year-old male with a past medical history of depression and polysubstance use presented with a week-long history of ascending bilateral lower extremity paresthesia, progressive lower extremity weakness, and multiple falls. In the preceding months, he had no illnesses, had not received any vaccinations, and had eaten a balanced diet with no dietary restrictions. The patient had a history of intermittent $N_2O$ use, which had recently escalated to inhaling multiple liters of $N_2O$ daily. He estimated he had spent over $10,000 in the past 90 days leading us to infer his total consumption was between 300 to 500L. The patient self-administered multiple cobalamin tablets in the days prior to presenting to the Emergency Department, as a friend experienced similar symptoms from a cobalamin deficiency. However, he had no symptomatic improvement following oral supplementation.

On presentation, neurological examination was remarkable for: bilateral foot drop, diminished sensation to light touch, impaired proprioception in his bilateral lower extremities, positive Romberg sign, and ataxic wide-based gait. No neurologic deficits in upper extremities. His physical examination was otherwise unremarkable.

Routine blood tests revealed a white blood cell count of 7.2 x $10^9$/L, hemoglobin of 14.4 g/dL, and mean cell volume of 94.6 fL, which were all within normal limits. Vitamin B12 level was 623 pg/mL (normal 211–911 pg/mL), but both homocysteine and methylmalonic acid (MMA) levels were markedly elevated to 104.8 umol/L (normal 5–13.9 umol/L) and 3.66 umol/L (normal 0–0.4 umol/L) respectively. Inflammatory serum markers were within normal limits, including the C-reactive protein

and the erythrocyte sedimentation rate. Thyroid stimulating hormone was within normal limits six months prior and was not rechecked on admission. Human immunodeficiency virus, hepatitis serologies, treponemal antibodies, and other vitamin levels, including folic acid, were not checked. Magnetic resonance imaging (MRI) of the cervical, thoracic, and lumbar spine with and without contrast was notable for T2 hyper-intensities predominantly involving the dorsal columns of the cervical cord (**Figure 1**), with questionable areas of patchy involvement in the thoracic cord. Given the clinical suspicion of SCD from his substantial $N_2O$ use, a lumbar puncture was not performed.

He received one intramuscular injection of Vitamin B12 1000 mcg, was counseled to cease $N_2O$ inhalation, and was discharged home with oral cobalamin supplements (100 mcg/day) and appointments for physical therapy and neurology follow-up.

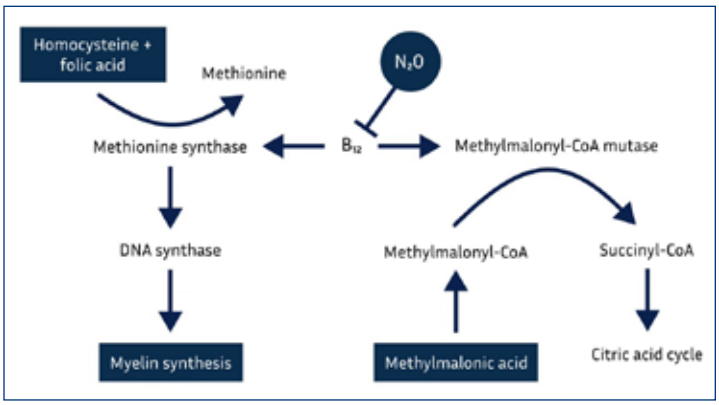
One week later, the patient was readmitted to the hospital after multiple falls at home. Since leaving the hospital, he had wholly abstained from ongoing $N_2O$ use and was compliant with his cobalamin supplementation. In addition to his persistent lower extremity symptoms, he had new complaints of cognitive slowing, headaches, upper extremity weakness, and hand paresthesias. Repeated neurological examination found decreased sensation to light touch in both distal upper and lower extremities, persistent bilateral foot drop, and mildly decreased strength (4 out of 5) in elbow flexion, finger flexion, and abduction.

Labs on readmission revealed normal Vitamin B12 levels again. Homocysteine and MMA remained elevated but dramatically improved to 19.8 umol/L and 0.96 umol/L, respectively, suggesting methionine metabolism and B12 cofactor activity was normalizing. However, as he was clinically more symptomatic, his cobalamin supplementation was increased to 1000 mcg daily, and he was started on Gabapentin 300mg nightly for his neuropathic pain and paresthesias. The patient was discharged to an inpatient rehabilitation facility. After three weeks of intensive physical and occupational therapy and daily oral and weekly intramuscular cobalamin supplementation, his cognition and motor skills had improved but not yet normalized. He was able to ambulate with a quad cane for short distances independently but continued to require a rolling walker for longer excursions due to his persistent ataxic gait and foot drop.

## DISCUSSION

This case underscores the importance of eliciting a comprehensive substance use history and recognizing chronic $N_2O$ use as a cause of functional cobalamin deficiency to prevent disabling neurologic consequences. Serum cobalamin deficiency develops in adults from inadequate dietary intake, gastrointestinal malabsorption, parasitic infection, or adverse drug effect.[3] Unlike true cobalamin deficiency, functional cobalamin deficiency occurs because of the body's inability to utilize cobalamin due to impaired intracellular transport or cellular processing. In the case of $N_2O$ inhalation, $N_2O$ irreversibly oxidizes the cobalt ion in cobalamin, rendering it inactive. This inactivation disrupts the normal metabolism and causes the accumulation of homocysteine and MMA (**Figure 2**). Demyelination occurs from both high breakdown of myelin from direct MMA toxicity and reduced myelin synthesis from decreased methionine stores.[4,5] As a result of dorsal and lateral spinal cord degeneration, patients typically present with weakness, ataxia, paresthesias, and falls, as well as a range of psychiatric complaints, including memory impairment and paranoia.[1] SCD most frequently occurs after prolonged recreational $N_2O$ exposure. However, there have been reports of SCD developing after minimal $N_2O$ exposure, including only 30 minutes of $N_2O$ anesthesia, in patients with subclinical B12 deficiency.[6]

**Figure 2.** Role of B12 in Methylmalonic Acid and Homocysteine metabolism




Diagnosis of functional cobalamin deficiency requires a high degree of clinical suspicion as serum B12 levels are normal. To detect B12 deactivation, look for elevated MMA and homocysteine levels. Megaloblastic changes in the bone marrow with or without anemia are a known complication of cobalamin deficiency. However, as with this case, most patients with only biochemical evidence of cobalamin deficiency present with MCV and hemoglobin within the reference range.[7] Imaging is required to diagnose subacute combined degeneration and to rule out other possible demyelinating etiologies, including multiple sclerosis or transverse myelitis.[8] In SCD, MRI shows T2 hyper-intensities confined to the dorsal column in the cervical and thoracic spinal cord without post-contrast enhancement.[5,9]

In cases of $N_2O$-induced functional cobalamin deficiency, treatment consists of abstinence from $N_2O$ and cobalamin supplementation. There are no established treatment guidelines. Review of the literature reveals a wide range of supplementation, from daily high-dose parenteral therapy to intermittent oral supplementation.[6,10,11] While the progression of neurologic deficits frequently arrests shortly after

initiation of cobalamin therapy, in this case stabilization of neurologic symptoms required increasing the daily cobalamin dose to 1000 mcg PO. On discharge, the patient's overall functional capacity remained below baseline. Recovery from SCD is often protracted and incomplete. An observational study of 57 cases of SCD found that while 49 patients (86%) improved, only eight (14%) achieved complete clinical resolution.[12] This patient required several weeks of intensive physical rehabilitation with ongoing ataxic gait and foot drop at time of discharge from physical therapy. Overall, this case report underscores the foundational importance of a detailed patient history and comprehensive diagnostic approach. In retrospect, higher cobalamin dosing after index hospitalization likely would have prevented the progression of his symptoms and subsequent readmission.

## CONCLUSION

This case report emphasizes the critical need for early recognition of SCD and functional cobalamin deficiency in the setting of $N_2O$ use. When serum cobalamin is normal, elevated homocysteine and MMA are indicative of cobalamin inactivation. Adequate cobalamin dosing is needed to prevent SCD symptom progression and re-admission. In this case, 1000 mcg was sufficient to halt neurologic symptoms. Further studies are needed to develop standardized protocols to treat functional cobalamin deficiencies. Given the complexity of managing the underlying substance use disorder and the debilitating resultant neurologic symptoms, a comprehensive and individualized treatment approach is recommended.

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# Micrococcus Peritonitis Complicating Peritoneal Dialysis

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## ABSTRACT

Peritonitis, a serious complication of peritoneal dialysis (PD), can be caused by opportunistic pathogens like *Micrococcus species* on rare occasions. We present a case of *Micrococcus sp* peritonitis in a 55-year-old female with end-stage kidney disease on continuous cycling peritoneal dialysis for one year who presented with cloudy effluent. Initial treatment against *Micrococcus sp* with vancomycin, gentamicin, and prophylactic oral nystatin was successful. However, one month later, the patient presented with abdominal pain and dialysate culture again grew *Micrococcus sp*. Treatment with vancomycin was unsuccessful in resolving culture positivity. The patient was transitioned to hemodialysis for non-medical reasons and then was later restarted on PD without further peritonitis episodes. *Micrococcus sp* peritonitis in PD poses treatment challenges due to limited guidelines. Intraperitoneal vancomycin is commonly used to target Micrococcus isolates although there is a high incidence of treatment failure. This case report highlights the need for continued reporting to enhance identification, prevention, and patient outcomes in *Micrococcus sp* peritonitis during PD.


**KEYWORDS:** peritonitis, micrococcus species, peritoneal dialysis, PD-associated peritonitis

## CASE REPORT

A 55-year-old female with a history of end stage kidney disease (ESKD) on PD secondary to diabetic kidney disease on continuous cycling peritoneal dialysis (CCPD) for one year presented to the PD clinic with cloudy effluent. She had been in her usual state of health until the evening prior to the day of presentation. Her PD prescription was automated peritoneal dialysis with 5 exchanges of 2.5 liters of dianeal (concentrations per weight/BP) over 9.5 hours with a 2-liter icodextrin day dwell. Past medical history was also significant for insulin dependent diabetes mellitus, coronary artery disease with coronary artery bypass grafting, peripheral arterial disease, hypertension, hepatitis C treated with direct acting antivirals, and gastroesophageal reflux. She had no prior episodes of peritonitis and reported no breaks in technique. She had no recent antibiotic administration and applied gentamicin ointment to her exit site daily. There were no known drug allergies.

On examination, the temperature was 98.6°F, the blood pressure was 138/82 mmHg, the heart rate was 91 beats per minute, and the respiratory rate was 20 breaths per minute. Cardiopulmonary exam was unremarkable. The mucous membranes were moist. Abdominal exam revealed a soft, non-tender abdomen without rebound or guarding. The peritoneal catheter exit site was mildly tender to palpation but did not show any drainage, granulation tissue, or erythema. Edema was absent. Effluent was hazy in appearance. The remainder of the physical examination was unremarkable.

Effluent leukocyte count was 204 cells/uL with 58% neutrophils. Peritonitis was diagnosed and treatment commenced with intraperitoneal (IP) vancomycin and gentamicin as well as oral nystatin for fungal prophylaxis. Cloudiness cleared within 48 hours. Peritoneal effluent culture grew *Micrococcus sp*. IP vancomycin was continued for 3 weeks due to intermittent low troughs. After completion of treatment, there was a complete resolution of symptoms and peritoneal cell count.

Cell count and culture were repeated one month later during evaluation of abdominal pain that was eventually found to be due to constipation. Leukocyte count was 6 cells/uL but culture again grew *Micrococcus sp*. After culture was repeated once more and remained persistently positive, repeat treatment to eradicate was attempted with two more weeks of IP vancomycin, but cultures remained positive. There were no breaks in technique. Eventually the catheter was removed due to a change in living situation, and the patient was transitioned to hemodialysis (HD).

After five months of HD, peritoneal catheter was replaced and the patient was restarted on PD, after which time she did not have any peritonitis episodes.

## DISCUSSION

PD as an initial therapy for kidney replacement therapy has grown in recent years in the United States.[1] This trend is expected to continue with the launch of The Advancing American Kidney Health Initiative in 2019. The initiative included a goal that by 2025, 80% of incident ESKD individuals receive a home modality of dialysis or a kidney transplant.[2] Therefore, complications of PD need to be

**Table 1.** Summary of published cases of *Micrococcus sp* complicating PD

| Reference number | Year Published | Age | Sex | Dialysis Modality* | Symptoms | Antibiotic Regimen | Catheter Removal for Improvement | Outcome |
|---|---|---|---|---|---|---|---|---|
| 18 | 1983 | 36 | M | CAPD | Abdominal pain, turbid effluent | Cefazolin Tobramycin | No | Two episodes of peritonitis. Improvement with antibiotic therapy. |
| 29 | 1990 | 42 | F | CAPD | Unknown | Cefuroxime | Yes | Seven episodes of peritonitis. No improvement with antibiotic therapy. Catheter removed with improvement. |
| 29 | 1990 | 77 | M | CAPD | Unknown | Vancomycin Cefuroxime | No | Two episodes of peritonitis. Improvement with antibiotic therapy. |
| 29 | 1990 | 56 | M | CAPD | Unknown | Vancomycin | No | Improvement with antibiotic therapy. |
| 30 | 2009 | 56 | F | CAPD | Fever, abdominal pain, nausea, turbid effluent | Teicoplanin | No | Improvement with antibiotic therapy. |
| 15 | 2014 | 63 | M | APD | Fever, abdominal pain, turbid effluent | Cefazolin Ceftazidime Vancomycin | Yes | No improvement with antibiotic therapy. PD replaced with HD. |
| 15 | 2014 | 40 | M | APD | Abdominal pain, turbid effluent | Cefazolin Ceftazidime | No | Thirteen episodes of peritonitis, 7 of which were Micrococcus-related. Improvement with antibiotic therapy. PD replaced with HD. |
| 15 | 2014 | 54 | M | APD | Abdominal pain, turbid effluent | Vancomycin | No | Improvement with antibiotic therapy. |
| 17 | 2019 | 59 | F | CAPD | Abdominal pain, turbid effluent | Cefazolin Ceftazidime Vancomycin | Yes | No improvement with antibiotic therapy. Catheter removed with improvement. Catheter reinsertion 1 month later with no subsequent complications. |
| 31 | 2023 | 69 | F | CAPD | Turbid effluent | Cefazolin Ceftazidime | No | Three episodes of peritonitis. Improvement with antibiotic therapy. |

*CAPD: Continuous ambulatory peritoneal dialysis; APD: Automated peritoneal dialysis

addressed to improve treatment and prevention. Peritonitis is a common but serious complication of PD, causing both morbidity and mortality. The most common causative organisms include gram-positive organisms up to 46% and gram-negative organisms up to 21%.[3] Other organisms include mixed growth (17%), fungal (2%), mycobacterium (2%), anaerobes (1%), and 11% were negative on culture.

*Micrococcus sp* are catalase-positive, coagulase-negative, gram-positive cocci that are commonly found on the skin, mucosal membranes, soil, and water. Although these organisms are not considered pathogenic, they have been implicated in immunocompromised individuals and in patients with indwelling catheters. There are some reports of micrococci, particularly *Micrococcus luteus*, causing meningitis, central nervous system shunt infections, endocarditis, septic arthritis, and pneumonia.[4-6]

Individuals with ESKD are in an immunocompromised state. Several hypotheses have been proposed to explain why these individuals are at a higher risk for infections: The retention of uremic toxins impair the normal functions of leukocytes, monocytes, lymphocytes, and antigen-presenting cells.[7-9] Hemodialysis itself has been seen to cause a decrease in T lymphocyte response due to premature activation, likely contributing to an immunocompromised state.[9] Low titer responses to vaccines may suggest a reduced ability to produce antibodies.[10-12]

Ten cases of *Micrococcus sp* complicating PD have been reported in the English literature (**Table 1**). There are reported cases in the non-English literature, but they were not included in our literature review. The median age of the 10 cases included was 56 years old but ranged from 36 to 77 years old. Six were males and four were females. Seven were on continuous ambulatory PD (CAPD) and three were on automated PD (APD). Vancomycin and cefazolin were the most used antibiotics, each in five cases. Other antibiotics used include ceftazidime, cefuroxime, teicoplanin, and tobramycin. Seven of the cases improved with antibiotic therapy and three did not, requiring removal of catheter or transition to hemodialysis. Four cases hypothesized resulting peritonitis was due to technique failures.

The International Society for Peritoneal Dialysis (ISPD) 2022 guidelines do not mention treatment recommendations for *Micrococcus sp*.[13] However as seen in our case, IP antibiotics were started immediately as recommended by the ISPD.[13] The National Committee for Clinical Laboratory Standards (NCCLS) does not provide disk diffusion susceptibility standards for *Micrococcus sp*, and any existing data in the literature is not updated.[14,15] The majority

of *Micrococcus* isolates are susceptible to many antibiotics including penicillin, methicillin, vancomycin, gentamicin, and erythromycin. Although resistance to these antibiotics has been reported, vancomycin is still the preferred choice for empiric therapy.[15-17] In our case, vancomycin was effective in treating the first episode of peritonitis but not effective in the second episode of peritonitis. However, as seen in the literature review, there are reports of antibiotic regimens without vancomycin that have treated *Micrococcus sp* PD peritonitis successfully.[18]

Prevention of PD-associated peritonitis is essential to improving costs and patient outcomes. Various preventative strategies have been endorsed and proposed. The use of double-bag Y system and flush-before-fill approaches have shown to significantly decrease peritonitis rates.[19-22] The ISPD recommends prophylactic antibiotics at the time of PD catheter insertion and the use of topical antibiotics at the catheter exit site.[13] The guidelines also recommend that catheter removal should be considered in a timely manner if treatment is refractory. This outcome was seen in the case presented here and in three cases in the literature. Patient education and retraining have been shown to reduce peritonitis rates; however, the frequency and intensity of retraining has not been well studied.[23,24] Patient education is likely dependent on the patient and their learning style.[25] To further decrease peritonitis incidence, a national standardized reporting system of PD-associated peritonitis for the U.S. has been proposed.[26] Existing systems seen in Australia and New Zealand have been shown to reduce peritonitis rates due to increased awareness, transparency, and accountability, serving as a potential framework for U.S.[27,28]

We present the eleventh case of *Micrococcus sp.* peritonitis in a PD patient, a rare and unusual causative organism of peritonitis. Prior cases have been associated with breaks in technique and have shown a pattern of recurrence with resultant technique failure being very common.

## CONCLUSION

Although PD-associated peritonitis secondary to *Micrococcus sp*. is rare, the treatment is challenging due to a lack of data on the infections and effective antibiotic regimens. Further cases and their treatment regimen need to continue being reported to improve identification, prevention, and patient outcomes.

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# Pseudohypoglycemia: A Pitfall in Everyday Practice

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## ABSTRACT

Hypoglycemia is a common clinical finding, especially in the inpatient setting. However, laboratory testing may show falsely low blood glucose levels. It is crucial for clinicians to recognize the existence of pseudohypoglycemia and know when and how to test for it.


**KEYWORDS:** pseudohypoglycemia, false positives, diabetes, hypoglycemia, clinical testing

## INTRODUCTION

Hypoglycemia is a common clinical entity, particularly in the inpatient setting. While hospitalized, patients' insulin regimens are often altered, and their oral intake may also be different than baseline, due either to their underlying acute medical condition or while awaiting invasive procedures. In one retrospective study from the Spanish National Health System, 2.8% of hospitalized patients with diabetes had recorded hypoglycemic events, and the presence of a hypoglycemic event was associated with an increased time to discharge and risk of in-hospital mortality.[1]

While clinicians may understandably take special precautions to avoid hypoglycemic events, there is an entity known as pseudohypoglycemia, where venous plasma glucose levels appear falsely low due to artifacts of laboratory testing methods. It has been reported in both patients with and without diabetes and is not associated with the same adverse effects as true hypoglycemia.[2,3] While its incidence is unknown, pseudohypoglycemia represents an important entity with which clinicians should be familiar, so as to avoid unnecessary testing and inappropriate treatments. Here, we present two cases of pseudohypoglycemia to illustrate this concept.

## CASE PRESENTATION

### Case One

A 49-year-old man with type 2 diabetes mellitus (T2DM) was admitted to the hospital because of recurrent chest pain. Other past medical history was significant for systemic sclerosis (SSc) with pulmonary hypertension (PH), schizophrenia, and recurrent vomiting of unclear etiology. Initial cardiovascular assessment was unremarkable, and his chest pain was attributed to severe PH secondary to his underlying SSc.

On examination, the patient was afebrile with a pulse of 78 beats per minute, a blood pressure of 110/75 mm Hg, and a respiratory rate of 18 breaths per minute. Physical examination revealed multiple manifestations of SSc, including skin thickening, decreased capillary refill, and peripheral cyanosis. Breathing was normal, and auscultation of the chest was unremarkable with good air entry bilaterally. Cardiovascular examination was significant for a hyperdynamic precordium, a normal S1, a loud S2 with grade 2/6 to 3/6 systolic regurgitant murmur at left lower sternal border, a right parasternal heave, and weak peripheral pulses. There was intermittent digital cyanosis. Echocardiography was suggestive of PH, with an estimated right ventricular systolic pressure of 75 mmHg. Esophagogastroduodenoscopy was consistent with a lack of peristalsis and gastroesophageal reflux disease.

During his hospitalization, the patient was found to have intermittently low capillary blood glucose (CBG) levels, as detected by the finger stick method, but there were no clinical symptoms of hypoglycemia. Specifically, there was no

**Table 1.** Capillary versus Venous Glucose Measurements, Case 1

| Hospital Day | Time (h:mm) | Capillary Glucose (mg/dL) | Venous Glucose (mg/dL) |
|---|---|---|---|
| 1 | 19:38 | NA | 146 |
| 1 | 20:00 | 42 | NA |
| 1 | 22:02 | 48 | NA |
| 1 | 23:47 | 164 | NA |
| 2 | 05:39 | 95 | NA |
| | 08:34 | NA | 116 |
| 2 | 12:49 | 25 | NA |
| 2 | 12:51 | 29 | NA |
| 2 | 13:18 | 111 | NA |
| 2 | 16:09 | 84 | NA |
| | 21:48 | 102 | NA |
| 3 | 09:17 | NA | 131 |
| 3 | 12:10 | 55 | NA |
| 3 | 16:00 | 31 | 146 |
| 3 | 20:15 | 20 | NA |
| | 23:37 | 158 | NA |

change in mental status, shivering, tachycardia, or sweating, even with CBG levels of as low as 20 mg/dL (**Table 1**). The patient was empirically treated for hypoglycemia with oral glucose, without any symptomatic changes. Initially, no simultaneous venous plasma glucose (VPG) levels were drawn. Later in his stay, simultaneous VPG and CBG levels were drawn, with the former found to be within normal range while the latter was persistently low (**Table 1**). Interestingly, when the patient was without peripheral cyanosis, CBG levels were normal.

### Case Two

A 59-year-old man with a history of coronary artery disease with heart failure with reduced ejection fraction (ejection fraction 15%), T2DM, and peripheral arterial disease (PAD) was admitted to the hospital for a worsening diabetic foot ulcer requiring below-the-knee amputation. His course was further complicated with acute-on-chronic renal failure, requiring hemodialysis, and an acute non-ST-elevation myocardial infarction requiring inotropic support. Physical examination revealed 1+ radial pulses bilaterally with sluggish capillary refill and a non-palpable *dorsalis pedis* pulse on left foot with noticeable dry gangrene of his left toes. He had generalized 2+ pitting edema. The remainder of the physical examination was unremarkable.

The patient was found to have an elevated CBG level of 250 mg/dL, treated with insulin. Overnight, CBG readings of 50, 35, and 30 mg/dL were obtained via the finger stick method. He was administered multiple boluses of dextrose 50% solution (D50W) and subsequently started on an intravenous dextrose 10% infusion. At 08:00 AM, he had a finger stick method reading of 34 mg/dL and was again given a bolus of D50W. A repeat value in 30 minutes was 65 mg/dL. At this point, simultaneous CBG and VPG values were obtained on an hourly basis. Simultaneous VPG and CBG readings supported the diagnosis of pseudohypoglycemia (**Table 2**). For subsequent monitoring and diabetic management, glucose samples were obtained via the patient's central venous catheter, as he continued to demonstrate sluggish capillary refill and a marked discrepancy between CBG and VPG measurements.

**Table 2.** Capillary versus Venous Glucose Measurements, Case 2

| Hospital Day | Time (h:mm) | Capillary Glucose (mg/dL) | Venous Glucose (mg/dL) |
|---|---|---|---|
| 1 | 14:30 | 206 | NA |
| 1 | 15:30 | 150 | NA |
| 1 | 16:25 | 151 | NA |
| 1 | 17:25 | 144 | NA |
| 1 | 18:30 | 50 | NA |
| | 19:30 | 73 | NA |
| 1 | 20:15 | 156 | NA |
| 1 | 21:15 | 174 | NA |
| 1 | 22:20 | 35 | NA |
| 1 | 23:15 | 30 | NA |
| | 00:00 | 214 | NA |
| 2 | 01:45 | 195 | NA |
| 2 | 02:45 | 126 | NA |
| 2 | 04:00 | 112 | NA |
| 2 | 05:00 | 136 | NA |
| | 06:30 | 49 | NA |
| 2 | 07:00 | 120 | NA |
| 2 | 08:00 | 34 | NA |
| 2 | 08:30 | 65 | NA |
| 2 | 09:00 | 64 | 369 |
| | 10:30 | 91 | 225 |
| 2 | 11:30 | 56 | 225 |
| 2 | 12:30 | 163 | 240 |
| 2 | 13:50 | 51 | 259 |

## DISCUSSION

The above cases demonstrate patients with significant discrepancies between CBG and VPG values. This, in combination with their lack of symptoms or subjective improvement with glucose administration, suggests that both patients had pseudohypoglycemia. However, given the significant risks associated with untreated true hypoglycemia, how can one reliably distinguish it from pseudohypoglycemia?

First, it is important to recall that hypoglycemia is a clinical diagnosis, rather than a descriptive feature of laboratory results. Hypoglycemia may be diagnosed when the three elements of Whipple's triad are met: a low VPG level, symptoms consistent with hypoglycemia, and reversibility of said symptoms upon administration of glucose. Because of the subjective nature of hypoglycemic symptoms, as well as their reversal, clinicians often place primary importance on low measured VPG values. The American Endocrine Society defines low VPG as less than 70 mg/dL, although some patients may experience symptoms above this value.[4] Pseudohypoglycemia, by contrast, is defined as apparent low blood glucose levels without the remainder of Whipple's triad.[5] This emphasizes, rather than minimizes, the significance of patient history and subjective assessments and recognizes that false-positive test results may occur.

Second, it is important for clinicians to keep in mind the existence of an entity known as "hypoglycemic unawareness," where true hypoglycemia is present but symptoms are not easily or correctly recognized by the patient. In a Malaysian cohort with 1,153 participants covering six months of retrospective and four weeks of prospective data, impaired awareness of hypoglycemia was present in 48.0% of patients with T1DM and 36.9% with T2DM.[6] Most

reported hypoglycemic events were self-managed by patients themselves, but 11.5% and 7.3% of patients with T1DM and T2DM, respectively, had hypoglycemic events severe enough to require another person to administer anti-hypoglycemic therapies. The study did not directly report the rate of severe events with apparent hypoglycemic unawareness. Regardless, this finding does complicate the clinical reliability of patient-reported hypoglycemia symptoms.

Distinguishing hypoglycemic unawareness from pseudohypoglycemia is inherently difficult, given that subjective symptoms (and their reversal with glucose administration) are a key feature in the clinical diagnosis of hypoglycemia. In the inpatient setting, we recommend apparently hypoglycemic patients be treated empirically; however, when sufficient clinical suspicion exists for pseudohypoglycemia, such as in patients without a known history of diabetes,[7] testing of venous and papillary blood glucose is the only way to definitively rule in or out pseudohypoglycemia.

The mechanism of this discrepancy between capillary and venous plasma measurements of glucose, as seen in our patients, may be better understood by looking at patients' underlying medical conditions seen in prior reports of pseudohypoglycemia. Associated conditions include hematological disorders, such as leukemias, hyperviscosity syndromes, and hemolytic anemias; here, the capillary-plasma measurement discrepancy is thought to be primarily due to *in vitro* glycolysis.[8-10] Pseudohypoglycemia has also been described in PAD, shock, and Raynaud's phenomenon, where the capillary-plasma difference is thought to be due to impaired microcirculation, leading to a slower transit time and increased local tissue uptake of glucose, resulting in an apparent lower CBG level relative to venous plasma samples.[11-16]

## CONCLUSIONS

The finger stick method of glucose is logistically simple and fast, and thus is often the preferred method for frequent glucose monitoring. However, the cases presented here demonstrate the potential unreliability of CBG measurements under specific circumstances. Clinicians should be aware of the existence of pseudohypoglycemia and consider it in cases where the clinical signs and symptoms of hypoglycemia are absent. One helpful feature that may be used to confirm pseudohypoglycemia is a discrepancy between capillary and venous plasma measurements of blood glucose. Relatedly, if pseudohypoglycemia is suspected, simultaneous CBG and VPG samples should be drawn.

Pseudohypoglycemia has been most commonly described in patients with either hematologic conditions or conditions associated with impaired microvascular circulation. In our presented cases, we suspect both patients' pseudohypoglycemia was likely secondary to impaired microvascular circulation (from Raynaud's phenomenon secondary to SSc and chronic PAD with reduced cardiac output in the setting of an acute myocardial infarction, respectively). As a caveat, the existence of pseudohypoglycemia should not deter clinicians from empirically treating suspected hypoglycemia, especially in cases where eliciting symptoms may be difficult or impossible. However, if patients consistently demonstrate low CBG levels yet remain asymptomatic, providers should consider the possibility that pseudohypoglycemia may explain an otherwise confusing clinical picture.

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# Hypertrophic Olivary Degeneration Following Clivus Meningioma Surgery

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## CASE PRESENTATION

A 60-year-old man had a symptomatic clivus meningioma removed in May 2017. Postoperatively, he had skew diplopia, numbness on the left side of his face, drooling, dysphagia, and gait ataxia. He gradually improved over the next several months and reported being able to walk one mile in 14 minutes without the need for a supportive device. He had left eye muscle surgery to reduce his skew diplopia, without success.

Approximately 11 months after surgery, having been slowly improving, he developed progressive weakness in his legs, imbalance, dysarthria, a dull headache on the left side, increased drooling, and worsened gait. It then took him 45 minutes to cover just one mile. An MRI in May 2018 showed signs of hypertrophic olivary degeneration (HOD), characterized by T2-hyperintensity and mild enlargement of both inferior olivary nuclei (See **Figures 1A,B,C**), a new finding compared to the MRI performed four months earlier.

At his first examination in our clinic in June 2018, he had gait ataxia, mild bilateral proximal leg weakness, left facial numbness. The left eye had limited movement in all directions, presumed post-surgical, while the right eye had full movement. When looking laterally to either side however, the right eye would jerk down then laterally and then up.

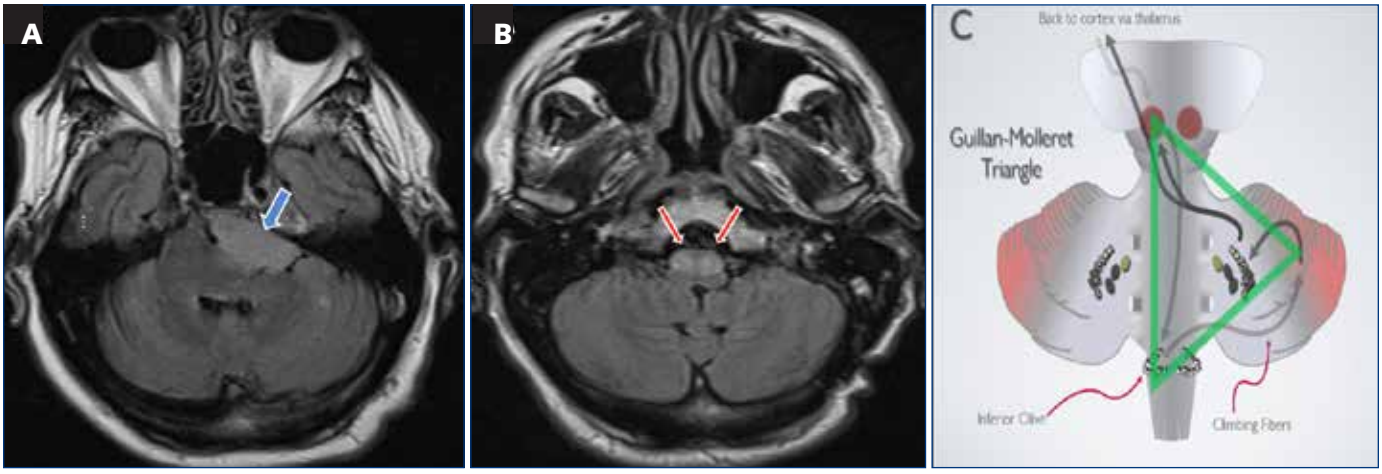
Over the following three years, ataxia, dysphagia, drooling, and dysarthria worsened, causing increased falls until 2021, when his symptoms stabilized, with no signs or symptoms of further deterioration. The MRI findings have remained unchanged however, as of May 2023.

## DISCUSSION

Hypertrophic olivary degeneration (HOD) is a rare disorder, characterized by degenerative hypertrophy of the inferior olivary nucleus (ION) following a lesion of any type, anywhere in the Guillain-Mollaret triangle (GMT). The GMT consists of the dentate nucleus in the cerebellum, contralateral ION in the medulla oblongata, and the contralateral red nucleus in the midbrain. When the afferent fibers of the GMT are disrupted, HOD may occur.[1]

HOD presents clinically with various symptoms, including palatal tremor, ocular myoclonus, cerebellar signs, or Holmes' tremor,[2] which develop insidiously after a latent period that varies between 15 days and 18 months and not acutely after the insult.[3] The pathophysiology is hypothesized to be caused by the loss of inhibitory input to the ION, leading to hyperactivity of the olivary neurons,[1] but there is no evidence to support this.

**Figure 1.** Hypertrophic olivary degeneration (HOD) attributed to pontine compression by petroclival meningioma. [**A**] T2-FLAIR pre-surgery image at level of mid-pons shows extra-axial mass consistent with meningioma (blue arrow). [**B**] T2-FLAIR MR image 12 months after surgery at level of upper medulla shows hyperintense signal in both inferior olivary nuclei (red arrows) consistent with HOD. [**C**] Guillan-Molleret Triangle.



The pathology is unique and is postulated to be a variant of Wallerian degeneration characterized by neuronal and astrocytic swelling, resulting in enlargement, followed by degeneration and eventual atrophy of the ION.[4] Although early pathological changes are thought to develop within days of damage to the GMT, imaging and clinical changes develop months later.[5] HOD can also be an occasional imaging finding in some asymptomatic patients, for which the underlying mechanism remains unknown.[6] The condition can occur unilaterally or bilaterally, with bilateral cases being more common. Bilateral HOD often lacks an obvious cause in over half of the cases.[7]

The diagnosis of HOD rests on the characteristic MRI findings. The MRI changes occur in three stages: increased signal on T2-weighted MRI involving ION without hypertrophy (early stage); persistent T2-enhancement with associated hypertrophy (intermediate stage); then atrophy of the ION with persistent T2-enhancement (late stage).[1] Differential diagnosis includes infarction, inflammation, demyelination, or tumor.[2] There is no treatment for HOD, or most of the symptoms it causes.

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# Direct Visualization of Diverticular Bleed on Colonoscopy

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## INTRODUCTION

Diverticula are small pouches that can develop in the colonic wall, affecting nearly half the population over the age of 60.[1] Diverticular bleeding, which occurs in approximately 5% of these patients, is characterized by spontaneous, intermittent, and often painless hematochezia, and is the most common cause of massive lower GI bleed, sometimes requiring urgent intervention.[2]

Colonoscopy is key to identifying and treating a diverticular bleed; however, bleeding stops spontaneously in roughly 70–90% of episodes.[3] Because of this, direct visualization of active diverticular bleeding during colonoscopy is quite infrequent, with only a limited number of case reports with imaging in the literature. This case represents a unique and valuable instance of direct visualization of diverticular bleeding during a colonoscopy. We discuss the patient's clinical presentation, colonoscopy findings, and subsequent therapeutic treatment.

## CASE PRESENTATION

A 77-year-old female presented with large-volume bowel movements of frank blood without any abdominal pain or other associated symptoms. When she arrived, she was hemodynamically stable, but her hemoglobin had dropped from a baseline of 9 g/dL to 5.4 g/dL [reference range: 11.2–14.9 g/dL] on presentation. She was transfused two units of packed red blood cells and monitored. A CT Angiogram of the abdomen and pelvis was obtained, showing accumulation of significant contrast in the ascending colon, compatible with a brisk GI bleed, and a small focus of additional extravasation in the transverse colon (**Figure 1**). Decision was made for colonoscopy

**Figure 1.** Computed tomography angiography (CTA) abdomen and pelvis (coronal view) demonstrating evidence of gastrointestinal hemorrhage. There is activity accumulation of significant contrast in the ascending colon, compatible with a brisk gastrointestinal bleed.

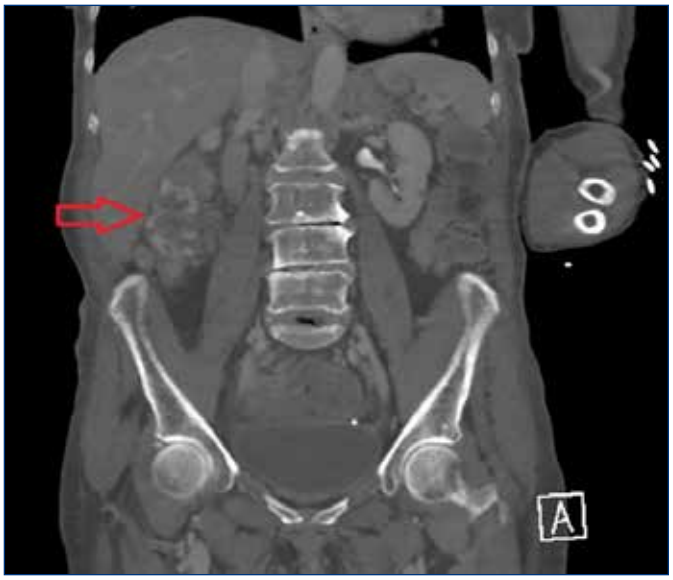



**Figure 2.** Bleeding vessel within diverticulum.

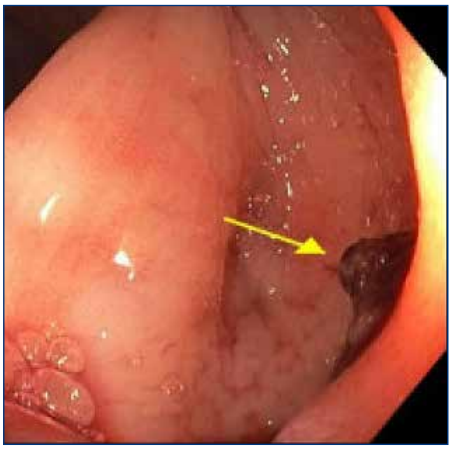


**Figure 3.** Hemostatic clip placement on bleeding diverticular vessel.

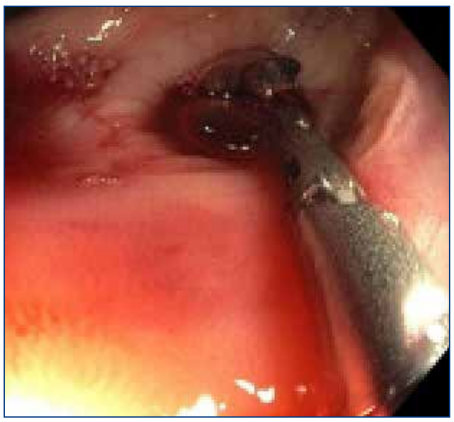
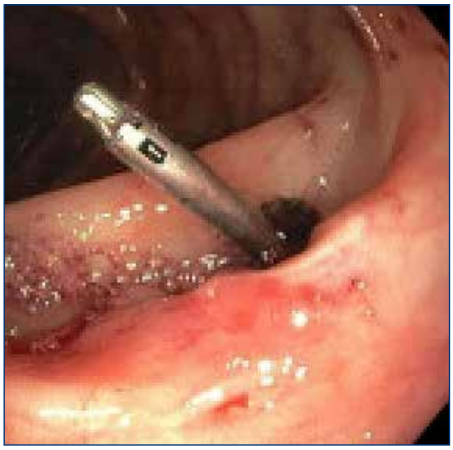


**Figure 4.** Hemostatic clip on diverticular vessel.



the next day after bowel preparation was completed. During the procedure, clotted and old blood was found in the rectosigmoid colon, sigmoid colon, descending colon, splenic flexure, transverse colon, and at the hepatic flexure. Near the hepatic flexure (**Figure 2**), there was one large-mouthed diverticulum with a visible vessel within the diverticulum with bleeding upon washing/agitation. The area was injected with 4 mL of a 0.1 mg/mL solution of epinephrine for hemostasis; however, this was unsuccessful. For hemostasis, three hemostatic clips were placed successfully (**Figures 3,4**). Bleeding resolved after the procedure and her hemoglobin remained stable.

## DISCUSSION

Current US guidelines recommend colonoscopy within 24 hours for patients with high-risk clinical features (such as hypotension, tachycardia, older age) or severe hematochezia, although current evidence for those recommendations remains low.[4] Colonoscopy is recommended as first line for evaluation of a lower-GI bleed, as you can perform both visualization and treatment interventions. Various therapeutic endoscopic interventions are available depending on the clinical scenario, including epinephrine injection, electrocoagulation, electrocoagulation, clips, and band ligation.[5] These can all be used as monotherapy or in multimodal scenarios if required.

In patients who are unable to tolerate bowel preparation or are not candidates for colonoscopy, angiography on CT scan can be a useful tool for identifying and treating a lower GI bleed via embolization. Unfortunately, the intermittent nature of diverticular bleeding reduces its sensitivity in this scenario.[2] In our patient specifically, the CTA findings indicated a brisk GI bleed, which helped inform the decision to perform urgent colonoscopy. It has been shown that extravasation findings for CT with IV contrast had high specificity for predicting stigmata of recent diverticular bleed during colonoscopy, regardless of the timing of the CT.[6] CTA In the acute setting may be a beneficial test in suspected lower GI bleed, as it can help further guide management.

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# Emergency Department Visit for Fever and Rash: DRESS Syndrome

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## CASE REPORT

A 47-year-old male with past medical history of hypertension, hyperlipidemia, psoriasis, asthma, gastroesophageal reflux disease, and gout presented to the emergency department (ED) with fever, myalgias, malaise, and a rash for three days. The rash (**Figures 1–4**) started on his face and moved inferiorly. He reported the development of painful "lumps" around his neck during the same timeframe. He tested negative for COVID-19 one day prior to presentation. The patient denied any similar rashes in the past. He started taking allopurinol for gout six weeks prior to the development of symptoms.

In the ED, the patient was febrile to 104.0 F and tachycardic to 116 beats per minute. Examination of the patient demonstrated an ill-appearing man with tonsillar and cervical adenopathy. He was noted to have a diffuse, erythematous, papular rash over his trunk and extremities with areas of confluence over the face and neck. Follicular pustules were also noted. Laboratory data yielded evidence of a new acute kidney injury, hepatic enzyme elevation, hematuria, and proteinuria. Eosinophilia was not present. A respiratory pathogen panel was negative.

Dermatology was consulted in the ED and performed a skin biopsy that demonstrated spongiotic dermatitis with perivascular lymphocytic infiltrate with scattered eosinophils. Combined with the patient's history and laboratory data, this result confirmed the diagnosis of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) Syndrome.

**Figure 1.** Papular, erythematous rash across anterior chest and abdomen.

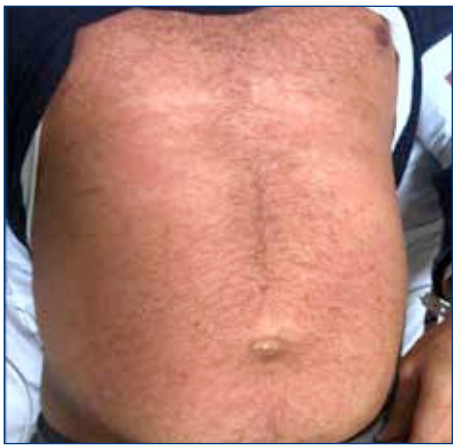
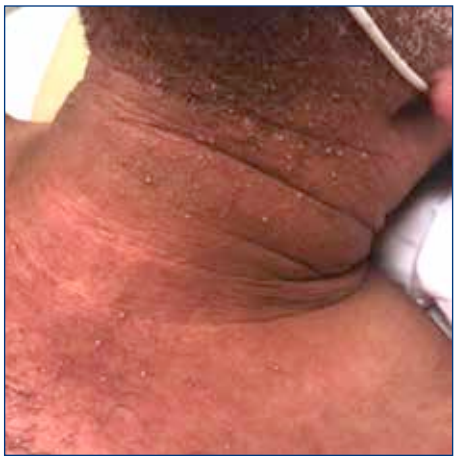


**Figure 2.** Pustular, erythematous rash across anterior neck.



## PATHOPHYSIOLOGY AND PRESENTATION

DRESS Syndrome occurs due to a life-threatening drug hypersensitivity reaction that causes constitutional symptoms, rash, and often organ dysfunction.[1,2] Common offending drugs include antiepileptics, allopurinol, sulfonamides, and other antibiotics.[1-5] Patients often present with prodromal symptoms including fever, pruritis, and lymphadenopathy.[1,4] These symptoms are followed by an erythematous, maculopapular rash that often starts on the face and

**Figure 3.** Erythematous rash across scalp.

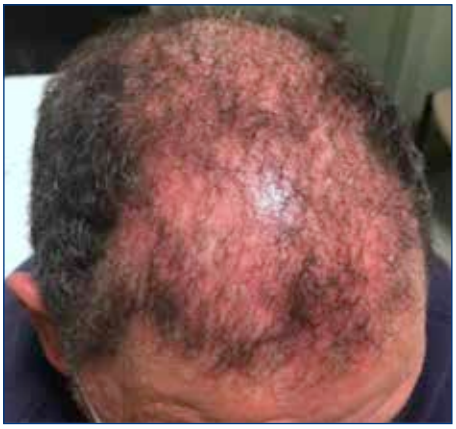
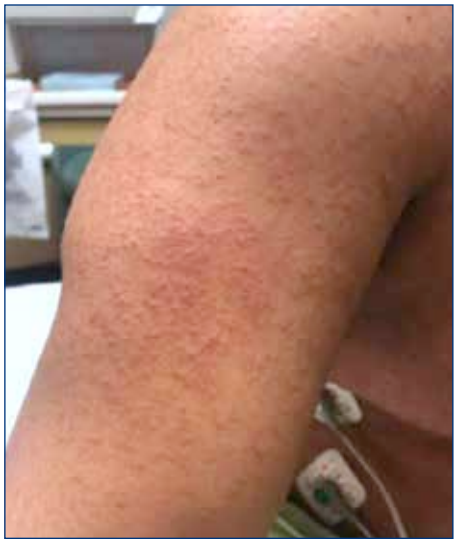


**Figure 4.** Papular rash across right upper arm.



moves inferiorly.[1,4] The rash may also be pustular in nature, involve mucosal surfaces, and be associated with facial edema.[1,2] Extracutaneous manifestations include cytopenias, acute hepatitis, myocarditis or cardiac dysrhythmias, pulmonary edema, lymphadenopathy, and acute kidney injury with hematuria or proteinuria.[1,2] Peripheral eosinophilia is common in DRESS Syndrome but is absent in up to 10% of cases.[2,3]

## DIAGNOSIS AND TREATMENT

Workup includes a broad lab evaluation; infectious etiologies must be ruled out. Diagnosis of DRESS Syndrome is made using the RegiSCAR Score which accounts for clinical signs and symptoms, presence of eosinophilia, and biopsy findings.[1,4] A RegiSCAR Score ≥5 indicates a definitive case of DRESS Syndrome.[6] Treatment involves immediate cessation of any suspected culprit drugs and admission to the hospital.[3] Patients with milder disease can be started on oral prednisone at a dose of 1 mg/kg/day or at an equivalent dose of intravenous methylprednisolone.[7] If patients do not improve, or if there are extracutaneous manifestations, intravenous methylprednisolone at a dose of 30 mg/kg is recommended.[7] Steroids are continued upon discharge and tapered over the course of several months.[7] Topical steroids can be used to treat pruritis.[7]

## PROGNOSIS

The mean recovery time for DRESS Syndrome is weeks to months.[4] Children and patients with isolated cutaneous disease often recover faster, while elderly patients have an increased risk for poor outcomes.[7] Hepatitis and renal impairment can be progressive and chronic, sometimes requiring dialysis.[1,4] Overall, the mortality rate is 10% and is mostly driven by fulminant liver failure and septic shock due to superimposed bacterial infections.[1,2,4-6]

## CASE RESOLUTION

The patient's RegiSCAR Score was 6. He was admitted to the hospital and started on oral prednisone. His liver injury progressively worsened (ALT 3,072/AST 973), necessitating an increase in his steroid dose to prednisone 2 mg/kg/day. He was discharged on hospital day 9 with overall improvement in symptoms and recovery from his acute kidney injury and acute liver injury.

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# Assessing Utility of 24-Hour Ambulatory Blood Pressure Monitoring to Distinguish Pediatric Populations Presenting with Elevated Blood Pressure in Rhode Island

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## ABSTRACT

This retrospective study aimed to assess the value of 24-hour ambulatory blood pressure monitoring (ABPM) in distinguishing primary from secondary hypertension in pediatric patients. Our study was conducted on 293 patients referred to a pediatric nephrology clinic over 11 years. Various ABPM parameters were analyzed, including daytime and nighttime systolic and diastolic blood pressures, heart rate, and blood pressure load. Among the participants, 74% were normotensive (white-coat hypertension), 21.5% had primary hypertension, and 4.4% had secondary hypertension. There were no significant differences in the analyzed variables between primary and secondary hypertension groups. Our findings suggest that ABPM might not reliably differentiate between the two in this cohort. As white-coat hypertension becomes more prevalent, ABPM remains a valuable tool in preventing unnecessary workups in children without sustained hypertension. However, our study did not identify specific endpoints for distinguishing primary from secondary hypertension.

**KEYWORDS:** pediatric hypertension, ambulatory blood pressure monitoring, white-coat hypertension

## INTRODUCTION

Elevated blood pressure is a prominent reason why children are referred to a pediatric nephrology clinic. It is the responsibility of the nephrologist to determine whether the patient has sustained hypertension versus white-coat hypertension, and whether the hypertension is essential or secondary in nature. Aside from the importance of diagnosing secondary hypertension and the associated primary etiology, identifying essential hypertension in children is crucial because of its relationship to adult hypertension. Multiple studies have shown that hypertension in childhood predisposes patients to hypertension in adulthood,[1,2] which is increasingly relevant as hypertension in the U.S. pediatric population is increasingly prevalent today than it was two or three decades ago.[3]

Hypertension can be essential in origin or result from secondary etiologies such as renal parenchymal disease, renovascular disease, endocrinopathies, cardiac disease (specifically aortic coarctation), medications or toxins. Secondary causes of hypertension have been shown to be prevalent in the pediatric population. A Polish study of 636 children with sustained hypertension showed that 55% had a secondary etiology.[4] Renal parenchymal disease was responsible for 68% of these cases of secondary hypertension, followed by renovascular and endocrine disorders. A U.S. cohort of 132 children with persistent hypertension from 1987 to 1991 showed a 77% prevalence of secondary causes.[5] Several factors have been identified to help predict which children have secondary hypertension. Secondary etiologies are more likely in children who are prepubertal, of normal weight, present with stage two hypertension, and with a negative family history for hypertension.[6,7] Unfortunately, these predictors are not highly sensitive and seldom preclude the need for an extensive workup to evaluate for secondary causes.

Along with primary and secondary hypertension, patients presenting to pediatric nephrology clinic with elevated blood pressure at their primary care office may be diagnosed as having white-coat hypertension. Identifying white-coat hypertension before an unnecessary workup is initiated is an immensely beneficial role of ambulatory blood pressure monitoring (ABPM). ABPM may serve a role in predicting or excluding patients with secondary hypertension if useful and statistically significant endpoints can be identified. Our study seeks to identify specific endpoints of pediatric ABPM data that can be used to distinguish primary hypertension from secondary hypertension. Moreover, it serves to characterize the evolving demographic and clinical features of a representative cohort referred to pediatric nephrology clinics for evaluation of hypertension.

## MATERIALS AND METHODS

### Study Population

Patients who underwent ABPM through the Pediatric Nephrology Clinic at Hasbro Children's Hospital between April 1999 and September 2010 were considered for inclusion. ABPM studies were excluded from consideration if any of the following criteria applied: 1) fewer than 50% of attempted readings were valid; 2) no height was available to permit determination of blood pressure percentiles with the exception of patients ≥18 years of age, in which case adult

**Figure 1.** Required Evaluation for Secondary Hypertension in All Hypertensive Patients

| **To qualify for inclusion, all hypertensive patients required:** |
|---|
| **1**) At least 3 of 5 of the following (first-line workup as recommended by the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents): |
| History and physical examination in the Pediatric Nephrology Clinic |
| BUN, creatinine, and electrolytes |
| Urinalysis +/- urine culture |
| CBC |
| Renal ultrasound |
| **AND/OR** |
| **2**) At least one of the following (workup for specific causes of secondary hypertension, as clinically indicated): |
| Urine and/or serum toxicology screen |
| Polysomnography |
| Plasma renin and/or aldosterone levels |
| Plasma and/or urine catecholamines / metanephrines |
| Plasma and/or urine steroid (including cortisol) levels |
| Renovascular imaging (including MRA, CTA, renal scintigraphy, and/or conventional arteriography) |
| Thyroid function panel |
| Renal biopsy |

**Table 1.** Demographic and Baseline Clinical Data on Patients Meeting Inclusion Criteria

| | Normotensive Group | Primary (1°) Hypertensive Group | Secondary (2°) Hypertensive Group | Overall | p-value (1° vs 2°) |
|---|---|---|---|---|---|
| Number of patients | 217 (74%) | 63 (22%) | 13 (4%) | 293 (100%) | |
| Gender (# of males) | 155 (71%) | 34 (54%) | 9 (69%) | 198 (68%) | |
| Age (years) | 13.8 ± 3.5 | 14.2 ± 3.3 | 12.2 ± 4.6 | 13.8 ± 3.5 | 0.17 |
| Race (Caucasian) | 127 (59%) | 45 (71%) | 12 (92%) | 184 (63%) | |
| Race (Hispanic) | 60 (28%) | 13 (21%) | 1 (8%) | 74 (25%) | |
| Race (Black) | 22 (10%) | 5 (8%) | 0 (0%) | 27 (9%) | |
| Race (Asian) | 3 (1%) | 0 (0%) | 0 (0%) | 3 (1%) | |
| Race (Indian) | 2 (1%) | 0 (0%) | 0 (0%) | 2 (1%) | |
| Race (Unknown) | 3 (1%) | 0 (0%) | 0 (0%) | 3 (1%) | |
| Height (cm) | 162.4 ± 17.9 | 160.3 ± 14.8 | 153.4 ± 20.7 | 161.6 ± 17.5 | 0.16 |
| Weight (kg) | 73.1 ± 26.2 | 80.8 ± 32.6 | 64.3 ± 31.6 | 74.4 ± 28.1 | 0.07 |
| BMI (kg/m²) | 26.8 ± 6.7 | 30.3 ± 8.9 | 25.8 ± 9.0 | 27.5 ± 7.5 | |
| Normal weight (%) | 66 (30%) | 15 (24%) | 6 (46%) | 87 (30%) | |
| Overweight (%) | 44 (20%) | 9 (14%) | 0 (0%) | 53 (18%) | |
| Obese (%) | 107 (49%) | 39 (62%) | 7 (54%) | 153 (52%) | |
| Urine sodium (mEq/L) | 162.8 ± 60.9 | 178.8 ± 67.8 | 108.5 ± 81.3 | 166.4 ± 63.3 | 0.17 |
| Urine creatinine (mg/dL) | 166.6 ± 82.5 | 156 ± 83.4 | 125.2 ± 85.7 | 162 ± 83.1 | 0.18 |
| Urine microalbumin (mg/g Cr) | 18.7 ± 45.6 | 19.6 ± 28.9 | 77.0 ± 176.3 | 21.2 ± 53.9 | 0.18 |

interpretive criteria were used; 3) the patient was receiving one or more antihypertensive medications at the time of ABPM; 4) the patient had a previous, valid ABPM study during the trial period.

Measures were taken to ensure that all hypertensive patients had undergone clinically appropriate workup to identify potential causes of secondary hypertension. This workup, as directed by the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents,[7] is delineated in **Figure 1**.

## Baseline Data

Demographic and clinical parameters were recorded on all patients (**Table 1**). These included age, gender, ethnicity, height, weight, body mass index (BMI), date of ABPM, and, when available, urine sodium, creatinine and microalbumin.

## Performance and Interpretation of ABPM

ABPM was performed using a validated oscillometric cuff, with reports generated by Rozinn Electronics, Model RZ250. The monitor was calibrated to record daytime readings (from 6:00 AM to 10:00 PM) every 20–30 minutes, and nighttime readings (from 10:00 PM to 6:00 AM) every 30–60 minutes. An automated report was generated for each ABPM study, with summarized data including daytime, nighttime, and overall systolic and diastolic BP (average + SD), daytime, nighttime, and overall pulse (average + SD), and the total number of readings attempted and obtained. For all patients between 1–17 years of age, 90th, 95th, and 99th percentiles for SBP and DBP were obtained using standardized tables from the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.[7] Hypertension was defined as a mean ambulatory SBP and/or DBP at or above the 95th percentile. For patients who were ≥18 years of age, ambulatory hypertension was defined in accordance with JNC-7 criteria:[8] overall ambulatory BP ≥130/80, daytime ambulatory BP ≥135/85, and/or nighttime ambulatory BP ≥120/75. All ABPM studies were reviewed by a pediatric nephrologist to calculate the percentage of systolic and diastolic BP readings at or above the 90th, 95th, and 99th percentiles (BP load).

### Determination of Hypertension Class

All subjects were referred to the Pediatric Nephrology Clinic due to elevated office or hospital BP readings. Those who did not meet criteria for hypertension by ABPM were classified as having white-coat hypertension. In patients confirmed to have hypertension by ABPM, comprehensive chart review was performed to determine adequacy of workup for secondary hypertension (**Figure 1**). Etiology of ABPM-confirmed hypertension was determined to be primary or secondary based on objective laboratory and radiologic data, and clinical judgment of the pediatric nephrologist.

### Statistical Methods

All demographic data were collected when ABPM was performed. Height percentile for age was determined using CDC clinical growth charts (published in 2000). Continuous variables are presented as mean ± SD; categorical variables are presented as numbers and percentages. Statistical analyses were performed via SPSS. P values of <0.05 were used to determine statistical significance.

## RESULTS

Over an 11-year period, 345 patients were considered for inclusion; 52 were excluded from analysis. Of the 293 remaining patients, 217 (74%) were found to be normotensive by ABPM (conferring white-coat hypertension diagnosis). Among the 76 patients (26%) who were hypertensive by ABPM, 63 had primary hypertension and 13 had secondary hypertension. Children with secondary hypertension appeared to be younger with lower height, weight, and BMI, compared to their counterparts with primary hypertension (see **Table 1**); however, none of these differences met the threshold for statistical significance.

ABPM procedures yielded an average of 45 valid readings per patient, with 88% of all attempted readings being valid. Mean BP readings by ABPM were 117/65 in the normotensive group, 135/75 in the primary hypertension group, and 136/79 in the secondary hypertension group. Peak BP readings averaged 151/91, 172/103, and 180/102, respectively. Peak SBP and DBP readings were significantly higher in both hypertensive groups compared to the normotensive group but were not significantly different between the primary and secondary hypertension groups (**Table 2**).

All categories of BP load exhibited a similar pattern, with significantly higher BP load in the hypertensive groups compared to the normotensive group. The average percentage of BP readings at or above the 95th percentile was 29% in the normotensive group, 74% in the primary hypertension group, and 78% in the secondary hypertension group. No significant differences in any of the BP load categories were identified between the primary and secondary hypertension group (**Table 3**).

The study population included a substantial proportion of non-dippers, with a mean SBP dip of 9.3% across the cohort. The average magnitude of nocturnal dipping in SBP was 9.5% in the normotensive group, 8.9% in the primary hypertension group, and 7.7% in the secondary hypertension group. Nocturnal dipping in DBP averaged 14.7%, 12.3%, and 11.4%, respectively. These figures were not statistically significant between the groups (**Table 4**).

Review of the heart rate data from the ABPM readouts revealed significant trends between groups of hypertension class and weight class. Mean heart rate was higher in both hypertensive groups (86 for primary hypertension, 89 for secondary hypertension) compared to the normotensive group (77), though not significantly different between both hypertensive groups. There was no difference in nocturnal HR dipping when comparing the primary and secondary hypertensive groups. Of the 293 children included in the analysis, 87 (30%) were of normal weight, 53 (18%) were overweight, and 153 (52%) were obese. Average BMI was 27.5 kg/m2. BMI exceeded 40 kg/m2 in 18 subjects. The standard deviation in heart rate during the 24-hour ABPM was significantly lower in overweight ($p = 0.007$) and obese ($p < 0.0001$) children than in their normal-weight counterparts.

**Table 2.** Comparing Peak Systolic and Diastolic BP in Primary versus Secondary Hypertensive Patients

| Variables | Normotensive Group | Primary (1˚) Hypertensive Group | Secondary (2˚) Hypertensive Group | p-value (1˚ vs 2˚) |
|---|---|---|---|---|
| Peak SBP | 151 ± 14 | 172 ± 17 | 180 ± 33 | 0.93 |
| Peak DBP | 91 ± 10 | 103 ± 16 | 102 ± 16 | 0.68 |

**Table 3.** Comparing BP Load in Primary versus Secondary Hypertensive Patients

| Variables | Normotensive Group | Primary (1˚) Hypertensive Group | Secondary (2˚) Hypertensive Group | p-value (1˚ vs 2˚) |
|---|---|---|---|---|
| BP Load at 90$^{th}$ %ile | 40 ± 19% | 81 ± 12% | 84 ± 15% | 0.77 |
| BP Load at 95$^{th}$ %ile | 29 ± 17% | 74 ± 13% | 78 ± 20% | 0.78 |
| BP Load at 99$^{th}$ %ile | 13 ± 10% | 56 ± 19% | 64 ± 24% | 0.62 |
| Systolic BP Load at 95$^{th}$ %ile | 26 ± 16% | 72 ± 13% | 77 ± 21% | 0.72 |
| Diastolic BP Load at 95$^{th}$ %ile | 9 ± 10% | 32 ± 28% | 42 ± 28% | 0.56 |

**Table 4.** Comparing Nocturnal Systolic and Diastolic BP Dips in Primary vs Secondary Hypertensive Patients

| Variables | Normotensive Group | Primary (1˚) Hypertensive Group | Secondary (2˚) Hypertensive Group | p-value (1˚ vs 2˚) |
|---|---|---|---|---|
| Nocturnal Systolic BP Dip (%) | 9.5 ± 6.8% | 8.9 ± 6.9% | 7.7 ± 6.2% | 1.00 |
| Nocturnal Diastolic BP Dip (%) | 14.7 ± 9.1% | 12.3 ± 7.9% | 11.4 ± 8.5% | 1.00 |

## DISCUSSION

This retrospective cohort study examined a population referred to an urban pediatric nephrology clinic for evaluation of hypertension and sought to identify categories of ABPM data that could discern causes of primary hypertension from secondary hypertension. Determining such ABPM criteria might prove beneficial in selecting which children warrant an extensive workup for secondary hypertension. As hypertension in U.S. children is more prevalent today than 20–30 years ago this has become increasingly important. The National Health and Nutrition Examination Survey (NHANES) provided information about the changing prevalence of hypertension in the pediatric population. A study that compared NHANES data from the years 1988–2004 to the years 1999–2008, the prevalence of elevated blood pressure (pre-hypertension or hypertension) increased from 15.8% to 19.2% in males and from 8.2% to 12.6% in females.[3] This increase in population-based pediatric blood pressures is closely related to the rising prevalence of obesity in the U.S. population. Most recent data, from 2011–2012, show that in children 2–19, 14.9% are overweight and 16.9% are obese.[9] A study of 1665 children 8–17 showed that the incidence of high or borderline high BP in normal weight children was 8.4%, whereas for overweight and obese children was 12.8% and 18.0%, respectively.[10] Another study of 5102 children showed that being overweight conferred a relative risk of 3.26 (95% CI 2.50–4.24) for hypertension.[11] Other pediatric studies[12,13,14] have documented significant correlations between BMI and risk of prehypertension or hypertension. In our study, the incidence of primary hypertension was as follows: 17% of patients with normal BMI, 17% of patients with overweight BMI, and 36% of patients with obese BMI. An obese BMI conferred a significant increased risk of primary hypertension.

Prior pediatric ABPM studies[15,16,17] identified significant (but disparate) findings in children with secondary compared to primary hypertension. One retrospective analysis examined ABPM data in 145 children with untreated hypertension (69% of which had secondary hypertension).[15] Results showed that in children with secondary hypertension, overnight non-dipping status (defined as 10% decrease in blood pressure at night) was found in 65% for systolic BP and 21% for diastolic BP, compared to 11% and 0%, respectively, for children with primary hypertension. This study also showed a greater likelihood of sustained nocturnal hypertension in the secondary hypertension group. Another series analyzed 97 ABPM reports obtained from 85 patients seen at the pediatric hypertension clinic. The presence of a daytime diastolic BP load ≥ 25% and/or a nighttime systolic BP load of ≥ 50% on ABPM were determined to be highly specific for secondary hypertension.[16] Lastly, a group reviewed ABPM reports from 76 children, of which 16 were subsequently diagnosed with white-coat hypertension, 50 with primary hypertension and 10 with secondary hypertension.[17] Daytime and nocturnal systolic and diastolic BP values were greater among children with secondary hypertension than in those with primary hypertension.

Compared to prior analyses regarding markers for secondary hypertension in ABPM, our cohort data did not corroborate these findings, and found no categories of ABPM data that were significantly different between the primary hypertension and the secondary hypertension group. Our study was limited by a small sample size of hypertensive patients, as our analysis of 293 ABPM procedures yielded 63 children with primary hypertension and 13 with secondary hypertension. This could explain our inability to find statistically significant differences in ABPM parameters between groups, especially if the differences sought were relatively subtle. Secondary hypertension is a heterogeneous diagnosis with a variety of cardiac, renal, endocrine, and iatrogenic causes and, as such, a central unifying diurnal blood pressure pattern for "secondary hypertension" may not exist but may instead depend upon the specific mechanism which is responsible. Many different causes of secondary hypertension were represented in our study population (**Table 5**). Furthermore, there was significant overlap between the primary hypertension group and secondary hypertension group in all categories of absolute blood pressure values, BP load, and nocturnal dipping.

Our study highlighted several characteristics of a pediatric hypertension cohort that were markedly disparate from figures previously published in the medical literature. The prevalence of white-coat hypertension was 74%. Only 26% of children referred from their primary care providers for suspected hypertension had confirmed hypertension based on ABPM results. The reported frequency of white-coat hypertension from prior studies in a pediatric population

**Table 5.** Etiology of Secondary Hypertension

| Etiology of Secondary Hypertension | Number of Patients, n |
|---|---|
| Total Patients with Secondary Hypertension | 13 |
| Renal Parenchymal Disease | 6 |
| Chronic kidney disease (obstructive uropathy) | 1 |
| Wegener's granulomatosis | 1 |
| Post-infectious glomerulonephritis | 1 |
| Dystrophic right kidney | 1 |
| Dysplastic right kidney | 1 |
| Renal scarring of unilateral kidney | 1 |
| Renovascular Disease | 1 |
| Thyroid Disturbances | 2 |
| Subclinical hypothyroidism | 1 |
| Hyperthyroidism | 1 |
| Hyperaldosteronism | 2 |
| Obstructive Sleep Apnea | 1 |

has ranged from 35–45%.[17,18,19] A study done between 2005–2006 showed that 46% patients that initially presented with elevated blood pressure had white-coat hypertension based on ABPM.[18] This same study showed the cost-effectiveness of using ABPM; it estimated that for every 1000 patients $2.4M can be saved by using ABPM to identify patients with white-coat hypertension who need not further hypertensive workup. If the increased prevalence of white-coat hypertension seen in our study is applicable on a broader scale, it implies substantial utility of ABPM in avoiding unnecessary treatment in children without sustained hypertension.

Conversely, the prevalence of secondary hypertension in our cohort was much lower than anticipated. Only 13 (4%) of all children evaluated, and 13 children from the 76 (17%) with ABPM-confirmed hypertension, had an identifiable secondary etiology. As our study was retrospective, there was no protocol in place guaranteeing an exhaustive workup for secondary causes; instead, a workup for pertinent secondary causes was undertaken at the discretion of the pediatric nephrologist. Criteria were established (as detailed in **Figure 1**) to identify a minimally appropriate workup for secondary hypertension, with 15 hypertensive children excluded from analysis due to insufficient workup. This may have led to cases of secondary hypertension having been overlooked, leading to a falsely low prevalence in the study population. Despite this, it remains difficult to reconcile the low frequency of secondary hypertension seen in our study with the figures of 55% and 77% obtained in pediatric cohorts from the 1980s and early 1990s.[4,5]

Our results regarding the low prevalence of secondary hypertension in our study, may, in fact, highlight that essential hypertension is an increasingly common phenomenon, due to the upsurge in obesity and metabolic syndrome in the pediatric population. NHANES data from 2007–2008[20] yielded a prevalence of overweight BMI or obesity of 35.5% in school-aged children (6–11 years), and 34.2% in adolescents (12–19 years). In contrast, children being evaluated in our office had a strikingly high prevalence of overweight (18%) and obesity (52%), with only 30% of all subjects being of normal weight. As previously mentioned, several large pediatric studies have documented strong associations between overweight/obesity and the risk of prehypertension or frank hypertension.[11,12,13,14] Sedentary lifestyles have also been frequently implicated in childhood obesity.[21] This may provide an explanation for the differential ABPM mean heart rate data that we observed between classes of weight and hypertension. Mean heart rate (by ABPM) was significantly higher in both hypertensive groups compared to their normotensive counterparts, which could reflect deconditioning or increased sympathetic activity. It was also interesting to find decreased heart rate variability in the overweight and obese groups, which we postulate is due to a lower level of physical activity over the 24-hour measurement period.

Importantly, in 2017 the American Academy of Pediatrics published Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents,[22] as an update to the 2004 Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. Significant changes in the updated guidelines included new normative pediatric BP tables based on normal weight-weight children, a simplified screening table for identifying BPs needing further evaluation, a simplified BP classification in adolescents ≥ 13 years of age, more limited recommendation to perform screening BP measurements only at preventative care visits, and an expanded role for ABPM in the diagnosis and management of pediatric hypertension. For children ages 1–13 yr. normal BP is <90th percentile, elevated BP ≥ 90th percentile to <95th percentile or 120/80 mm Hg to <95th percentile (whichever is lower), stage 1 hypertension is ≥ 95th percentile to < 95th percentile + 12 mm Hg, or 130/80 to 139/89 mm Hg (whichever is lower), and stage 2 hypertension is ≥ 95th percentile + 12 mm Hg, or ≥ 140/90 mm Hg (whichever is lower). For children ages ≥ 13 yr normal BP is <120/<80 mm Hg, elevated BP is 120/80 t0 129/80 mm Hg, stage 1 hypertension 130/80 to 139/89 mm Hg, and stage 2 hypertension is ≥ 140/90 mm Hg.

This study had several limitations which hindered its ability to find significant differences in ABPM variables between children with primary hypertension and children with secondary hypertension. These included the unexpectedly low prevalence of secondary hypertension (leading to a small sample size), the retrospective nature of the investigation, and the lack of a predefined protocol for identifying secondary etiologies of hypertension. Our study also carried unique advantages compared to prior pediatric ABPM research, such as the omission of children who were already on anti-hypertensive therapy (thereby avoiding any iatrogenic alterations in blood pressure and heart rate trends), and the near-universal application of ABPM on children referred to our pediatric nephrology clinic for evaluation of hypertension. Further prospective studies with larger sample sizes are needed to better clarify whether ABPM can be reliably used as a predictive tool of secondary hypertension. Nonetheless, the paradigm of hypertension in the pediatric population may be shifting. The previously observed prominence of secondary hypertension as a primary etiology is now being overshadowed by the rising incidence of essential hypertension, likely due to obesity and other metabolic risk factors. The notably high prevalence of white-coat hypertension in our study also reinforces the value of ABPM to further evaluate office hypertension in children.

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# Impact of Cancer on Nutrition in the Geriatric Cancer Population

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## ABSTRACT

Malnutrition in geriatric cancer patients is a leading cause of morbidity and mortality. A nutrition risk assessment should be done early to identify and treat those at risk for cancer-related malnutrition. The goal of this study was to assess nutritional status in geriatric patients diagnosed with all cause cancer. We conducted a single institutional prospective cohort study of geriatric patients with cancer from 2013–2018. Patients 65 years old and above had undergone a comprehensive geriatric assessment before starting treatment (day 0), post-treatment (day 30), and post-post treatment (day 90). Body Mass Index (BMI) and the Mini Nutritional Assessment (MNA) were used to assess nutrition status. Results showed an increase in nutrition status from pretreatment (day = 0) to treatment (day =30), followed by a decrease in MNA scores at day 90. Results showed a decrease in BMI across all time points. This study supports that cancer and anti-cancer therapy in geriatric patients cause malnutrition, indicating the importance of early nutritional evaluation and intervention.


**KEYWORDS:** nutrition, cancer, geriatric population

## INTRODUCTION

The U.S. population aged 65 years and older is expected to grow from 54.1 million in 2019 to nearly 81 million in 2040.[1,2] 80 % of cancer diagnoses occur among those who are 55 or older, with 57 % of diagnoses occurring among those 65 and older.[1,3]

Cancer-related malnutrition is defined as a continual loss of skeletal muscle associated with loss of appetite and alteration in absorption and metabolism of nutrients.[4,5,6,7] This is typically caused by cancer-induced metabolic changes or response to anti-cancer treatment side effects. Cancer treatment options include immunotherapy, chemotherapy, radiation, hormone therapy, surgical intervention, or most often, a combination of these. Common side effects of these treatments include anosmia, dysgeusia, stomatitis, gastric and duodenal ulcers, persistent nausea, vomiting and constipation, all contributing to net low-caloric intake despite the higher caloric need necessitated by cancer pathology and treatment. If surgery is part of the treatment plan, it can contribute even further to higher metabolic demands, leaving the cancer patient with a hefty caloric deficit.[8]

Approximately, 15–40% of cancer patients report weight loss at the time of diagnosis and 40–80% of all cancer patients will meet malnourishment status during the disease and treatment phase.[9] Geriatric syndromes, defined as an accumulated effect of impairment, increase the vulnerability of the older adult to situational challenges. A study published in 2011 cited that 60.3% of older adults with cancer reported one or more geriatric syndromes as compared to 53.2% of those without cancer.[10] Given that almost 50% of the geriatric population is malnourished at baseline,[11] it should come as no surprise that cancer-associated malnutrition is very common in geriatric cancer patients. This is especially concerning as malnutrition may increase the chance of side effects, including mortality in this patient population. Malnutrition is associated with increased rates of infections, poor wound healing, prolonged hospital stays and increased mortality.[11] Geriatric patients with solid tumors who were malnourished had an 87% higher risk of all-cause mortality than those who were well-nourished.[12]

Conventional nutritional therapy, such as oral nutritional supplements, can partially reverse cancer-related malnutrition, making nutritional status assessment imperative for the identification and treatment of high-risk individuals. Examinations of involuntary weight loss, low body mass index (BMI) and Mini Nutritional Assessment (MNA) are among the screening techniques validated for use in geriatric oncology patients.[6,13]

The goal of this study was to assess the impact of cancer and malnutrition among geriatric patients diagnosed with all cause cancer with surgically resectable disease, using validated noninvasive screening assessment tools, BMI and MNA, across 3 time points from diagnosis and treatment.

## METHODS

This was a cohort study conducted at Roger Williams Medical Center (RWMC), a community teaching hospital located in Rhode Island. Institutional review board (IRB) waiver was obtained, and research meets requirements for protection of human subjects. Inclusion criteria for this study were patients 65 years of age or older with a new cancer diagnosis and surgically resectable disease. The patients included

did not receive chemotherapy or radiation therapy. Eligible patients were further assessed for nutritional status using MNA and BMI between January 1, 2013 and December 31, 2018. Assessments occurred at day 0 (*t=1*), day 30 (*t=2*), and day 90 (*t=3*), day 0 being at the time of diagnosis. Data for this study was obtained from the RWMC electronic medical record system, Meditech.

### Mini Nutritional Assessment (MNA)

MNA is a rapid, non-invasive and inexpensive method for assessing nutritional deficiency and malnutrition in these patients.[13] The MNA assessment is composed of simple measurements of height, weight, weight loss, lifestyle, medication, mobility, nutritional adequacy, food and fluid intake, and self-perception of health and nutrition.[14] Nutrition status is indicated by scores obtained by the MNA assessment. A score of 0–7 indicates malnutrition, 8–11 a risk for malnutrition and a score of 12–14 indicates well nourishment.

### Body Mass Index (BMI)

Weight loss and BMI are also valuable in clinical practice for assessing malnutrition in geriatric cancer patients.[15] They are strongly predictive of patient survival across all stages and types of cancer.[16] A BMI of 20–25 kg/m2 represents healthy nutrition, whereas less than 20 kg/m2 represents malnutrition. Previous studies have reported that low BMI is a significant risk factor for increased mortality in certain cancers, such as lung cancer and colorectal cancer.[17,18,19]

## RESULTS

All statistical analyses were performed using SPSS, version 28.0. All analyses were conducted separately on MNA and BMI results. Descriptive statistics, including mean, standard deviation, standard error and confidence intervals were calculated, respectively. Repeated measure analysis of variance (ANOVA) test was used to investigate the changes in mean scores over three points day 0, 30, and 90 (t=1,2,3), a $p$ value of less than 0.05 indicated statistical significance. Furthermore, a post-hoc pairwise comparison using the Bonferroni correction was used to compare difference among the means between the different time points. MNA and BMI values were evaluated across all time points for significance.

We assessed 311 geriatric patients with a new cancer diagnosis who were undergoing active treatment, including surgery, chemotherapy, radiation, or any combination of the same. 65 of the 311 participants had complete records across all time points observed and were included in our final analysis. All results were evaluated for significance across time points observed. On day 0, 48 (74%) participants were malnourished according to MNA and BMI values respectively. At day 30, 42 (65 %) of participants were malnourished, and at day 90 this increased to 52 (80 %) of participants were malnourished according to MNA and BMI values. Descriptive statistics of MNA and BMI values for 65 participants at day 0, day 30, day 90. (see **Table 1**). Mauchly's Test of Sphericity indicated that the assumption of sphericity had not been violated, $\chi^2(2) = 4.917$, $p = 0.086$. Therefore, a repeated-measures ANOVA was used and determined that mean MNA scores differed significantly across the 3 time points (see **Tables 2,3**). A post-hoc pairwise comparison using the Bonferroni correction showed an increase in MNA scores between day 0 and day 30, 5.4 vs. 6.5 respectively, with a statistically significant $p$-value of 0.02 (see **Table 4**). Although, the MNA scores decreased between day 30 and day 90 from 6.5 to 5.7. $P$-value of 0.067 and was not statistically significant. Mauchly's Test of Sphericity indicated that the assumption of sphericity had been violated

**Table 1.** Descriptive statistics for MNA and BMI values at pre- and post-treatment days.

| | Source | | Type III Sum of Squares | df | Mean Square | F | Sig. | Partial Eta Squared |
|---|---|---|---|---|---|---|---|---|
| MNA | Time | Sphericity Assumed | 46.779 | 2 | 23.390 | 4.140 | 0.018 | 0.061 |
| | Error (Time) | Sphericity Assumed | 723.221 | 128 | 5.650 | | | |
| BMI | Time | Greenhouse-Geisser | 36.856 | 1.518 | 24.277 | 7.069 | 0.003 | 0.099 |
| | Error (Time) | Greenhouse-Geisser | 333.677 | 97.160 | 3.434 | | | |

**Table 2.** Mauchly's Test of Sphericity

| | t | Mean | Std. Deviation | N | Std. Error | 95% Confidence Interval | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower Bound | Upper Bound |
| MNA | 1 | 5.3692 | 3.67665 | 65 | 0.456 | 4.458 | 6.280 |
| | 2 | 6.5231 | 3.53159 | 65 | 0.438 | 5.648 | 7.398 |
| | 3 | 5.6615 | 2.98055 | 65 | 0.370 | 4.923 | 6.400 |
| BMI | 1 | 26.4723 | 6.74172 | 65 | 0.836 | 24.802 | 28.143 |
| | 2 | 25.8538 | 5.96665 | 65 | 0.740 | 24.375 | 27.332 |
| | 3 | 25.4123 | 5.81664 | 65 | 0.721 | 23.971 | 26.854 |

**Table 3.** Tests of Within-Subjects Effects for MNA and BMI.

| | Measure | MEASURE_1 | | | | | | |
|---|---|---|---|---|---|---|---|---|
| MNA | Within Subjects Effect | Mauchly's W | Approx. Chi-Square | df | Sig. | Epsilon[b] | | |
| | | | | | | Greenhouse-Geisser | Huynh-Feldt | Lower-bound |
| | Time | 0.925 | 4.917 | 2 | 0.086 | 0.930 | 0.957 | 0.500 |
| BMI | | 0.683 | 24.057 | 2 | 0.000 | 0.759 | 0.774 | 0.500 |

**Table 4.** Pairwise Comparisons between different time periods for MNA Scores.

| | Measure | MEASURE_1 | | | | | |
|---|---|---|---|---|---|---|---|
| | (I) Time | (J) Time | Mean Difference (I–J) | Std. Error | Sig.[b] | 95% Confidence Interval for Difference[b] | |
| | | | | | | Lower Bound | Upper Bound |
| MNA | 1 | 2 | –1.154* | 0.412 | 0.020 | –2.166 | –0.142 |
| | | 3 | –0.292 | 0.466 | 1.000 | –1.438 | 0.853 |
| | 2 | 1 | 1.154* | 0.412 | 0.020 | 0.142 | 2.166 |
| | | 3 | 0.862 | 0.367 | 0.067 | –0.042 | 1.765 |
| | 3 | 1 | 0.292 | 0.466 | 1.000 | –0.853 | 1.438 |
| | | 2 | –0.862 | 0.367 | 0.067 | –1.765 | 0.042 |
| BMI | 1 | 2 | 0.618 | 0.280 | 0.093 | –0.071 | 1.308 |
| | | 3 | 1.060* | 0.347 | 0.010 | 0.208 | 1.912 |
| | 2 | 1 | –0.618 | 0.280 | 0.093 | –1.308 | 0.071 |
| | | 3 | 0.442 | 0.205 | 0.104 | –0.062 | 0.945 |
| | 3 | 1 | –1.060* | 0.347 | 0.010 | –1.912 | –0.208 |
| | | 2 | –0.442 | 0.205 | 0.104 | –0.945 | 0.062 |

Based on estimated marginal means (**1= Pretreatment, 2 = 30 days, 3= 90)**

* The mean difference is significant at the .05 level.

b Adjustment for multiple comparisons: Bonferroni.

$\chi^2(2) = 24.057$, $p = 0.000$. Therefore, Greenhouse-Geisser method was used. Corrected results showed significant differences among the means across all time points ($p$ =0 .003) (**Table 3**). A post-hoc pairwise comparison using the Bonferroni correction showed a continuous decrease in BMI values across all time points, 26.5, 25.9, 25.4 (shown in **Table 4**). However, the difference among the means was only statistically significant between day 0 and day 90, p =0.01 (**Table 4**).

## DISCUSSION

America's population of older adults is expected to double by 2030. It is expected that the rate of cancer diagnoses in the geriatric population will rise accordingly.

Natural aging changes, as well as the presence of geriatric syndromes, make geriatric patients more vulnerable to acute events such as cancer diagnoses and demanding treatment regimens. A decrease in basal metabolism occurs which causes metabolic rate decline and muscle atrophy. There are changes at the level of the digestive system as well, namely diminished digestive secretions which impair digestion and absorption of nutrients.[20] As such, frailty, sarcopenia, and weight loss, are highly prevalent in geriatric population, with 50 % of the population being malnourished at baseline.

Malignancy and associated anti-cancer treatment led to additional metabolic derangements such as elevated energy expenditure, increased catabolism, and chronic inflammation, further undermining this patient population's nutritional status. The results from this study demonstrate that as patients are diagnosed and continue with their respective anti-cancer treatment, MNA and BMI scores decline, indicating higher rates of malnourishment at day 30 and day 90.

### Limitations

The study is a pilot project. The power of the study needs to be improved to identify the interventions required. The interventions need to be standardized so that the outcomes can be appropriately measured. Multi-institutional studies are required in the future to increase more patients within the study.

## CONCLUSION

Geriatric cancer patients are vulnerable to malnutrition, not only as a response to cancer and associated treatment regimens, but also due to natural aging and the high prevalence of geriatric syndromes. This study, which used MNA and BMI assessments to evaluate the nutritional status of newly diagnosed cancer patients undergoing active treatment, showed decreasing values for both assessments across all time points observed. Malnutrition alone carries increased risk of negative outcomes such as infections, poor wound healing, and prolonged hospital stay. Malnutrition in the geriatric patient, particularly in patients with solid tumors, is even more detrimental, carrying a significant mortality risk of 87 %.[12] This suggests that proactive rather than reactive nutritional interventions should always be considered an integral part of cancer care in geriatric patients to improve clinical outcomes and quality of life. Assessment and intervention should start at the time of diagnoses and be re-evaluated at each touch point with the patient by all care team members, despite individuals having normal BMI and or MNA values, due to the demonstrated high risk of becoming malnourished quickly after diagnosis (day=0) and at 30 to 90 days thereafter. Interventions can be multifaceted; for example, nutrition referral, dietary consultations, high protein nutritional education, simple encouragement, daily weights, and food diaries may all be beneficial. Repeated screening with MNA and careful monitoring of BMI will help with early identification and offer the possibility of early intervention.

Malnutrition in geriatric cancer patients poses increased risk of impairing patient's chances of endurance, treatment, and recovery, along with carrying an increased risk of morbidity and mortality. More studies are needed to explore this notion and provide more information on the types of intervention that are most efficacious and if early identification and preemptive treatment for malnutrition is as effective as this study seems to suggest it has the potential to be.

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## Disclosure

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# International Medical Graduates in US Orthopedic Residency Programs: A Comprehensive Analysis

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## ABSTRACT

**BACKGROUND:** This study aims to provide insight regarding the different qualities of international medical graduates (IMGs) involved in US orthopedic residency programs.

**METHODS:** Orthopedic residency programs accredited by the ACGME and listed in the AMA database were screened. Data on program size and location, IMG year of training, the geographic region of IMG's medical schools, their research experiences and number of gap years were included.

**RESULTS:** A total of 167(80.3%) orthopedic residency programs were included. A total of 3838 residents were identified, of which 44 (1.15%) were IMGs. The United Kingdom and Ireland had the highest number of matched IMGs with four (9.1%) each. Massachusetts was the state with the highest number of enrolled IMGs. On average, IMGs had 26.3 publications and joined US orthopedic residency 4.66 years following medical school graduation.

**CONCLUSION:** Despite the many hurdles experienced by IMGs, a decent number succeeds in matching into US orthopedic residency programs each year.

**KEYWORDS:** international medical graduate; residency training; orthopedics; geographic distribution; IMG

## INTRODUCTION

International medical graduates (IMGs), or physicians who obtained their medical degrees from countries other than the United States (US), account for 25% of the physician workforce in the US.[1] Over the past several decades, IMGs have played a pivotal role in US healthcare, especially in poor rural areas that are underserved with regards to medical and surgical services and providers.[2] IMGs have shown an increasing interest in seeking to pursue residency training in the US, mainly due to the prestigious reputation of US residency training worldwide, the greater potential to pursue scientific and academic endeavors, and the better living conditions when compared to other developing parts of the world.[3,4] In 2020, the National Residency Matching Program (NRMP) statistics reported that approximately 2580 IMGs (61.1% of IMG applicants) matched into first year residency positions – the highest match rate for IMGs since 1990.[5]

Orthopedic surgery is one of the most competitive specialties in the US, for both IMGs and graduates of US medical schools.[6] In general, applicants seeking to pursue orthopedic residency are expected to have attained high USMLE scores, demonstrated good research productivity, and/or achieved multiple accolades in order to match into their first-choice orthopedic program.[3,7,8] Matching into orthopedic surgery as an IMG is considered a rare and difficult feat, considering the high academic requirements of the competitive specialty, and the burdensome logistic hurdles imposed by being a graduate from a foreign medical school.[3,7-9]

Exploring the characteristics and geographic distribution of IMGs who matched into orthopedic residency programs may provide valuable insight into the prospects of matching in such a competitive specialty in the US. Accordingly, the purpose of this study is to evaluate publicly available data pertaining to IMG residents in US orthopedic residency programs and describe the demographic, academic and geographic qualities of matched IMGs.

## METHODS

In January 2023 we accessed publicly available data on all orthopedic surgery residency programs accredited by the Accreditation Council for Graduate Medical Education (ACGME) and listed in the American Medical Association (AMA) FREIDA™ residency programs database from 2018 to 2022.[10] Only programs that had information on current residents readily available to the public were included. The individual residency program websites with current data were reviewed to obtain a list of current orthopedic surgery residents; IMGs were identified by analyzing the data available on the residents' profiles. An IMG was defined as any resident who had obtained their medical degree (MD, MD-PhD, MBBS, etc.) from a medical school located outside of the United States.

Data on identified IMGs in orthopedic residency programs was recorded, and this included the size and location of their current US orthopedic residency program, their year of training, the countries from which they received their medical degrees, and the geographic region of their medical schools. A PubMed search was conducted to determine the number

of articles published by IMGs prior to the start of their residency training. We included all articles published up until the year prior to the start of residency training. For example, if an IMG matched in 2021, we included all published articles up until the end of 2020. In addition, we searched the Doximity and LinkedIn accounts of identified IMGs in order to screen whether they attained postgraduate degrees (Doctorate of Philosophy (PhD) or Master's degrees) prior to their enrollment into a US orthopedic residency program.[11,12] We also reported the year of their medical school graduation, and calculated the time difference between their graduation and their acceptance into orthopedic residency in the US.

Statistical analyses were performed using Statistical Package for the Social Sciences for Windows software version 25.0 (IBM SPSS, 2017). Categorical variables were expressed as percentages, and continuous variables were expressed as means, ranges and standard deviations. Significant differences between geographic regions were evaluated using the One-Way analysis of Variance (ANOVA) test. In case of ANOVA significance, Tukey's Multiple Comparison Test was performed to show significant differences among different groups. P values < 0.05 were used to declare significance for all analyses.

**Table 1.** Distribution of international medical graduates (IMGs) in 167 US orthopedic residency programs by postgraduate year (PGY) of training, 2018–2022

| PGY Year | PGY-1 | PGY-2 | PGY-3 | PGY-4 | PGY-5 |
|---|---|---|---|---|---|
| Total number of residents | 785 | 780 | 773 | 768 | 776 |
| Number of IMGs | 12 | 5 | 9 | 8 | 10 |
| Percentage of IMGs from total number of residents | 1.53 | 0.64 | 1.16 | 1.04 | 1.29 |

**Table 2.** Distribution of international medical graduates (IMGs) in 167 US orthopedic residency programs according to the regions of their medical schools. (p=0.73)

| Region | Number of IMGs | Percentage (%) |
|---|---|---|
| Asia | 6 | 13.6 |
| Europe | 13 | 29.5 |
| Middle East | 11 | 25.0 |
| Central America/Caribbean | 8 | 18.2 |
| Oceania | 1 | 2.3 |
| South America | 5 | 11.4 |
| Total | 44 | 100 |

## RESULTS

A total of 167 programs (80.3%) out of 208 orthopedic residency programs were included in our study. These programs had a total of 3838 residents, of which 44 (1.15%) were identified as IMGs. The percentage of IMG residents by year was similar throughout the study period, ranging between 0.64% in 2021 and 1.53% in 2022. **Table 1** presents the distribution of IMGs across US orthopedic residency programs by year of training.

IMGs obtained their medical degrees from 22 different countries, with Ireland and the United Kingdom having the highest number with four matched IMGs each over the course of the study period. (**Figure 1**) When categorizing the production of matched IMGs by region, Europe produced the highest percentage of enrolled IMGs with 13 IMGs (29.5%), followed by the Middle East with 11 IMGs (25%) **(Table 2)**. When comparing the number of produced IMGs between different geographic regions, no statistically significant differences were found ( p=0.73).

IMGs enrolled in US orthopedic residency programs were distributed across 16 different US states. Massachusetts had the highest number of enrolled IMGs with eight, followed by Ohio and New York with five each. (**Figure 2**) Massachusetts also had the highest percentage of IMGs, with 6.3% of all orthopedic residents being IMGs, followed by Missouri and North Carolina at 3.4% each. (**Figure 3**) (*Note: Email corresponding author for Figures.*)

The average matched IMG had a total of 26.3+/–32.86 (median = 11.5 articles) published articles on PubMed, with a range from zero to 142. On average, IMGs had a 4.66 (+/–3.78) years gap following their medical school graduation and prior to enrolling into US orthopedic surgery programs, with a range between 0 and 17 years. Information on medical school graduation and additional degrees was available for 36 out of the 44 included IMGs (n=36). Eight IMGs (22.2%) were reported to have attained nine postgraduate degrees at the time of their enrollment into orthopedic residency: four had PhDs, three had Master's degrees, and one IMG had both a PhD and a Master's degree.

## DISCUSSION

Our study showed that IMGs constitute a very small percentage of the total cohort of orthopedic residents in the US. The United Kingdom and Ireland were the countries with the highest numbers of matched IMGs. Eastern states had a higher probability of enrolling IMGs than Western states. On average, enrolled IMGs had around 26 publications (median= 11.5 publications), and joined US orthopedic residency around five years following medical graduation.

A very small portion of US orthopedic residency positions is occupied by IMGs. That is expected given that every country has a particular interest in and obligation to train its citizens, who are more likely to stay and practice there when compared to foreigners. In addition, many program directors may have concerns regarding the logistic implications of enrolling IMGs, who may require visa sponsorships with obligatory renewal hindrances and time duration limits.[13,14] This adds complexities and stress to both IMGs and

residency program directors alike, especially when considering IMGs hailing from politically unstable countries, in which visa renewal may be delayed or terminated due to international diplomatic disputes.[13,14] Challenges for IMGs in more competitive specialties have been documented. One study by Moore et al explored the perceptions of general surgery residency program directions towards accepting IMGs and reported that 20% felt pressured to rank American medical graduates over IMGs, even when the IMGs were more qualified.[15] Regardless, American residency programs remain highly attractive to IMGs due to their excellent reputation in surgical training worldwide, and the vast opportunities provided for research-oriented physicians.

Europe was the region with the highest number of matched IMGs in our study. In particular, the United Kingdom and Ireland were the countries with the highest number of IMGs. Several factors may explain this finding. Numerous research partnerships exist between European countries and the US, and research collaborators may wish to obtain surgical training in the US.[16-18] Orthopedic surgical training in the US is generally shorter than that of European countries, and mean attending physician salaries in the US are higher than those in European countries.[19,20] The majority of IMGs in our study matched in states on the East Coast. Khachfe et al suggested that the geographical proximity of the East Coast to Europe, the Caribbean and South America may play a role in attracting IMGs from those regions.[3] In addition, IMGs are often attracted to metropolitan areas where social and cultural diversity is embraced and institutions that show higher levels of acceptance towards physicians from different backgrounds.[21] Other factors that may explain this finding include presence of international faculty, and availability of visa sponsorship.[3]

Orthopedic surgery is one of the most competitive specialties to match in in the US. Being an IMG introduces additional hurdles that the applicant must overcome in order to secure a training position.[13,14] As a matter of fact, the percentage of IMGs in orthopedic residency programs found in our study is much lower than that of other competitive specialties like general surgery (9%) and neurosurgery (6%).[3,8] These applicants often have to work very hard and build impressive research portfolios in order to strengthen their applications and improve their chances of matching. As such, many IMGs spend years after medical school in pursuit of other academic degrees or postdoctoral research experience in order to improve their chances of matching in a US orthopedic residency program. Some IMGs also opt to complete orthopedic residency training in their home country, before reapplying for training in the US. This contributes to the average IMG having a total of 26 published articles, and eight out of 36 IMGs in our study having at least one additional graduate degree (Master's degree or PhD) at the time of matching. This also explains why the average IMG matched at around five years following their medical school graduation, with some IMGs matching more than 15 years later.

IMGs are a critical source of health care in the US. Despite the hurdles they must overcome to successfully match into US residency programs, an inspiring number succeed in matching into orthopedic residency programs each year.[22] Many of these IMGs often come from challenging backgrounds in their home countries, and excel in their medical school and research endeavors in order to train in the US.[4,9,13,15,23] They add value to the US postgraduate education system and help instill a sense of cultural diversification into the healthcare force.[23] Many of these IMGs stay in the US following their training and serve the American population, while others return to their home countries and act as ambassadors of the US training system abroad. As such, accepting outstanding IMGs into orthopedic residency programs is a helpful and beneficial endeavor to both the US and the world, and is a testament to the prestige of US orthopedic residency training.

To our knowledge, this is the first study to explore the distribution of IMGs among US orthopedic residency programs and analyze the academic characteristics of these applicants. Nevertheless, several limitations exist. Our cross-sectional study included the 2018–2022 cohort of orthopedic residents, and distribution may have differed in previous years. In addition, not all residency program public websites included data on their residents and not all identified IMGs had public LinkedIn or Doximity accounts. As a result, not all programs and IMGs were included in our analyses. Nevertheless, we were able to include a high percentage of the orthopedic residency programs and retrieve information on the majority of included IMGs. Finally, as it was not possible to comprehensively explore the characteristics of all orthopedic residents in US orthopedic residency programs, we were not able to provide quantitative comparisons between US medical graduates and IMGs.

## CONCLUSION

IMGs constitute a small but important portion of orthopedic residents in the US. Europe has contributed the highest number of matched IMGs in orthopedics in recent years, with the United Kingdom and Ireland being the highest contributing countries. States like Massachusetts, Ohio, and New York enrolled the highest number of IMGs in the US. The average IMG matched into a US orthopedic residency program approximately five years following their medical graduation, with many having at least one graduate degree prior to matching.

Encouraging increased openness towards accepting outstanding IMGs into orthopedic residency programs will increases the cultural diversity within the US health force, attract surgical and research talent from different parts of the world, and serve to empower the role of the US as a beacon of surgical education and training worldwide.

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# Pushing for IV Push Medications: Cost-Effectiveness Model of Switching from IV Piggyback to IV Push for Frequently Used Emergency Department Medications

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**ABSTRACT**

In considering the potential to reduce the carbon footprint of our emergency department (ED) via decreasing plastic waste, we aimed to evaluate the effects of changing certain common emergency department medications from an intravenous (IV) piggyback administration route to IV push. Our team queried hospital pharmacy data to determine the number of doses of several frequently utilized antibiotics administered over a six-month time period, then calculated the resultant cost savings of a switch to IV push. Based upon our modeling calculations, switching certain medication administration routes to IVP can have significant impacts on cost, with an estimated cost savings of about $47,000 every six months. Maximizing the use of push administration could result in even more dramatic cost savings. In some scenarios, using IVP administration results in less than half the amount of plastic waste generated. Future research including a full life-cycle analysis is needed in order to precisely determine the impact on carbon footprint created by making this change.

**KEYWORDS:** IV piggyback; IV push; cost; antibiotics; sustainability

## BACKGROUND

Waste reduction in healthcare is critically important for two reasons: it is beneficial for the environment, and it can result in significant cost savings. According to a report on waste in the United States healthcare system, an estimated $75.7 to $101.2 billion is spent annually in the U.S. on "overtreatment or low-value care."[1]

One way to curb costs associated with waste is through addressing excess use of premixed bags or "piggybacks" (IVPB) for medication administration, rather than using vials of medications which can be reconstituted and pushed via syringe. Several frequently used emergency department medications, including common antibiotics, are often "piggybacked" when they could be administered via intravenous push (IVP), saving time and money, and potentially, reducing the amount of plastic waste.

Giving medications via the "piggyback" route requires resources, including a primary and a secondary set of tubing, a plastic bag of IV fluid for the primary line, a plastic bag of medications "piggybacked" onto the primary line, and often, an infusion pump to control the flow rate. IV push administration involves injecting the medication directly into the IV line, utilizing only a needle and syringe to withdraw and inject the diluent for reconstitution and subsequently withdraw the required dose of medication. Full life-cycle analysis research to determine the precise quantity of carbon savings has not been published; however, comparing the weights of all the materials involved in each process, IVP administration involves a much smaller weight of plastic waste, and less waste by weight overall compared to IVPB when considering the need for two separate sets of tubing and bags. The IVP route has been shown to decrease time to administration of critical medications – for example, patients are more likely to receive broad-spectrum antibiotics for sepsis within 60 minutes of arrival to the ED when administered IVP versus IVPB.[2] This benefit of decreased time to administration has been shown in multiple studies across settings from the ED to the OR and ICU.[3,4,5] Switching to IVP has also been associated with cost savings and is reportedly preferred by nursing staff in sites that have made the change.[6] Additionally, prior studies have demonstrated that the IV tubing is often not flushed after administering a medication as IVPB, resulting in up to 20% of the medication remaining in the tubing instead of reaching the patient.[7] The steps involved in the processes of IVPB administration versus IVP are outlined in **Table 1**. **Images 1** and **2** illustrate the waste utilized in each approach, and **Table 2** details the weights of the materials for comparison.

Levetiracetam has been highlighted in recent studies as a drug frequently given by IVPB but that can also be safely administered by IVP.[8] In the authors' hospital system in Rhode Island, a recent change to IVP administration of levetiracetam has resulted in significant realized cost savings.

In order to pursue a goal of reductions in medical waste and CO2 equivalents, as well as cost savings, the research team created a proposal and plan to implement the use of IV push medications as a standard for administration of several other commonly used medications and modeled potential results.

**Table 1.** Comparison of Processes for IVP Administration Versus IV Push

| IV Push Administration | IV Piggyback Administration |
|---|---|
| Collect vial and saline flush | Collect premixed bag, secondary tubing, and saline flush |
| Reconstitute medication: inject diluent into vial and shake until dissolved | Optional: locate and collect infusion pump |
| Draw up reconstituted medication into syringe | Spike premixed bag on secondary tubing |
| Scrub the end of the IV line port with alcohol pad | Scrub the end of the IV line port with alcohol pad |
| Saline flush IV line | Saline flush IV line |
| Attach the antibiotic syringe and push the IV medication over 3 to 5 minutes, or as directed | Attach secondary tubing to primary IV line and hang bag |
| After push is complete, disconnect syringe | Optional: set up infusion pump for desired rate, attach to line |
| Saline flush IV line | When infusion is complete, disconnect tubing/pump |
| | Saline flush IV line |

**Image 1.** Supplies for IVP Medication Administration

**Image 2.** Supplies for IVPB Medication Administration

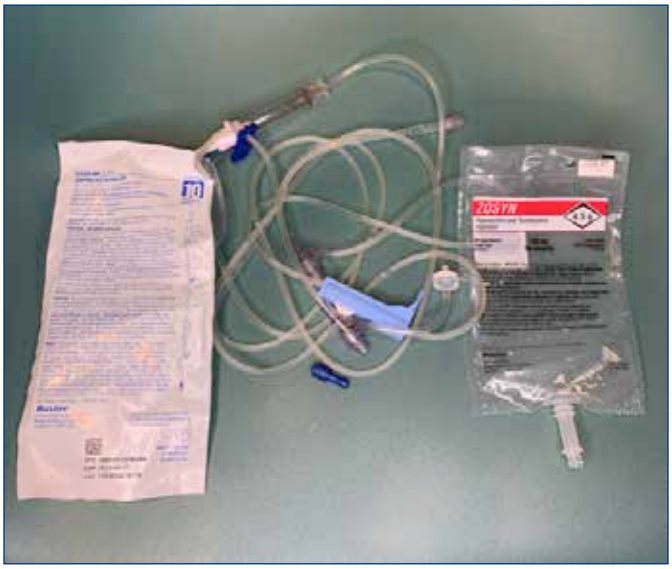


**Table 2.** Weight of Waste for Unique Products Used in IVP Versus IVPB Routes

| | |
|---|---|
| All unique products used in IVP route | 63 grams |
| Uncapped, empty glass vial weight | 37 grams |
| Weight of plastic waste used in IVP route | 26 grams |
| All unique products used in IVPB route | 60 grams |
| IV tubing and accessories for primary line, plus liter bag to run primary line | 52 grams |
| Weight of plastic waste used in IVPB route, total including primary line | 112 grams |

## METHODS

We began by researching the logistics of changing over to primary use of vials for targeted medication, including costs, and creating educational materials such as electronic presentation slides, letters and flyers to promote awareness about the project. The data from the ED medication orders were queried for number of doses given over the six months from January 1, 2023 to June 30, 2023, of a number of commonly used medications that are administered by IVPB but could be given by IVP (**Table 3**).

### Cost Analysis

Reviewing this list of medications which could be administered by the IVP route, we decided to further evaluate the administration of antibiotics commonly used in the ED and model the potential results of switching routes from IVPB to IVP with regards to the potential cost savings of the change. Further expansion of the program to maximize the usage of the IVP route whenever feasible would potentially result in significantly greater cost savings of almost $50,000 in a six-month period as seen in **Table 4**.

**Table 3.** Medications Amenable to IVP Administration Used in the RIH AED (Six-month Time Period)

| Medication Name | Doses (6 mo) | IV Piggyback (IVPB) Details | IV Push (IVP) Details |
|---|---|---|---|
| Ceftriaxone | 1935 | 1 Gram/50 Ml In Dextrose (Iso-Osmotic) | 1 Gram Vial |
| Cefazolin | 983 | 2 Gram/50 Ml In D5W IV Wrapper | 1 Gram Vial |
| Cefepime | 725 | 2 Gram/100 Ml In Dextrose (Iso-Osmotic) | 2 Gram Vial |
| Ceftriaxone | 682 | 2 Gram/50 Ml In Dextrose (Iso-Osmotic) | 1 Gram Vial |
| Cefepime | 320 | 1 Gram/50 Ml In Dextrose (Iso-Osmotic) | 1 Gram Vial |
| Cefazolin | 168 | 1 Gram/50 Ml In Dextrose (Iso-Osmotic) | 1 Gram Vial |
| Meropenem | 139 | 1 Gram/50 Ml In 0.9% Sodium Chloride | 1 Gram Vial |

*Pricing current as of September 2023

**Table 4.** Estimated Cost Savings of Transition from IVPB to IVPB Administration (Six-month Time Period)

| Medication Name | IVPB Per Dose Cost | IVPB Total Cost | IVP Per Dose Cost | IVP Total Cost | Savings Per Unit (IVPB → IVP) | Total Savings Per Medication |
|---|---|---|---|---|---|---|
| Ceftriaxone | $10.04 | $19,427.40 | $1.20 | $4,644.00 | -$7.64 | -$14,783.40 |
| Cefazolin | $9.64 | $9,476.12 | $0.66 | $1,297.56 | -$8.32 | -$8,178.56 |
| Cefepime | $15.43 | $11,186.75 | $4.31 | $3,124.75 | -$11.12 | -$8,062.00 |
| Ceftriaxone | $19.43 | $13,251.26 | $1.20 | $1,636.80 | -$17.03 | -$11,614.46 |
| Cefepime | $9.91 | $3,171.20 | $2.30 | $736.00 | -$7.61 | -$2,435.20 |
| Cefazolin | $3.80 | $638.40 | $0.66 | $110.88 | -$3.14 | -$527.52 |
| Meropenem | $14.53 | $2,019.67 | $4.18 | $581.02 | -$10.35 | -$1,438.65 |
| | | | **Average Savings Per Unit** | | **-$9.32** | |
| | | | **Total Savings** | | | **-$47,039.79** |

## DISCUSSION

In conducting this analysis of two potential administration routes for certain IV medications, our main goal was to clarify the effects that shifts between these routes in clinical practice might have on the generation of plastic waste and overall carbon footprint. A full life-cycle analysis would include evaluation of the materials used in each administration route, from materials extraction to manufacture and distribution, through use, and disposal. Further study will be needed to conduct these holistic studies of the impacts of these processes; however, in simply comparing the weight of plastic waste generated through each process, IVPB generates four times as much plastic weight when accounting for the fact that a primary line running a bag of IV fluids is obligatory with this process. It should be noted that the glass vial used in IVP is not recyclable currently as it is treated as hazardous waste, and that its weight means that shipping these products has a larger carbon footprint. If solely considering the unique materials used for each process in total, both plastic and glass, the materials for IVP weighed 63 grams to IVPB's 60 grams.

While the environmental effects are more complicated to consider, our modeling calculations did predict a significant cost savings by adoption of the use of IVP route administration for certain antibiotics that are commonly used in the ED, and prior studies cited above have described potential benefits of pushing certain medications or in certain scenarios with regard to patient outcomes. However, logistical challenges are inevitable for any program aiming to make a process change, such as gaining widespread support from staff for the change and buy-in from all members of the team. To help promote the benefits of IVP route use, we planned an educational campaign to share potential improvements that could affect patients, such as faster time to administration of antibiotics for patients with sepsis, ensuring medication doses are fully administered, and elimination of the need to find a medication pump to use.

As the cost savings is realized only by the institution and not by staff members themselves, we hoped to incentivize making the change by creating a campaign in which successful implementation of the process change would result in tangible rewards to staff members, such as by providing new amenities in the staff break room, ordering out food for staff on each shift, or providing small gift certificates to the cafeteria. We met with the departmental nurse educator and other members of nursing staff to discuss the project. Potential barriers to the transition to IVP presented by our nursing colleagues included concern that the process of preparing a dose for IVP administration may take longer than the process of preparation for IVPB, as well as concern that medications requiring a prolonged IVP administration time (five minutes or longer) may remove the nurse from their other patient care responsibilities for too long. Nursing staff did agree that searching for a pump to use with IVPB use can be frustrating and time consuming and would be a potential benefit of transitioning to IVP administration. Our team aims to continue to address these potential barriers as we work to develop our IVP medication administration process. Prior studies involving similar projects in other EDs suggested nursing had a positive reaction to the changes after the implementation was complete.[3]

While researching the process for adopting this change, we learned of several other issues that could arise. For example, our automated dispensing cabinets for the ED are currently

stocked with premixed preparations of these medications for IVPB administration. In order for the automated dispensing cabinet to know to dispense a vial preparation for IVP, the order placed in the electronic medical record (EMR) would need to reflect the vial preparation. Currently, our institution's standardized electronic orders for these antibiotics default to the premixed bag preparations; therefore, changes will need to be made to the standardized orders prior to transitioning to IVP administration. The information technology (IT) specialists we consulted regarding making the change recommended making IVP administration the exclusive order available for ED use in order to ensure the correct product is dispensed from the automated dispensing cabinets for IVP administration. Other institutions could choose to approach this differently; however, at our institution, this was recommended due to the above outlined constraints in our electronic ordering process. IT recommendations also included ensuring the order was changed in all ED quicklists and preference lists in order to allow seamless transition to the new route of administration, which would be done via a service request for the EMR.

## CONCLUSION

Reduction of waste is an important goal for environmental and cost efficiency reasons. Switching the route of administration of commonly used medication can save money, decrease time to administration, and potentially reduce the plastic waste created by the department. Future studies are planned to clarify the full impact of the use of common ED materials on the department's carbon footprint. Promoting the simple use of IVP medication administration, when appropriate, for certain antibiotics, based on our modeling calculations could result in a significant projected resultant cost savings for our department of close to $100,000 annually.

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# An Analysis of the Number of Patients Screened, Approached and Enrolled in Randomized Controlled Trials

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## OBJECTIVE

A randomized controlled trial (RCT) is the gold-standard study design to assess if there is a causal relationship between an intervention and an outcome. It is critical for RCTs to be representative of the study population for there to be external validity. The generalizability of several recent RCTs have been questioned due to a high ratio of participants assessed for eligibility compared to those ultimately enrolled in the RCTs.[1,2] While the challenges for recruiting patients for RCTs are established, it has been proposed that a high ratio of assessed to enrolled patients results in a study population that is not truly representative.[3,4] This study seeks to investigate the assessed-to-enrolled participant ratios in RCTs and determine whether this is impacted by the nature of the primary outcome of the study.

## METHODS

During a one-year period (January 2021–December 2021), we identified all RCTs published in three journals (*NEJM, JAMA, Lancet*). The journals were manually reviewed by two co-authors (AA, KD) to ensure all RCTs were identified and abstracted accurately. Reported patient recruitment data, per CONSORT recommendations, was abstracted from each RCT.[5] For secondary outcomes, the purpose of the trial was categorized as preventative or therapeutic, and those classified as therapeutic RCTs were sub-categorized as a procedural versus non-procedural intervention. Medians were compared using Wilcoxon-rank sum testing and P <0.05 was considered significant.

**Table 1.** Recruitment Differences by Objective of Primary Outcome

| | Prevention as primary outcome (N= 43) | Therapy as primary outcome (N= 141) | P |
|---|---|---|---|
| Median # assessed | **9624 (1591–28768)** | **771 (445–1931)** | **<0.01** |
| Median # Eligible | **3402 (708–10656)** | **503 (269–1019)** | **<0.01** |
| Median # declined | **148 ( –458)** | **16.5 (1–89)** | **<0.01** |
| Median # Randomized | **2883 (676–10218)** | **411 (240–749)** | **<0.01** |
| # of Studies that did not meet enrollment target (Total Randomized < Sample Needed) – N (%) | **15 (34.9)** | **16 (11.4)** | **<0.01** |
| Median # Lost to follow-up | **122 (28–444)** | **33 ( –87)** | **<0.01** |
| Median # Withdrew | 11.5 (0–33) | 7 (1–23) | 0.63 |

Data presented as N (%) or median (interquartile)
**Bolded** if significantly different

**Table 2.** Recruitment Differences By Intervention

| | Procedural Intervention (N= 41) | Nonprocedural (N= 137) | P |
|---|---|---|---|
| Median # assessed | **1093.5 (562–3496)** | **931 (363–5534)** | **0.04** |
| Median # Eligible | 689 (374–1780) | 421 (173–1182) | 0.87 |
| Median # declined | 22.5 (2–148) | 37 (1–186) | 0.70 |
| Median # Randomized | **583 (320–1251)** | **377 (163–1106)** | **0.02** |
| # of Studies that did not meet enrollment target (Total Randomized < Sample Needed) – N (%) | 24 (17.5) | 7 (17.1) | 0.95 |
| Median # Lost to follow-up | **48 (13–135)** | **22 (5–57)** | **<0.01** |
| Median # Withdrew | **9 (1–27)** | **2 (0–8)** | **<0.01** |

Data presented as N (%) or median (interquartile)
**Bolded** if significantly different

## RESULTS

Of 611 original research studies, 265 RCTs were identified. Of these,184 (69.4%) reported data on the number of individuals screened and recruited; 31 trials (16.9%) failed to reach their patient recruitment target.

The median number of individuals screened per preventative trial was 9,624, of which 3402 (35.3%) were eligible and 148 were randomized (1.53%). For trials with a therapeutic intervention, the median number of individuals screened was 771, of which 503 (66.5%) were eligible and 16.5 (3.28%) were randomized. Of note, significantly more studies did not meet their enrollment target in the therapeutic group compared to the prevention trial group (11.4% vs. 34.9%, p <.01). (See **Table 1.**)

The median number screened for procedural interventions was 1,093 participants, of which 689 (63.0%) were eligible and 22.5 (2.06%) were randomized. For non-procedural interventions, a median number of 931 individuals were screened, of which 421 (45.2%) were eligible and 37 (3.97%) were randomized. (See **Table 2.**)

## CONCLUSION

This study demonstrates that a significantly higher number of individuals are screened for preventative trials compared to therapeutic trials. However, a greater proportion of screened individuals are eligible and subsequently enrolled in the trials that studied a therapy as the primary outcome. These results are encouraging that individuals are willing to participate in experimental trials for novel interventions. A trial that requires many patients to be screened to extract a sample size may not be as applicable and generalizable as a condition that is more prevalent and inclusion criteria that are less stringent. As such, these results may also call into question the generalizability of RCTs assessing prevention measures as their primary outcome, given the relatively high screened-to-enrolled ratios in that group. Further research is warranted to determine best practices to recruit and enroll participants in such trials to maximize the external validity of their results.

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# Prescription Drug Exposure Among Pregnant Individuals in Rhode Island, 2019–2022

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## INTRODUCTION

Since the 1990s, the United States has faced a rise in opioid overdose deaths, which began as an increase in deaths involving prescription opioids. In Rhode Island (RI), accidental drug overdose deaths have risen nearly 42% from 2019 to 2022.[1] As of 2021, RI ranks 15th for the highest drug overdose death rate in the nation, with 41.7 deaths per 100,000 people.[2] In response to the opioid overdose epidemic, in 2012, RI implemented the Prescription Drug Monitoring Program (PDMP). The PDMP collects data on all controlled substances dispensed by retail pharmacies in RI or to RI residents and receives prescription information from 34 other states (including all neighboring New England states). This helps to identify high-risk prescribing activity and diversion, as well as prescribing risks associated with individual patients, and promotes patient education.

Studies suggest that prenatal use of opioids and benzodiazepines are linked to possible adverse outcomes and birth defects.[3] Healthcare professionals can monitor pregnant individuals taking these prescriptions for maternal and infant health outcomes. Additionally, the Centers for Disease Control and Prevention (CDC) suggest buprenorphine as a safe, first-line therapy option for pregnant individuals with opioid use disorder (OUD).[4]

In pregnancy, the use of prescriptions opioids to manage pain, benzodiazepines to manage mental health conditions, and buprenorphine or methadone to manage OUD may be warranted as part of a comprehensive approach to managing the biopsychosocial health and well-being of the pregnant individual. Although adverse outcomes of prenatal exposure may include but are not limited to neonatal abstinence syndrome (NAS), neonatal opioid withdrawal syndrome (NOWS), low-birth weight, and preterm birth, the risk involved with their use versus potential benefits to the pregnant individual should be discussed by the patient and their healthcare professional. Specifically, treating with buprenorphine or methadone is the standard of care for OUD in pregnancy and has been associated with improved maternal, infant, and birth outcomes.

To better understand the magnitude of prenatal prescription medication dispensations in RI, we aim to analyze the prevalence of in-utero exposure to prescription opioid analgesics, benzodiazepine, and buprenorphine medication for opioid use disorder (MOUD).

## METHODS

We utilized birth certificate data from the Rhode Island Department of Health's (RIDOH) Center for Vital Records to identify live births occurring between 2019 and 2022 to RI residents with births occurring in RI and out-of-state. The conception date was calculated by subtracting the number of weeks of gestational age by obstetrical estimate from the infant's birth date.

PDMP data and birth certificate data were linked using both deterministic and probabilistic techniques via SAS Version 9.4 (SAS Institute, Cary, NC). The birthing parent's birth date, along with first, last, and maiden names (if applicable) were used to capture any opioid analgesics, benzodiazepine, or buprenorphine MOUD prescriptions (excludes Butrans™, Belbuca™, and Buprenex™ formulations, and generic equivalents) during each pregnancy, which was defined as a dispensed prescription on or after the conception date and before the infant's birth date.

For all descriptive analyses, 'no prescription involvement' was defined as the absence of any opioid analgesic, benzodiazepine, or buprenorphine MOUD prescription dispensed during pregnancy. For pregnancies with any involvement with these substances of interest, involvement was further examined by trimester, which was defined as follows: 1st trimester (conception date through 13 weeks); 2nd trimester (13 weeks to 26 weeks); and 3rd trimester (26 weeks through end of pregnancy).

Birthing parent demographic information was obtained from self-reported birth certificate data, and included maternal age, highest education level, maternal race and ethnicity, insurance type at delivery, marital status, and city/town of residence, which was further defined as 'Core City' or 'Rest of State' ('None-Core'). A core city was defined as a RI municipality with 25% or more children living below the poverty threshold and includes Central Falls, Pawtucket, Providence, and Woonsocket. Combined maternal race and ethnicity categories were defined as: Hispanic (all races), non-Hispanic White, non-Hispanic Black or African American, Other/Unknown (included non-Hispanic Multiple Race). Insurance categories were defined as: Private, Public and Other/Unknown (included "Self-Pay" and "No Insurance").

## RESULTS

There were 40,955 RI resident births from 2019-2022, and 2,189 (5%) matched to PDMP opioid analgesic, benzodiazepine, and/or buprenorphine MOUD records (**Table 1a**). The proportions of birthing individuals dispensed an opioid analgesic, benzodiazepine, and buprenorphine MOUD have decreased from 2019 to 2022. The proportion of pregnant individuals dispensed opioid analgesics decreased 31% from 2.9% in 2019 to 2.0% in 2022 and benzodiazepines decreased 7.7% from 2.6% in 2019 to 2.4% in 2022 (**Figure 1**).

Overall, 5.3% of pregnancies involved an opioid analgesic, benzodiazepine, or buprenorphine MOUD prescription (**Table 1a**). Of these, 46.2% involved an opioid analgesic prescription, 51.7% involved a benzodiazepine prescription, and 8.5% involved a buprenorphine MOUD prescription. About 44% of births with no prescription involvement and 46% of births that involved opioid analgesics had a birthing parent younger than 30 years old. Contrastingly, 28% of births involving benzodiazepine prescriptions, and 33% of births involving buprenorphine MOUD had a birthing parent younger than 30 years old. Greater than 70% of births involving buprenorphine MOUD and/or benzodiazepine prescriptions were to White, non-Hispanic birthing parents, whereas greater than 65% of births involving opioid analgesics, or having no prescription involvement had White, non-Hispanic birthing parents (**Table 1a**). Greater than 70% buprenorphine MOUD and/or benzodiazepine-involved births were to birthing parents residing in a non-core city (**Table 1b**). Of births involving an opioid analgesic, benzodiazepine, and/or buprenorphine MOUD, 52% had public insurance compared to 45% of births with no prescription involvement. Of benzodiazepine-involved births, nearly 71% had a birthing parent with greater than a 12th grade education. Contrastingly, 43% of births involving buprenorphine MOUD had a birthing parent with an education greater than high school. Of births involving these substances, 54% of birthing parents were single compared to 43% birthing parents with no prescription involvement (**Table 1b**). For benzodiazepine-involved births, 71% filled their prescriptions during the first trimester, and 19% filled prescriptions during all three trimesters (**Table 2**).

**Figure 1.** Percent of birthing individuals dispensed controlled substances during pregnancy in Rhode Island, 2019–2022.

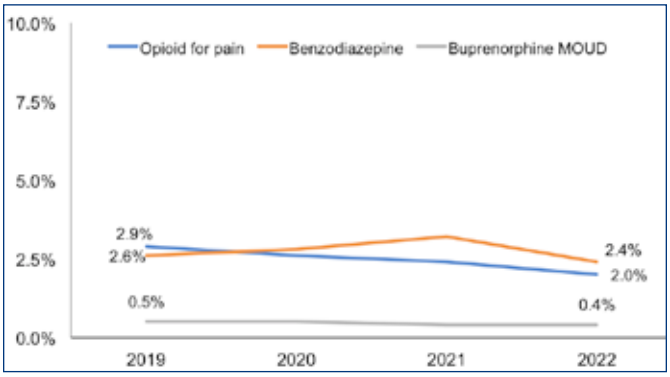


**Table 1a.** Maternal demographics by prescription involvement in Rhode Island, 2019–2022

| | No Prescription Involvement N (%) | Any Opioid, Benzodiazepine, and/or Buprenorphine MOUD involvement during pregnancy N (%) | Opioid Involvement N (%) | Benzodiazepine Involvement N (%) | Buprenorphine MOUD Involvement N (%) |
|---|---|---|---|---|---|
| Total | 38,766 (94.7%) | 2,189 (5.3%) | 1,012 (46.2%) | 1,132 (51.7%) | 183 (8.4%) |
| **Maternal Age** | | | | | |
| <25 | 6,778 (17.5%) | 246 (11.2%) | 166 (16.4%) | 80 (7.1%) | 14 (7.7%)[c] |
| 25–29 | 10,252 (26.5%) | 543 (24.8%) | 300 (29.6%) | 236 (20.9%) | 46 (25.1%) |
| 30–34 | 13,119 (33.4%) | 767 (35.0%) | 292 (28.9%) | 452 (39.9%) | 62 (33.9%) |
| 35–39 | 6,926 (17.9%) | 492 (22.5%) | 198 (19.6%) | 283 (25.0%) | 45 (24.6%) |
| 40+ | 1666 (4.3%) | 140 (6.4%) | 55 (5.4%) | 81 (7.2%) | 16 (8.7%)[b] |
| **Maternal Race/Ethnicity** | | | | | |
| Hispanic | 11,307(29.2%) | 367 (16.8%) | 244 (24.1%) | 123 (10.9%) | 17 (9.3%)[b] |
| Non-Hispanic White | 19,368 (50.0%) | 1,412 (64.5%) | 526 (52.0%) | 839 (74.1%) | 141 (77.1%) |
| Non-Hispanic Black | 2,771 (7.2%) | 126 (5.8%) | 90 (8.9%) | 41 (3.6%) | <5[a] |
| Non-Hispanic | 2,318 (6.0%) | 159 (7.3%) | 79 (7.8%) | 78 (6.9%) | 14 (7.7%)[b] |
| Other/Unknown | 2,875 (7.4%) | 113 (5.16%) | 67 (6.6%) | 41 (3.6%) | 10 (5.5%)[c] |

**a** Counts for sensitive information less than 5 are suppressed according to the RIDOH's Small Numbers Policy
**b** Per RIDOH's Small Numbers Policy, estimates in this group are statistically unstable (Relative standard error between 20% and 30%) and need to be interpreted with caution.
**c** Per RIDOH's Small Numbers Policy, estimates in this group are not statistically unstable (Relative standard error greater than 30%) and percentages will not be reported.

**Table 1b.** Maternal demographics by prescription involvement in Rhode Island, 2019–2022

| | No Prescription Involvement N (%) | Any Opioid, Benzodiazepine, and/or Buprenorphine MOUD involvement during pregnancy N (%) | Opioid Involvement N (%) | Benzodiazepine Involvement N (%) | Buprenorphine MOUD Involvement N (%) |
|---|---|---|---|---|---|
| **City/Town** | | | | | |
| Core City[a] | 15,333 (39.6%) | 671 (30.7%) | 399 (39.4%) | 263 (23.2%) | 54 (29.5%) |
| Rest of State (Non-Core) | 23,276 (60.1%) | 1,511 (69.0%) | 608 (60.1%) | 866 (76.5%) | 129 (70.5%) |
| **Insurance Type at Delivery** | | | | | |
| Private | 20,776 (53.6%) | 1,027 (46.9%) | 436 (43.1%) | 607 (53.6%) | 26 (14.2%) |
| Public | 17,489 (45.1%) | 1,138 (52.0%) | 569 (56.2%) | 506 (44.7%) | 157 (85.8%) |
| Unknown/Missing[c] | 502 (1.3%) | 24 (1.1%) | 7[b] | 19 (1.7%) | 0 (0.0%) |
| **Highest Education Level** | | | | | |
| Less than 12th Grade | 4,402 (11.4%) | 228 (10.4%) | 119 (11.8%) | 91 (8.0%) | 41 (22.4%) |
| 12th Grade | 7,801 (20.1%) | 500 (22.8%) | 269 (26.6%) | 208 (18.4%) | 53 (29.0%) |
| Greater than 12th Grade | 25,724 (66.4%) | 1,394 (63.7%) | 595 (58.8%) | 800 (70.7%) | 78 (42.6%) |
| **Marital Status** | | | | | |
| Single | 16,577 (42.8%) | 1,182 (54.0%) | 556 (54.9%) | 562 (49.7%) | 147 (80.3%) |
| Married | 21,989 (56.8%) | 991 (45.3%) | 449 (44.3%) | 565 (49.9%) | 31 (16.9%) |

**a** Core cities include Central Falls, Pawtucket, Providence, and Woonsocket. These are municipalities in Rhode Island that had 25% or more children living below the poverty threshold.
**b** Per RIDOH's Small Numbers Policy, estimates in this group are not statistically unstable (Relative standard error greater than 30%) and percentages will not be reported.
**c** Includes "Self-Pay" and "No Insurance".

**Table 2.** Maternal substance involvement by trimester in Rhode Island, 2019–2022

| Substance | Any Pregnancy Involvement | 1st Trimester N (%) | 2nd Trimester N (%) | 3rd Trimester N (%) | All 3 Trimesters N (%) |
|---|---|---|---|---|---|
| Opioid for pain | 1,012 | 383 (37.8%) | 380 (37.5%) | 383 (37.8%) | 32 (3.2%) |
| Benzodiazepine | 1,132 | 801 (70.8%) | 453 (40.0%) | 481 (42.5%) | 213 (18.8%) |
| Buprenorphine MOUD | 183 | 150 (82.0%) | 154 (84.2%) | 163 (89.1%) | 133 (72.7%) |

## DISCUSSION

Overall, the proportion of births involving prenatal use of opioid analgesic, benzodiazepines, and buprenorphine MOUD have all decreased since 2019. Since 2020, prenatal use of benzodiazepine is higher than opioid analgesics and buprenorphine MOUD. While maternal substance use is prevalent in RI, it is decreasing and below overall self-reported national levels.[5] Prenatal prescription opioid and benzodiazepine use mirrors trends in the overall population, with the number of pregnant individuals dispensed these prescriptions decreasing since 2017.[6]

Disparities exist within prenatal use of controlled substance prescriptions, as births involving benzodiazepine and buprenorphine MOUD tend to have birthing parents who are non-Hispanic White, non-core municipality residents, and older in age when compared to births with opioid analgesic involvement, and without controlled substance involvement. Benzodiazepine-involved births appeared to have birthing parents with an overall higher education level than other groups. Births involving buprenorphine MOUD had birthing parents with the lowest education level and a higher proportion of single birthing parents over any other exposure group. These results compare to studies suggesting that among the general population, non-White, lower-income patients are less likely to receive benzodiazepine and buprenorphine MOUD prescriptions when compared to their white counterparts.[7,8,9]

Despite the increase in buprenorphine MOUD in the general population, dispensation to pregnant individuals has decreased,[6] which may be due to several factors, including barriers to treatment including but not limited to access, stigma, or misinformation on the safety of buprenorphine use in pregnancy. As opposed to illicit opioid use or supervised/unsupervised withdrawal, buprenorphine during pregnancy is recommended to treat OUD by the Substance Abuse and Mental Health Services Administration (SAMHSA), American College of Obstetricians and Gynecologists (ACOG), and the CDC, as it engenders safe and monitored use of an opioid agonist for the pregnant individual and less severe NAS or NOWS symptoms in the neonate that can be monitored and appropriately treated.[4]

Prenatal benzodiazepine use is more common during the first trimester, when many expecting individuals may be unaware of their pregnancy. Benzodiazepine use decreases greatly in the second and third trimester, which is concerning given this may result in adverse mental health outcomes for the pregnant individual. The risks of discontinuing benzodiazepine use in pregnancy should be carefully weighed with the potential risks to the neonate, and decisions should be made in tandem between healthcare professionals and their patients. In contrast, prenatal increase in buprenorphine MOUD use each trimester may suggest similar conversations are occurring between prenatal and/or treatment providers and their pregnant patients.

Future analyses are planned to compare linkage findings with RIDOH's Substance Exposed Newborn (SEN) surveillance system to evaluate how well it captures prenatal prescription drug exposure. Additionally, MOUD maintenance among pregnant individuals and how it relates to neonatal and childhood health and developmental outcomes should be explored. Given RI's recent increase in stimulant use, studies should also examine the prevalence of prenatal stimulant involvement to determine if there are concerning trends. Future interventions should focus on underserved populations to increase MOUD access and provide education regarding appropriate maternal benzodiazepine use to decrease disparities in maternal mental health and substance use. Healthcare professionals should continue to discuss the risks and benefits of controlled substance medications with pregnant patients to choose an appropriate treatment plan that is in the best interest of both the patient and their baby.

## LIMITATIONS

Although the PDMP is a vital resource for prescription data in RI, it does not contain data on 1) substances prescribed and not dispensed; 2) if prescriptions were taken as prescribed; 3) unprescribed use of these substances; 4) inpatient prescriptions; 5) prescriptions dispensed to incarcerated individuals; or 6) MOUD dispensations from opioid treatment programs (OTPs). The analysis did not look specifically at how many prescriptions were dispensed or the total days during the trimester with prescription coverage to ascertain more detailed exposure information. Birth certificate data used in this analysis were self-reported, which may under- or over-estimate some characteristics.

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

| VITAL EVENTS | REPORTING PERIOD | | |
|---|---|---|---|
| | JUNE 2023 | 12 MONTHS ENDING WITH JUNE 2023 | |
| | Number | Number | Rates |
| Live Births | 996 | 11,029 | 10.4* |
| Deaths | 862 | 10,970 | 10.4* |
| Infant Deaths | 4 | 50 | 4.5# |
| Neonatal Deaths | 1 | 32 | 2.9# |
| Marriages | 795 | 6,849 | 6.5* |
| Divorces | 167 | 2,663 | 2.5* |

* Rates per 1,000 estimated population
# Rates per 1,000 live births

| Underlying Cause of Death Category | REPORTING PERIOD | | | |
|---|---|---|---|---|
| | DECEMBER 2022 | 12 MONTHS ENDING WITH DECEMBER 2022 | | |
| | Number (a) | Number (a) | Rates (b) | YPLL (c) |
| Diseases of the Heart | 230 | 2,397 | 218.4 | 3,294.5 |
| Malignant Neoplasms | 175 | 2,171 | 197.8 | 4,299.5 |
| Cerebrovascular Disease | 46 | 502 | 45.7 | 667.0 |
| Injuries (Accident/Suicide/Homicide) | 86 | 1,065 | 97.0 | 14,301.0 |
| COPD | 59 | 450 | 41.0 | 362.5 |

(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.

# David Connolly Hall, MD: RI's First Olympic Winner in Paris 1900 Games

## *Games return to Paris in 2024*

MARY KORR
RIMJ MANAGING EDITOR

In the Olympic Games, seconds – and in this case, perhaps a shoe – matter.

David Connolly Hall during his Brown running days, photo circa 1898–1901. Hall was a 2004 inductee into the RI Heritage Hall of Fame. [RI HERITAGE HALL OF FAME]

**DAVID CONNOLLY HALL, MD**, Brown 1901 alumnus, was the first in Rhode Island to win an Olympic medal, as a track and field competitor during the 1900 Paris Games. The *Jeux Olympiques* were part of a Universal Exposition which celebrated a new century and heralded the modern era. After 1900, Paris again hosted the Olympic Games in 1924 and this summer will host its third Olympiad.

In the 1900 games, Hall was primed for the Gold. In the semi-final heat he set the Olympic record for 1:59:0 in the 800-meter race. But in the finals at the halfway mark a competitor stepped on the heel of Hall's shoe, and off it flew. Hall won the Bronze at 2:03.8, behind Silver medalist John Cregan (US) at 2:03:0, and Gold medalist Alfred Tysoe (UK) at 2:01.2.

As a footnote, the ancient Olympians ran barefoot before running sandals, which increased traction and forward propulsion, became the norm. Throughout his long life, Dr. Hall witnessed the evolution of running shoes, from the 1900 leather and spiked shoe which flew off his foot, to the introduction of the rubber-soled "sneaker" and later iterations.

What brings Dr. Hall's story to mind is the return of the summer games to Paris this year, and the recently released movie, *The Boys in the Boat*, directed by George Clooney, and the book on which it was based, by Daniel James Brown.

The book and film capture the true grit and resilience of a band of underdog junior varsity rowers at the University of Washington (UW) in Seattle, who, against all odds, won the Gold in the 1936 Berlin Olympic Games, under the grueling eyes of Hitler and the Nazis.

No doubt Olympian Dr. Hall celebrated the 1936 victory as only a former champion could – in fact, probably on the spot, as a UW faculty member.


Poster of the Paris 1900 Olympic Games, which were part of the Universal Exposition or World's Fair, held over a period of five months. [WIKIMEDIA, IN THE PUBLIC DOMAIN]

### Background

Born in 1875 in Quebec, David Connolly Hall was the only son of Irish immigrant John Marveau Hall, and his wife, Ellen Augusta Thornton, of New York, whose great-grandfather was a Rhode Islander. At Brown, Hall was a star track and field athlete and was Brown's team captain from 1899–1901. Hall was also a two-time New England champion, and set a national record in the half-mile run.

Upon graduation, he earned a ScM degree from the University of Chicago in 1903, and then an MD from Rush Medical College in Chicago in 1907. In 1908, he took a position at UW as director of physical training and professor of hygiene. Dr. Hall and his wife, Katherine, raised their three children here and spent leisure time mountaineering.

Eiffel Tower illuminated at the Paris Exposition, 1900. [LIBRARY OF CONGRESS, PHOTOPRINT BY WILLIAM H. RAU]

His tenure was interrupted during World War I, when he served as a Lt. Col. in charge of an ambulance corps stationed on the Italian frontlines in 1918. Returning after the war to UW, he ultimately became its director of student health services. The David C. Hall Health Center on campus is named in his honor.

Dr. Hall passed away in Seattle in 1972, at the age of 97, after a long life of accomplishments – athletic, medical, civic – and, like the ancient Olympians, competing (half) shoeless to cross the Olympic finish line. ❖

Runners at the Paris 1900 Olympic games. [PINTEREST/NZ, IN THE PUBLIC DOMAIN]

At the Bois de Boulogne in Paris, July 16th, 1900, 800-meter winner Alfred Tysoe of Great Britain crosses the finish line to win the Gold.
[WIKIMEDIA, OLYMPEDIA, IN THE PUBLIC DOMAIN]

# We are read everywhere

In 2023, approximately **59,000** unique viewers worldwide read *Rhode Island Medical Journal* articles or researched topics from its archives, rimedj.org.

**Top 10 countries:**

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8. Australia
9. Brazil
10. China


**AMELIA ISLAND, FLORIDA**

RIMS Public Laws Committee Chair **Michael E. Migliori, MD, FACS**, Ophthalmologist-in-Chief at Lifespan, reads RIMJ on his iPad between sessions at the AMA State Advocacy Summit, held January 11–13 at the Ritz-Carlton on Amelia Island.

Every January, the AMA convenes this Summit where more than 250 physician leaders and state and national medical society staff have the opportunity to hear from national experts and strategize with advocacy leaders on the critical issues affecting medicine at the state level. This year the conference focused on key health care issues states will likely address in the coming legislative sessions, including prior authorization, scope of practice, physician wellness, AI in medicine, the overdose epidemic, and reproductive health.


The AMA Advocacy team discussing legislative and regulatory successes and challenges facing physicians and their patients in the coming year and beyond. [L–R] **Todd Askew**, Senior VP for Advocacy; **Jason Marino**, Director of Congressional Affairs; **Rob Jordan**, VP for Political Affairs; **Margaret Grarikes**, VP Federal Affairs; **Kai Sternstein**, VP Advocacy Resource Center; **Rob Ottenm**, VP Health Policy.

Wherever you may be, or wherever your travels may take you, check the Journal on your mobile device, and send us a photo: **mkorr@rimed.org**.

# Working for You: RIMS advocacy activities

### January 2, Tuesday

RIMS Physician Health Committee (PHC): **Herb Rakatansky, MD**, Chair

### January 8, Monday

RIMS Council meeting: **Heather Smith, MD, MPH**, President

Protect our Health Care Policy Group: Stacy Paterno, staff

### January 9, Tuesday

AMA Medicare Payment Update: Stacy Paterno, staff

### January 10, 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

CTC-RI Primary Care Workforce Taskforce Meeting: Past Presidents **Peter Hollmann, MD**; **Elizabeth Lange, MD**; and **Mariah Stump, MD, MPH**, Secretary

Neighborhood Health Plan of Rhode Island Quarterly Meeting: **Heather Smith, MD, MPH**

### January 11, Thursday

Medicaid Consumer Advisory: Stacy Paterno, staff

Raising RI Monthly Update: Stacy Paterno, staff

Meeting with Senator Whitehouse Staff: Stacy Paterno, staff

American Academy of Neurology Introduction: Stacy Paterno, staff

### January 16, Tuesday

EPI Revenue Roundtable: Stacy Paterno, staff

Office of Health Insurance Commissioner Health Insurance Advisory Council: **Catherine Cummings, MD**

### January 17, Wednesday

Primary Care Physician Advisory Committee: **Mariah Stump, MD, MPH**, Secretary

Warren Alpert School of Medicine State House Tour: Stacy Paterno and Steve DeToy, staff

Speaker Joe Shekarchi Fundraiser: **Michael Migliori, MD**, Public Laws Chair

### January 18, Thursday

OHIC Administration Simplification Task Force: **Peter Hollman, MD**; **Beth Lange, MD**

Health Information Technology Steering Committee: Stacy Paterno, staff

### January 22, Monday

Protect our Health Care Policy Group: Stacy Paterno, staff

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

### January 23, Tuesday

Miriam Hospital Medical Executive Committee: **Thomas Bledsoe, MD**, Immediate Past President

CMS National Stakeholder Call: Stacy Paterno, staff

Health Professions Loan Repayment Program Reception at State House: Stacy Paterno, staff

### January 25, Thursday

Board of Medical Licensure Interstate Medical Licensure Compact: Stacy Paterno, staff

### January 29, Monday

Executive Office of Health and Human Services Healthcare Workforce Taskforce: Stacy Paterno, staff

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

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For more information about group rates, please contact Ali Walz, RIMS Director of Member Services

# American Lung Association 'State of Tobacco Control' report releases Rhode Island grades

PROVIDENCE – On January 24, the American Lung Association released the 22nd annual "State of Tobacco Control" report, which finds that Rhode Island received one F, one D, one C, and two B grades for efforts to prevent and reduce tobacco use.

This year's report noted the need for Rhode Island policymakers to focus on increasing and protecting funding for the tobacco prevention and control program, establishing tax parity for all tobacco products, closing loopholes in smokefree air policies to include casinos, and ensuring that all FDA-approved cessation medication is accessible to those who need it.

## Rhode Island grades

The "State of Tobacco Control" report grades states and the District of Columbia in five areas that have been proven to prevent and reduce tobacco use and save lives. In the 2024 report, Rhode Island received the following grades: (**Figure 1**)

1. Funding for State Tobacco Prevention Programs – Grade F
2. Strength of Smokefree Workplace Laws – Grade C
3. Level of State Tobacco Taxes – Grade B
4. Coverage and Access to Services to Quit Tobacco – Grade B
5. Ending the Sale of All Flavored Tobacco Products – Grade D

**Rhode Island Report Card 2024**

| Tobacco Prevention and Cessation Funding | F |
|---|---|
| FY2024 State Funding for Tobacco Control Programs: **$429,205** | |
| FY2024 Federal Funding for State Tobacco Control Programs: **$1,383,858*** | |
| FY2024 Total Funding for State Tobacco Control Programs: **$1,813,063** | |
| CDC Best Practices State Spending Recommendation: **$12,800,000** | |
| Percentage of CDC Recommended Level: **14.2%** | |
| State Tobacco-Related Revenue: **$188,900,000** | |

**Includes tobacco prevention and cessation funding provided to states from the Centers for Disease Control and Prevention.*

| Smokefree Air | C |
|---|---|
| **Overview of State Smoking Restrictions:** | |
| Government Workplaces: **Prohibited** | |
| Private Workplaces: **Prohibited** | |
| Schools: **Prohibited** | |
| Childcare Facilities: **Prohibited** | |
| Restaurants: **Prohibited** | |
| Bars: **Prohibited (allowed in smoking bars)** | |
| Casinos/Gaming Establishments: **Allowed in designated areas** | |
| Retail Stores: **Prohibited** | |
| E-Cigarettes Included: **Yes** | |
| Preemption/Local Opt-Out: **Yes** | |

*Citation: R.I. GEN. LAWS §§ 23-20.10-1 et seq. (2018).*

*Thumbs down for Rhode Island for failing to pass legislation to close the loophole for casinos in its smokefree air law.*

| Tobacco Taxes | B |
|---|---|
| Cigarette Tax per pack of 20: **$4.25** | |
| Tax on little cigars: **Equalized: Yes; Weight-Based: No** | |
| Tax on large cigars: **Equalized: No; Weight-Based: No** | |
| Tax on smokeless tobacco: **Equalized: No; Weight-Based: Yes** | |
| Tax on pipe/RYO tobacco: **Equalized: Yes; Weight-Based: No** | |
| Tax on E-Cigarettes: **Equalized: N/A; Weight-Based: N/A** | |

| Access to Cessation Services | B |
|---|---|
| **Overview of State Cessation Coverage:** | |
| State Medicaid Program: | |
| Medications: **All 7 medications are covered** | |
| Counseling: **All 3 types of counseling are covered** | |
| Barriers to Coverage: **Some barriers exist to access care** | |
| Medicaid Expansion: **Yes** | |
| State Employee Health Plan(s): | |
| Medications: **All 7 medications are covered** | |
| Counseling: **All 3 types of counseling are covered** | |
| Barriers to Coverage: **No barriers exist to access care** | |
| State Quitline: | |
| Investment Per Smoker: **$1.91; the median investment per smoker is $1.93** | |
| Other Cessation Provisions: | |
| Private Insurance Mandate: **Partial mandate** | |
| Tobacco Surcharge: **Prohibits tobacco surcharges** | |

| Flavored Tobacco Products | D |
|---|---|
| Restrictions on Flavored Tobacco Products: **All flavored e-cigarettes prohibited in all locations** | |

## Legislative advocacy plans

"Tobacco use is the leading cause of preventable death in Rhode Island and across the country, and takes the lives of 1,780 Rhode Islanders each year. The tobacco industry will do anything to protect their profits at the expense of Rhode Island lives, so we must push forward in our efforts to prevent and reduce tobacco use," said **DANIEL FITZGERALD**, director of advocacy at the American Lung Association in Rhode Island. (**Figure 2**).

| Rhode Island Facts |
|---|
| Healthcare Costs Due to Smoking: **$639,604,224** |
| Adult Smoking Rate: **11.80%** |
| High School Smoking Rate: **3.00%** |
| High School Tobacco Use Rate: **17.50%** |
| Middle School Smoking Rate: **1.60%** |
| Smoking Attributable Deaths per Year: **1,780** |

Adult smoking data come from CDC's 2022 Behavioral Risk Factor Surveillance System. High school smoking and tobacco use data come from the 2021 Youth Risk Behavior Surveillance System. Middle school smoking rate is taken from the 2019 Rhode Island Youth Risk Behavior Survey.

Health impact information is taken from the Smoking Attributable Mortality, Morbidity and Economic Costs (SAMMEC) software. Smoking attributable deaths reflect average annual estimates for the period 2005-2009 and are calculated for persons aged 35 years and older. Smoking-attributable healthcare expenditures are based on 2004 smoking-attributable fractions and 2009 personal healthcare expenditure data. Deaths and expenditures should not be compared by state.

He added, "In 2023, we had a lot of 'almost' wins for tobacco control, and this year, we aim to push some of those initiatives over the finish line. We are urging the state legislature to adequately fund tobacco control efforts at or above the CDC-recommended level and pass legislation to ensure all Rhode Islanders are protected from a lifetime of tobacco dependence and disease."

The report stated that, despite receiving $188.9M from tobacco taxes, Rhode Island only funds tobacco control efforts at 14.2% of the level recommended by the Centers for Disease Control and Prevention (CDC). In the report, The Lung Association urges Governor McKee and the legislature to increase funding for this critical program.

In the 2024 session, the Lung Association also plans to revisit the successful hearings on legislation that would enable pharmacists to prescribe FDA-approved smoking cessation therapies. The pharmacist's prescribing authority was passed in the House of Representatives but was never moved forward for a vote in the Senate. Additionally, the Lung Association plans to pursue a vote on legislation that would close a nearly 20-year-old loophole and make casinos smokefree.

"Closing the loophole in our smokefree air law to eliminate smoking in all public places and workplaces, including casinos, would protect workers across the state from deadly secondhand smoke," Fitzgerald said. ❖

## CNE, AMS create EPIC information systems opportunity for medical students

PROVIDENCE – Care New England (CNE) has announced that it is partnering with The Warren Alpert Medical School of Brown University to offer medical students the opportunity to serve as an Epic Physician Builder/Informaticist. The medical students will work at CNE under the supervision of a Brown faculty member and receive a stipend.

"At Care New England, we are pleased to partner with Brown and the outstanding medical students at The Warren Alpert Medical School, to provide them with a truly unique opportunity to learn the digital tools of the trade while still in school, putting them ahead of the game upon graduation," said **TOM GREGORIO**, Chief Information Officer, Care New England Health System. He added, "As part of the Physician Builder team, medical students will be planning, designing, and building content for medical or surgical specialties within CNE's Epic electronic medical record (EMR) system, which is a hands-on opportunity not ordinarily available to medical students."

In this role, medical students will:

- Gain experience and proficiency as physician builders in Epic EMR, the EMR vendor with the largest share of the acute care hospital market.
- Learn how an EMR is built and learn how to use documentation tools to create items such as SmartTexts, SmartLists, and Smart Phrases and ordering tools that are used to create order sets and panels.
- Collaborate with users, clinician champions, and department executive leadership to gain an understanding of current state workflow and help inform future workflows that will provide opportunities for streamlining and promoting efficiencies.

This year-long program will be offered to Brown medical students from April 29, 2024, through April 25, 2025.

"We are excited to partner with Care New England to offer this unique educational opportunity to our medical students," said **STEVEN ROUGAS, MD, MS, FACEP**, Assistant Dean of Medical Education and Director of the Clinical Curriculum at The Warren Alpert Medical School. "As future clinical providers, access to and experience with developing EMR content is critical in today's digital technology landscape. This experience will complement the strong curricular foundation students are provided at The Warren Alpert Medical School through real-world immersion in the design and implementation process."

Rising fourth-year medical students at Brown who are interested in bioinformatics and electronic health records are encouraged to apply. Care New England anticipates this will be a full-time (40 hours/week) position for the length of the program. The deadline for submission is February 21, 2024. ❖

## Rhode Island joins Compact for Interstate Nurse Licensing

PROVIDENCE – Governor **DAN MCKEE** and the Rhode Island Department of Health (RIDOH) announced on Jan. 11th that Rhode Island has joined the national Nurse Licensure Compact, allowing nurses in 41 states who hold a Multi-State License to come to Rhode Island and work. Rhode Island nurses with Multi-State Licenses will also be able to work in any of these other states.

This change affects registered nurses (RNs) and licensed practical nurses (LPNs) who are currently licensed in Rhode Island or who are applying for initial licensure. Within these license categories, three groups of people are impacted.

- Anyone who is currently licensed in Rhode Island and who has Rhode Island as their primary state of residency will be applying for a Multi-State License when renewing next (March 1, 2024, or March 1, 2025).
- Anyone who is currently licensed in Rhode Island and whose primary state of residency is a Compact State will receive a Multi-State License when renewing, and have their single-state Rhode Island license changed to inactive.
- Anyone who is currently licensed in Rhode Island and whose primary state of residency is not a Compact State will continue to work in Rhode Island with a single-state license. Their license status will not change, and they will renew their license by their scheduled renewal date.

"Any nurse who practices in Rhode Island under a Multi-State License will be held to the same professional standards as a nurse with a single-state license. Our standards for quality will remain as high as ever," said Interim Director **UTPALA BANDY, MD, MPH**. "Our goal in joining this compact is reducing the time that qualified nurses spend filling out multiple licensing applications and making these workers available to patients for care as soon as possible in Rhode Island."

Licensed nurses can find more information, quick reference charts, and updated forms on RIDOH's Nurse Licensure Compact web page. Anyone looking to verify any type of RN or LPN license can visit the Nursys website. ❖

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

*Applications are due by Thursday, Feb. 15th, at 5 p.m.*

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 100 sites statewide that have demonstrated they are providing safe, affirming, and inclusive care to Rhode Island's LGBTQ community.

Applications are due by Thursday, Feb. 15th, at 5 p.m.

"Feeling respected and safe while seeking care is a critical part of achieving one's own health and well-being, particularly the LGBTQ community, which has historically experienced mistreatment and discrimination in healthcare settings," said **SCOTT GOWRIE**, program lead for Safe Zone. "The Safe Zone Program helps direct Rhode Islanders to safe, affirming, and inclusive settings when they are seeking care."

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 117 Safe Zone locations in more than 25 cities and towns 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.

Facilities that meet certification requirements will be given a customized Safe Zone plaque and 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 March. ❖

# Appointments

## Cindy Peterson, MBA, named Executive Vice President of Ambulatory Care at Lifespan

PROVIDENCE – Lifespan has hired **CINDY PETERSON, MBA**, to serve as Executive Vice President of Ambulatory Care, overseeing physician practices, health care clinics and urgent care centers. Peterson started in this new role in December 2023 and is responsible for the overall leadership of Lifespan clinical ambulatory services across Rhode Island.

Most recently she was the vice president of regional ambulatory operations and business development for a major teaching hospital in Boston. In that role she was responsible for driving ambulatory growth across competitive markets and expanding the hospital's ambulatory offerings into metro Boston, greater Foxborough, and the south shore of Massachusetts.

"Cindy's knowledge of the ambulatory care landscape in southeastern New England will help Lifespan develop outpatient programs that offer premier care in the communities where patients live and work," said Lifespan President and CEO **JOHN FERNANDEZ**.

Peterson holds a BA from Amherst College and an MBA in healthcare management from Boston University. ❖



# Places

## Brown School of Public Health collaborating with partners on creating systems training to improve disability, chronic condition care

The Agency for Healthcare Research and Quality and the Patient-Centered Outcomes Research Institute have partnered in awarding a five-year, $5 million grant to create the Learning Health systems training to improve Disability and chronic condition care (LeaHD) Center. The LeaHD Center is a collaborative effort of the Brown University School of Public Health, the University of Pittsburgh School of Health and Rehabilitation Sciences and Boston University School of Public Health, together with nine health system and health organization partners including University of Pittsburgh Medical Center (UPMC).

LeaHD's mission is to improve the health-related quality of life of persons with disability and chronic conditions by addressing inequities in access to and quality of rehabilitation and long-term services and supports (LTSS) for persons with disability and chronic conditions. The center will achieve its mission by training a new generation of scientists in learning health systems (LHS) research methods to address these issues.

LeaHD's principal investigator is **LINDA RESNIK, PT, PhD, FAPTA**, professor of health services, policy and practice at Brown's School of Public Health. Dr. Resnik also serves as a research career scientist at the Providence VA Medical Center.

In a Brown School of Public Health press release, she stated that "efforts to address these inequities have never been more important. Chronic conditions affect more than half of adults in the U.S., with 27% having multiple chronic conditions and one in four American adults living with a disability."

She noted that these figures are steadily increasing, and disproportionately affect persons 65 years and older, those living in poverty and those from some racial or ethnic minority groups. "A learning health systems approach offers potential solutions by embedding knowledge and best practices into care delivery, thereby supporting improvement, innovation, and equity." ❖

# Recognition


## South County Hospital re-designated as Baby-Friendly hospital

WAKEFIELD – South County Hospital has been re-designated as a "Baby-Friendly" hospital for the optimal level of care, education and support provided to breastfeeding families. In 2000, South County Hospital became the first in Rhode Island to achieve this status.

"It is an honor to receive re-designation as a Baby-Friendly hospital. At South County Health, our expert team of providers, nurses, and support staff are committed to high-quality care, and nurturing a supportive environment, both for breastfeeding families and for those who cannot or decide not to breastfeed," said **MEGIN DALTON, MD**, Medical Director, Center for Women's Health, South County Health.

Baby-Friendly hospitals undergo a rigorous review process and site visit. Facilities are evaluated for their adherence to the highest standards of care for breastfeeding families. These standards are built on the Ten Steps to Successful Breastfeeding, a set of evidence-based practices recommended by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) for optimal infant feeding support in the precious first days of a newborn's life.

In addition to education and breastfeeding support services, South County Health has lactation consultants, certified childbirth educators, and nurses who are specially trained to help all families accomplish their breastfeeding and newborn feeding goals. The team at The Women and Newborn Care Unit at South County Hospital also features Neonatal Nurse Practitioners. ❖

## Westerly Hospital recognized with Press Ganey's 2023 Guardian of Excellence

WESTERLY – Westerly Hospital announced that the hospital has been recognized with Press Ganey's 2023 Guardian of Excellence –Patient Experience–Medical Practice service award, specifically for the clinicians at Smilow Cancer Hospital at Westerly.

The Press Ganey award is the organization's annual ranking of the top hospitals and health systems in the country, according to performance in patient experience. The Guardian of Excellence Award is given to organizations that have achieved the 95th percentile or higher for performance in patient experience. Press Ganey works with more than 41,000 healthcare facilities in its mission to enhance caregiver resilience and to improve the overall safety, quality and experience of care.

"This honor is a reflection of the exceptional patient-centered care and treatment provided by our outstanding team of physicians who treat patients who are going through a difficult diagnosis," said **RICHARD C. LISITANO**, president, Westerly Hospital. "Our world-class team is committed to providing the greatest of care by treating patients and their families with compassion and empathy."

Smilow Cancer Hospital is affiliated with Yale Cancer Center, one of only 56 National Cancer Institute (NCI)-designated comprehensive cancer centers in the nation and the only such center in Connecticut and Rhode Island. Smilow Cancer Hospital locations provide patients with individualized, innovative, convenient and caring medical treatment.

"The Smilow cancer care sites, around Connecticut and in Westerly, ensure that we deliver world-class care to our patients where they are most comfortable and that includes being closer to home," said **ERIC P. WINER, MD**, director, Yale Cancer Center and president and physician-in-chief, Smilow Cancer Hospital. "This award is well deserved recognition of the excellent work by clinicians at the Smilow Cancer Hospital at Westerly."

"We strive to deliver high-quality healthcare to all our patients and this recognition from them is a testament to the dedication and compassion of our team," said **ROBERT LEGARE, MD**, medical director, Smilow Cancer Hospital at Westerly; associate professor, Clinical Medicine (Medical Oncology), Yale School of Medicine. ❖

# Obituaries

**GALEN V. HENDERSON, MD, FNCS**, 56, passed away on December 26, 2023, surrounded by his loving family following a recent illness. A resident of Taunton, MA, Dr. Henderson was the beloved husband of Vanessa M. Britto, MD, MSc, FACP. Dr. Henderson was born in Memphis, TN, and raised in Tunica, MS.

Dr. Henderson attended high school in MS where he excelled academically going on to pursue a BS (cum laude) in chemistry from Tougaloo College in Jackson, MS, and his MD from Warren Alpert Medical School at Brown University in Providence, RI. Meeting at Brown University, Dr. Henderson and Dr. Britto married during Brown's Commencement weekend. For decades that followed they took great pride in the festivity of Brown's Commencement Weekend, always marking their wedding anniversary.

Dr. Henderson had a tremendous and lasting positive impact on every institution and community he was involved in, including Brown University, Tougaloo College, and Brigham and Women's Hospital where he served as Director of Neurocritical Care in the Department of Neurology and Chief Diversity & Inclusion Officer (CDIO). Dr. Henderson was universally known for his warm smile, thoughtful and insightful assessment of challenging and thorny issues, as well as his steadfast commitment to the well-being of his patients, his colleagues, students of Brown University's Alpert Medical School and everyone he met.

Dr. Henderson completed his residency in the Harvard-Longwood Neurology Training Program and a fellowship in Neurocritical Care at the Brigham. He subsequently joined the Brigham's Neurology Department, where he became the director of Neurocritical Care in 2001. He was the country's first African-American neurology-based neurointensivist and the first African-American Fellow to be inducted into the nation's Neurocritical Care Society (FNCS). During his tenure as Director of the Neurological Intensive Care Unit, the neurocritical care service grew from five to twenty beds and is now one of the busiest ICUs at the Brigham.

Dr. Henderson was the recipient of many academic, service, and community awards, including induction into his Mississippi hometown Tunica Hall of Fame. Dr. Henderson was a thoughtful and collaborative leader and gifted physician who leaves an indelible mark on the Brigham community, the countless patients and families he cared for, and the thousands of faculty, trainees and students whom he served as the Chief Diversity and Inclusion Officer the Brigham's Center for Diversity and Inclusion (CDI).

In addition to his work at the Brigham, Dr. Henderson was the founding deputy editor of Journal Watch Neurology, editor of Reprints in Stroke and the associate medical director of two federally designated organ procurement organizations. He received awards from three different secretaries of Health and Human Services for his contributions to the development of the Organ Donation National Collaborative. An Assistant Professor of Neurology at Harvard Medical School, where his research focused on clinical trials regarding treatments for stroke and cerebral hemorrhage, Dr. Henderson lectured extensively at the Neurocritical Care Society, the American Academy of Neurology, throughout the country and internationally.

At Brown, he served two terms as a Trustee on the Corporation. He was also the president of the 100,000 member Brown Alumni Association and president of the Brown Medical Alumni Association, a member of the Brown Medicine Magazine Editorial Board, and a member of the Advisory Council on Biology and Medicine and the Advisory Council on Relations with Tougaloo. In 2014, he received the Brown Bear Award from Brown University, the highest honor given for distinguished service and leadership.

In his memory, please consider a donation to the Galen V. Henderson MD'93 and Vanessa M. Britto MD MMSc'96 Medical Scholarship to support underrepresented minority medical students at Brown University by using the following link: https://go.brown.edu/GalenHendersonMemorialGifts

Arrangements by Chapman Funerals & Cremations-Wareham. To leave a message of condolence visit: www.chapman-funeral.com ❖

**GEORGES PETER, MD,** 85, of Brookline, MA, died peacefully at home on January 11, 2024. He is survived by his wife of 59 years, Carolyn McClintock Peter, former Head of Winsor School, and their two children, Allison Fairchild Peter, of Newton, MA, and Marc Phillips Peter, of Portsmouth, RI. He is also survived by two grandchildren, nieces and nephews, and his sister, Linette Peter French of Annisquam, MA.

Born in Cambridge, MA, to J. Georges Marc Peter and Helen Mann Peter, he graduated from the Loomis Chaffee School and Harvard College. He attended Dartmouth Medical School and graduated from Harvard Medical School. He trained in pediatrics at Strong Memorial Hospital in Rochester, NY, and Children's Hospital, Boston, followed by fellowships at the National Institutes of Health and Children's Hospital. In 1972, he joined the faculty of the Brown Medical School, where he remained until his retirement, when he was appointed Professor Emeritus. During his 34-year career at Rhode Island Hospital and Hasbro Children's Hospital, he established the board-certified Division of Pediatric Diseases. He authored or co-authored approximately

175 publications. An active teacher, he was greatly respected by residents and medical students.

Dr. Peter was a devoted pediatrician; he was particularly committed to the prevention of once-common pediatric infectious diseases through immunizations. During his career, he witnessed the disappearance of polio myelitis, marked reduction in cases of measles, and near-elimination of bacterial meningitis. His advocacy for the prevention of infectious diseases led to national recognition, respect, and leadership roles.

He was an active member of the American Academy of Pediatrics (AAP), serving on the Committee on Infectious Diseases for 13 years. He edited five editions of the AAP's highly influential Red Book (Report of the Committee on Infectious Diseases). He served on three federal committees: the Advisory Commission on Childhood Vaccines, the National Vaccine Advisory Committee, and the CDC's Advisory Committee on Immunization Practices. He was a member of the World Health Organization's Strategic Advisory Group of Experts on Immunization, and he was a president of the Pediatric Infectious Diseases Society. An elected member of the Society of Pediatric Research, the American Pediatric Society, and the Infectious Diseases Society of America, he was also a member of the Board of Directors of the American Committee for the American Memorial Hospital in Reims, France.

Dr. Peter received numerous awards, including the Distinguished Physician Award of the Pediatric Infectious Diseases Society, the AAP Award for Lifetime Contribution to Infectious Diseases Education, and a Special Recognition Award from the US Department of Health and Human Services. At Brown, he was awarded an Emeritus Citation "for 34 years of distinguished service as a teacher, counselor, and scholar."

Dr. Peter was dedicated to his family, spending summers in Annisquam, traveling, and sailing competitively. Devoted to Harvard athletics, he managed the Harvard Stadium scoreboard for 29 years; in 2022, he received the President's Special Award from the Harvard Club of Boston. He was a lifetime fan of the Boston Red Sox. He loved sailing, primarily in the Lightning Class, in which he competed for more than 60 years, winning numerous regattas and sailing in national and international championships. He was a member of the Annisquam Yacht Club, Boston Harvard Club, Rhode Island Harvard Club, University Club (Providence), Niantic Bay Yacht Club, and Longwood Cricket Club.

Georges Peter was a man of integrity, honor, and distinction, and he will be dearly missed by his family, friends, and colleagues. A memorial service in Brookline is being planned for the spring. ❖

**WILSON FISKE UTTER, MD**, 96, died peacefully on January 4, 2024. He was born in Providence and attended Moses Brown School. He went on to attend Amherst College for one year before entering the Army where he served in Japan during the occupation at the end of World War II. After his time overseas, he finished his degree at Amherst, went to Tufts University School of Medicine, and followed in his father's footsteps, becoming a pediatrician in Providence.

They only practiced together for nine years before his father retired, but there was an Utter pediatrician in Providence from 1914 to 2003. Dr. Utter was beloved by generations of patients and parents. He was known for his common sense, good humor and his youthful appearance. In 1994 the atrium at Hasbro Children's Hospital was named in honor of him and his father.

He was an avid fisherman and, from his childhood through to his old age, enjoyed extended hiking and canoeing trips with friends and family to the woods, lakes, and rivers of New Hampshire and northern Maine. Cragged Mountain Farm, a much beloved children's summer camp in Freedom, NH, was founded by his father in 1927. Dr. Utter and his sister Betsey ran the camp for decades, and it was also a central part of his life.

He was predeceased by his wife Isabel Hobson Utter in 2018. He is survived by his daughter Katherine Utter of Brookline, MA, and his three sons and their spouses: Henry and Nancy Utter of Arlington, MA, Philip and Christine Utter of Exeter, NH, and Benjamin Utter and Kathy (Kay) Patch of North Berwick, ME. He is also survived by nine grandchildren, and six great-grandchildren.

There will be a celebration of his life at the Providence Friends Meeting House on April 6, 2024 at 10:30 a.m. The Meeting House is located at 99 Morris Ave in Providence. All are invited to bring a story to share. In lieu of flowers please make donations to the Jimmy Fund in his name or to an organization of your choice that supports vulnerable children in your community. ❖