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Volume 75
Number 2

South Dakota medicine

THE JOURNAL OF THE SOUTH DAKOTA STATE MEDICAL ASSOCIATION

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Note: This is a representation of a patient's possible care connections through Avera and Avera Health Plans.

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PURPOSE BEFORE PORTFOLIO

KENT KRAMER, CFP®, AIF®, *Chief Investment Officer*

"I'm looking for maximum return with as little risk as possible."

That probably sounds familiar because it seems to be on every investor's wish list. The problem is that risk and return are (still) directly and positively related: To increase a portfolio's expected return requires, historically speaking, the assumption of greater risk, including the risks of permanent loss and price volatility.

But is maximum return really the best way to state your investment goal?

In professional golf, there are two major kinds of competition. One is PGA Tour tournament golf, where players try to shoot the lowest score over four eighteen-hole rounds. Of the approximately 280 strokes they will take, keeping virtually every shot in play is imperative. To win you need a combination of consistency, power, and finesse. The other popular golf competitions are Professional Long Drivers Association (PLDA) contests where players try to hit a golf ball as far as possible. To win, requires only one drive of the 5-10 balls they hit to stay in bounds and be longer than everyone else's. No one on the PLDA circuit wins PGA tournaments, and no golfer who wins PGA tournaments wins PLDA competitions. They are playing different games.

It is important that investors know what game they are playing before designing a portfolio or choosing an investment. To win the "game" that investors are playing is usually more complex than a single rate of return over one year or even twenty years. Investors have goals, stated or unstated, and the portfolio ultimately needs to contribute to the realization of the investor's definition of financial success. For most individual investors:

1. The portfolio likely needs to grow some assets faster than the rate of inflation in order to meet long-term goals like retirement.
2. It also needs to provide some liquidity (readily available cash) for planned spending and emergencies along the way.
3. The portfolio needs to have a degree of risk control to prevent temporary market losses from becoming so severe that the investor sells at precisely the wrong time.
4. For some investors, the portfolio should not rely on the success of companies and industries that conflict with the investor's deeply held values.

Those are just four kinds of investment success, among many, that are not measured simply by highest total return. Successful experiences, winning the investment game, usually looks more like winning a four-day golf tournament, with a combination of consistency, power, and finesse, as opposed to swinging as hard as you can at every opportunity and hoping one stays in bounds when you need it.

My 25 plus years of working with investors has taught me that clients make the best investment and portfolio decisions after they have established a clear financial plan. Investors construct their portfolios to achieve many purposes, as expressed in their plan – the map that describes what big-picture financial success means to them. A well-constructed financial plan defines the game that the individual or institution is trying to win.

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The Importance of Being an Emotionally Intelligent Physician

Kara Dahl, MD
President, South Dakota State Medical Association

When we think of an intelligent physician, many of us consider the extensive clinical knowledge that a physician has acquired throughout the numerous years learning and practicing medicine. We are likely to believe a physician who processes complex information with accuracy and efficiency to diagnose and treat patients is intelligent. This type of intelligence is certainly important for the practice of medicine but is not the only form of intelligence that physicians should focus on, learn, and strengthen. Emotional intelligence, also referred to as EI or EQ (emotional intelligence quotient) is extremely valuable for physicians. Emotional intelligence is defined in the Cambridge Dictionary "as the ability to understand and control your own feelings, and to understand the feelings of others and react to them in a suitable way." The four main pillars of Emotional intelligence are self-awareness, self-management, social awareness, and relationship management.

This is not a new concept, we have recognized the importance of skills such as stress management, interpersonal communication, empathy, and self-awareness for years, although the term became more popularized in the 90's after the book by Daniel Goleman was published titled 'Emotional Intelligence: Why It Can Matter More Than IQ.' This put a spotlight on EI generating more interest and attention on the topic which has continued over the past two decades. We have learned much through the expansive body of research that has been done, especially regarding ways to improve one's EI. Many tools and resources have been created, including some specifically for physicians.

Most physicians are working in emotionally demanding and complex environments, this was true even prior to COVID-19, but has been greatly magnified subsequently. That is why it is essential for physicians to strengthen and amplify their emotional intelligence skills and should be an ongoing priority for physician leaders. Ted James, MD, MHCM in his article titled 'Emotional Intelligence for Physician Leaders' in the Harvard Medical School Trends in Medicine wrote that "Physician leaders who are able to exhibit high degrees of emotional intelligence, particularly in how they manage their own emotions and react to the emotions of others, demonstrate better clinical outcomes, greater professional satisfaction, increased empathy, and improved teamwork within health care organizations." This has been continually demonstrated by the research done on this subject. Physicians who can emotionally engage well with their patients and others in the healthcare team have better outcomes. Patients who perceive that their physician cares and listens to their concerns are more likely to comply with recommendations regarding their medical care and return for follow up visits.

What are some tools that physicians can utilize to enhance their EI? Mindfulness is a critical component, being focused and present in the moment. Learn to pause, take a deep breath and reflect on what is going on inside you as well as your external environment especially in a stressful situation. Stress management is crucial for physicians and a key part of increasing one's EI. Everyone has different ways of coping with stress; however, some ways are more productive and healthier and lead to higher emotional intelligence. Exercise, meditation, and fostering meaningful relationships, especially sharing laughs with close friends and family are essential to one's overall health to name just a few. Some find significant benefit in journaling, listening to therapeutic music, practicing yoga, or taking a long walk. In the moment of stress however, one can focus on mindfulness and deep breathing exercises to quickly reduce stress.

Another key aspect of EI is self-awareness and management. There are several tools that have been developed to help with this. Some resources call it a 360- degree feedback, this identifies your strengths and weakness by completing a self-assessment survey and then comparing that data with what a trusted friend or family member completes about you. You will gain important insight into any blind spots or differences of perception between yourself and others. In addition to this, try to stay open-minded and give people the benefit of the doubt as much as possible. There are many potential reasons a person may have for acting or believing a certain way at any given time, understanding this will help build empathy and give you social awareness. You don't have to agree with their thoughts or actions in order to have a better understanding of them.

If you would like more information on ways to enhance your emotional intelligence there are numerous articles and online resources including those by Psychology Today, Harvard Health, Vital WorkLife and helpguide.org that has an online EI toolkit. There is also an extensive online video library that has been created for physicians who are seeking to increase their EI. In addition to the above, please consider physician coaching which has been shown to be an extremely effective way to improve one's EI and in turn boosting career and overall life satisfaction.

Seven Steps to Effective Clinical Teaching

Jason Kemnitz, EdD

German physician and father of modern-day pathology Rudolf Virchow once penned in the mid 1800's that "medical education does not exist to provide students with a way of making a living, but to ensure the health of the community." As a collector of quotations, I was struck by the veracity of this quotation almost one hundred and seventy years later. As our faculty face the ongoing physical, mental, and political challenges of a global pandemic they continue to teach our students their craft for the betterment of society. Unfortunately, due to exhaustion, sickness, and other issues, we need active clinical teaching faculty now more than ever. The USD SSOM currently has one thousand five hundred and seventy-nine clinical faculty, and of that number, less than half are actively teaching. While we know this is for many reasons, if one of those reasons is you are not sure how to approach teaching a medical student, I offer the following brief primer. If you are a veteran teacher, thank you, and this primer may serve as a great refresher.

Step 1. Set the Learning Climate – Try to set a positive learning climate. A great deal of climate is set by YOUR interpersonal skills. It's great to challenge students and we expect faculty to hold our students to the highest standard, but keep in mind they are still learning. Remember, students can often feel intimidated in situations where their decisions can carry great weight. It is also important to include your whole team in the teaching process as interprofessional teamwork is a valuable part of our students learning process.

Step 2. Control the Session – Seek to stimulate the learner and challenge them to learn new ideas and concepts. Uniquely, the more rigid you teach the less likely your learner is to learn. Remember, adult learners value experiential learning or guided autonomy, they like to have ownership in their learning.

Step 3. Communicate Goals – Remember you need to tell the learner what you would like them to learn *before* the session. This communication should include the time frame, learning action, and assessment method. This can be easily accomplished with a quick conversation. "Today we will be working on H&P's, I'm going to have you talk to all the patients first, I'm specifically looking for...". By stating your goals, the student has a better chance of learning and you may be less frustrated.

Step 4. Promote Understanding and Retention – While recall is important for testing, we seek to create the complete physician with a deep foundation of knowledge. To help build the foundation faculty should strive to focus on synthesis and analysis of information, supplanted by meaningful explanation of strength and weakness for later recall.

Step 5. Offer Effective Evaluation – This is often the hardest step for physician educators. Try to evaluate based on knowledge, skills, and attitudes of your students. Remember, effective evaluation starts before the learning encounter when you set the goals you will be evaluating.

Step 6. Give Abundant Feedback – While this step is closely related to step 5, evaluation and feedback are different. Evaluation looks at specific goals, and feedback is the assistance you offer a learner continuously to get better. This is where you can offer tips and tricks you may use to accomplish the goal you set before your student. One of the easiest ways to give feedback is to use the reflective feedback conversation which we addressed earlier.

Step 7. Encourage Self-Directed Learning – In this step the educator helps the learner expand their knowledge. Unfortunately, this often just becomes "you need to read more". While likely true, this is not an effective commentary as learners struggle to identify reliable sources. In this instance you can offer some of the resources that you may use to find information, or some of the resources that we have available for students to use to broaden their foundation of knowledge. It may also be helpful to point them in the correct direction instead of tacking a topic and hoping they find what you are looking for.

I understand that clinical teaching can be difficult. Add to that, the needs of your practice, your staff, and your patients, and it can become overwhelming. Hopefully the use of these steps can help ease the burden you may feel. To our current teaching faculty, I want to say thank you for all that you do for the benefit and improvement of our students. Your contribution is not lost on me or the administration of the USD SSOM. To our faculty who choose not to teach, or those that may not be faculty, please consider joining us, I guarantee you we will do our best to support you every step of the way. To ALL healthcare workers, THANK YOU for all that you have done in the last two years to help keep us all healthy. If the goal of medicine is as Virchow states, "the betterment of society" then society owes you a great debt of gratitude.

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COVID-19 and Cardiovascular Disease: A Comprehensive Review

Fouad Khalil, MBBCh; Filip Oleszak, MD; Tom Stys, MD; and Adam Stys, MD

Abstract

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a pandemic that impacted the lives of billions of people worldwide. Angiotensin-converting enzyme 2 (ACE2) receptor act as a gate for viral cell entry through binding to virus S-protein. Cardiovascular patients are thought to be more susceptible to severe COVID-19 infection due to overexpression of ACE2 receptors in these patients. There is a growing body of evidence suggesting worse outcomes and increased mortality among COVID-19 patients with preexisting cardiovascular diseases. SARS-CoV-2 is capable of causing a wide range of cardiovascular diseases including myocarditis, heart failure, arrhythmia, myocardial ischemia and venous thromboembolism.

Drug-disease interaction in COVID-19 patients with preexisting cardiovascular conditions has become a major concern. In this review, we discuss different aspects of the relationship between COVID-19 and the cardiovascular system along with a brief pharmacological overview.

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared as a pandemic by the World Health Organization in 2020. COVID–19 remains one of the leading causes of morbidity and mortality with severe economic impact worldwide. By the end of January 2022, more than 360 million individuals were infected with more than 5.6 million deaths over the world. SARS-CoV-2 infection occurs by the binding of the virus S-protein to the angiotensin-converting enzyme 2 (ACE2) receptor, which acts as a gate for cell entry. ACE2 receptors are mostly expressed in the lungs. However, these receptors are also present in other organs including the heart. Cardiovascular overexpression of ACE2 occurs in patients with cardiac diseases such as hypertension, aortic stenosis, and heart failure or those on renin-angiotensin-aldosterone system (RAAS) inhibiting medications.[1] The increased concentration of ACE2 in cardiac patients makes them prone to SARS-CoV-2 infection with a higher incidence of cardiovascular complications.[2] Studies have shown that cardiovascular patients had more than three times increase in mortality with COVID-19 infection.[3-5]

Data about COVID-19 is rapidly evolving. Therefore, this review aims to summarize the current literature on the relationship between cardiovascular disease and COVID-19 infection along with an overview of pharmacological aspects in this patient population.

Search Methods

A comprehensive search of literature from Jan. 1, 2020 to Sept. 30, 2021 was conducted for original and review articles along with professional societies advisories using PubMed and Google search engines to prepare for this review article. Keywords “coronavirus”, “SARS-CoV-2” and “COVID-19” were used in combination with “cardiac”, “cardiovascular”, “heart failure”, “myocarditis”, and “arrhythmia.”

COVID-19 Impact On Cardiovascular Patients

The coronavirus pandemic has changed people’s approach to the health system. There has been a reluctance to activate the emergency medical system for fears of infection and overwhelming the system.[6,7] A study has shown a 38 percent reduction in the U.S.’ cardiac catheterization lab activations during the pandemic.[8] Similarly, European studies showed a significant reduction of acute myocardial infarction (AMI), arrhythmia, valvular heart disease, peripheral

vascular disease, and arterial hypertension admissions during the COVID-19 pandemic.[9,10] The previously mentioned studies also illustrated the reluctance of patients with milder clinical conditions to seek medical help in addition to providers' tendency to use more conservative approaches such as pharmacological reperfusion.[9,11] Although most studies addressed the COVID-19 impact on the acute care of cardiovascular patients, it is likely that preventive care was affected as well. Chronic care visits and rehabilitation programs were significantly impacted by COVID-19. Furthermore, the COVID-19 pandemic increased cardiovascular risk factors such as inactivity, stress and unhealthy food habits associated with lockdown, working from home and unemployment.[12]

Although cardiovascular patients' care was negatively impacted by the pandemic, there have been a few positive aspects as well. Virtual visits allowed providers to see the actual patients' environment and get input from patients' families. This could provide a more comprehensive assessment of patients' risk factors. Additionally, this might be a more convenient alternative for non-compliant patients and patients who have difficulties with transportation or time to attend in-person visits.

Cardiovascular Complications in COVID-19

Myocarditis

Viral infection is the leading cause of myocarditis. Like other viruses, COVID-19 has been reported to be associated with myocarditis.[13] Myocardial involvement with COVID-19 infection may occur even in the absence of lung involvement.[14] The mechanism of myocarditis in COVID-19 infection is not completely delineated. However, hypotheses include: 1) direct damage through binding to ACE2 receptors, 2) cardiomyocytes hypoxia and apoptosis through cytokine-induced severe systematic inflammatory response and 3) interferon-mediated hyperactivation of the immune system.[15-17]

The incidence of myocarditis is not well-defined in COVID-19 patients. Studies reported myocardial injury incidence of 7-17 percent of COVID-19 patients.[18] Several studies have demonstrated an association between myocardial injury and increased complications in COVID-19 patients. A study from Wuhan showed that myocardial injury, defined by elevated troponin levels was associated with higher mortality in COVID-19 patients (51.2 vs. 4.5 percent; $p < 0.001$).[19] A Meta-analysis that included 341 patients reported a positive correlation between troponin levels and severity of COVID-19 infection.[20] Patients with myocardial injury were reported to have higher incidence of ARDS, non-invasive, invasive ventilation, acute kidney injury and coagulopathy with associated higher levels of leukocytes, D-dimer, CRP, ferritin, and IL-6.[19] These data suggest that troponin level, as well as the inflammatory markers, might help to predict prognosis in this patient population. Severe complications such as pericarditis, cardiac tamponade and acute ventricular dysfunction have been reported with COVID-19-associated myocarditis.[21,22] Therefore, screening through EKG, troponin, inflammatory markers and echocardiography should be considered in all patients with severe COVID-19 infection.

Arrhythmia

Cardiac arrhythmias ranging from sinus tachycardia or bradycardia to cardiac arrest have been reported in COVID-19 patients.[23,24] Both atrial and ventricular arrhythmias can occur in the setting of fulminant myocarditis and cardiogenic shock.[25,26] Viral myocarditis seems to be the main mechanism of arrhythmia caused by SARS-CoV-2.[27] Some reports showed a correlation between high troponin and NT-ProBNP levels with a higher incidence of arrhythmias, suggesting a relationship between acute myocarditis and arrhythmias.[28] Other important triggers include hypoxemia, systemic inflammation, electrolyte imbalance and proarrhythmic effect of some COVID-19 medications.[29]Although several studies documented arrhythmias in COVID-19 patients, it is unknown if this is mainly related to direct viral effect on the heart or due to associated hypoxemia and metabolic derangements especially with the associated comorbidities and risk factors in most of the patients. However, a study of 234 COVID-19 patients suggested that cardiac arrhythmia, noted in 10 (4.3 percent) patients, was likely related to COVID-19 because most of the patients had no prior cardiovascular morbidities.[30]

The true incidence of arrhythmias in COVID-19 patients is not well-defined. In a study of 138 hospitalized COVID-19 patients, cardiac arrhythmia was observed in 16.7 percent and was more common in ICU patients compared to non-ICU patients (44.4 vs. 6.9 percent).[31]

Atrial fibrillation (AF) is thought to be the most common arrhythmia in COVID-19 patients. A study that included 7,162 patients with COVID-19 reported 1.8 percent AF prevalence. The study showed that COVID-19 patients with AF had greater comorbidity rates and worse prognoses in terms of ICU admission and mortality rates.[32] However, the

study failed to show an independent association of AF with adverse clinical outcomes likely due to the small sample and heterogeneous baseline characteristics. Heart rate variability (HRV) might be a useful tool to predict adverse cardiac outcomes.[33,34] Reduced HRV reflects a lower cardiac parasympathetic tone, which was found to be an independent predictor of cardiovascular all-cause mortality in patients with AF.[35] A recent study has demonstrated reduced HRV in patients with AF during COVID-19 infections compared to prior illnesses, irrespective of the use of AV nodal blocking agents.[36]

Ventricular arrhythmia (VA) including premature ventricular complexes (PVCs), ventricular tachycardia (VT) and ventricular fibrillation (VF) was less frequently reported compared to AF in COVID-19 patients. A study that included 187 patients with COVID-19 has reported a VA incidence of 5.9 percent where malignant arrhythmia such as VT with hemodynamic instability or VF were more common in patients with higher troponin levels (11.5 vs. 5.2 percent).[37] A retrospective study of 1,284 patients with COVID-19 showed that among 170 patients with elevated troponin levels, 44 (25.9 percent) patients developed arrhythmias, including six patients with VA, all of whom died.[38]

Transient complete heart block has been reported with COVID-19 infection in a pattern that is thought to be similar to Lyme disease.[39] Previous reports suggest AV node as the origin of AV block in COVID-19 patients as the escape rhythm was found to be narrow and morphologically similar to sinus rhythm with adequate rate to maintain hemodynamic stability.[39] Similarly, heart block in Lyme disease is transient and occurs at the AV node level proximal to the bundle of His.[40,41] The inflammatory process secondary to direct heart tissue invasion by *Borrelia burgdorferi* is believed to be the mechanism of AV block in Lyme disease.

Heart Failure

Heart failure is an important COVID-19 complication that can occur mainly because of direct myocardial injury and viral myocarditis. Severe inflammatory response and ischemia are other possible mechanisms as well.[14,28]

A study from Wuhan reported that myocardial damage and heart failure accounted for 7 percent of death causes in COVID-19 patients. The study also demonstrated that myocardial damage and heart failure were responsible for 33 percent of death causes when associated with respiratory failure.[28]

Elevated troponin, NT-proBNP and decreased left ventricular ejection fraction (LVEF) on transthoracic echocardiography have been the main parameters used to identify cardiac injury in COVID-19, which was reported in 8 to 28 percent of patients.[42,43] Recent studies that used more sensitive parameters such as cardiac MRI and 2-D left ventricular-global longitudinal strain (LV-GLS) reported cardiac injury in up to 80 percent of patients with COVID-19.[44,45] Furthermore, a recent study suggested that COVID-19 may cause subclinical LV dysfunction evidenced by LV-GLS in the early recovery, asymptomatic, low-intermediate cardiac risk patients.[46] Therefore, cardiovascular follow-up might be more important than appreciated even in asymptomatic patients.

Thromboembolism

Venous thromboembolism (VTE) is the major form of thromboembolism in COVID-19 patients. However, arterial and microvascular thrombi have been reported as well.[47,48] Although many risk factors have been identified for VTE in COVID-19 patients, the exact mechanism of VTE in these patients is not completely understood. Diffuse lymphocytic endothelial injury and apoptosis secondary to direct viral infection have been suggested as possible mechanisms.[49] Additionally, the increased prothrombotic factors such as factor VIII, fibrinogen and neutrophil extracellular traps along with the immobility associated with severe COVID-19 infection might contribute to VTE.[50]

The prevalence of VTE in COVID19 varied widely among current reports. A recent meta-analysis reported an overall weighted frequency of 14.7 percent for VTE and 4 percent for arterial thromboembolism in COVID-19 patients.[51] ICU admission was the main reported risk factor for thromboembolism in this study. Other risk factors included elevated D-dimer, increased activated partial thromboplastin time, high levels of plasma factor VIII activity and factor Willebrand antigen, lymphopenia, and mechanical ventilation.[52,53] VTE has been reported with COVID-19 deaths at autopsy despite systematic thrombosis prophylaxis.[54] However, there is a growing body of evidence that suggests better outcomes in COVID-19 patients who received anticoagulation. A study included 2,773 hospitalized COVID-19 patients, in whom 28 percent received systemic anticoagulation, anticoagulation was associated with improved in-hospital survival in intubated patients (71 vs. 37 percent for those who were not anticoagulated).[55] Another study of 4,297 patients hospitalized with severe COVID-19, in which 84 percent were started on

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prophylactic anticoagulation, found improved survival in the anticoagulated group (mortality at 30 days was 14.3 vs. 18.7 percent in those with no prophylactic anticoagulation).[56] However, the dose of anticoagulation is still controversial. Randomized trials have not been able to demonstrate a consistent improvement in outcomes with more intensive anticoagulation compared to prophylactic doses. Some trials demonstrated better outcomes with therapeutic dose anticoagulation compared to prophylactic dose in non-critically ill patients.[57,58] Conversely, other trials found no major differences in outcomes with therapeutic versus prophylactic doses of anticoagulation.[59,60] The most recent American Society of Hematology (ASH) guidelines suggest using prophylactic-intensity over therapeutic-intensity anticoagulation for acutely-ill COVID-19 patients who don't have suspected or confirmed VTE. However, this recommendation was based on very low certainty in the evidence about effects. Therefore, anticoagulation dosing should be individualized according to the provider's assessment of the risks and benefits.

Acute Coronary Syndrome (ACS)

Although the incidence of ACS in COVID-19 patients is still not clearly defined, it is thought to be elevated through multiple mechanisms including severe inflammatory response, hypoxemia, plaque destabilization and the pro-thrombotic state as evidenced by elevated D-dimer in this patient population.[61] Patients with preexisting heart failure have elevated risk of ACS and worse outcomes after COVID-19 infection.[62]

Takotsubo cardiomyopathy (TTC) is an important differential diagnosis for ACS. TTC is characterized by transient apical wall motion abnormality, mimicking myocardial infarction, but without angiographic evidence of obstructive coronary artery disease. TTC causes apical ballooning due to apical hypokinesis in the setting of hyperkinetic basal and inferior walls. Reverse TTC is characterized by apical hyperkinesis with a depressed basal segment. TTC and its reverse presentation have been reported as a complication of COVID-19 infection.[63,64] In addition to the previously discussed mechanisms of cardiac injury, the profound emotional stress caused by the pandemic with the associated excessive release of catecholamines might be contributing to the pathophysiology of TTC in COVID-19.[65]

Pharmacological Aspects

Medications Approved for COVID-19

Remdesivir is a prodrug of an adenosine analog that has a broad-spectrum antiviral effect through inhibition of viral RNA polymerase.[66] Remdesivir was approved by the FDA for the treatment of patients with severe COVID-19 requiring hospital admission.[67] Reported cardiac adverse events in COVID-19 patients receiving remdesivir include bradycardia, hypotension, and less commonly; complete heart block, QT prolongation and cardiac arrest.[68-71,72] Providers should be aware of these adverse effects especially in patients with cardiovascular risk factors and concomitant use of beta-blockers.

Janus kinase inhibitors (JAKIs) have been an established therapy for resistant rheumatoid arthritis (RA). Some JAKIs such as baricitinib and tofacitinib were recently approved by the FDA for treatment of hospitalized COVID-19 patients requiring supplemental oxygen.[73,74] Venous and arterial thromboembolism are major concerns with these agents especially in the setting of the hypercoagulability state of COVID-19. A study has reported a five-fold increase in pulmonary embolism risk with Tofacitinib compared with tumor necrosis factor therapy in RA.[75] A recent meta-analysis has illustrated an increased incidence of VTE reported with baricitinib in RA trials.[76] Therefore, these agents should be used cautiously in patients with cardiovascular risk factors.

Tocilizumab is an interleukin-6 (IL-6) inhibitor that was recently authorized for hospitalized COVID-19 patients on steroids and supplemental oxygen.[77] Several studies have demonstrated low-density lipoprotein (LDL) increase in patients receiving tocilizumab.[78-80]

Macrolides and antimalarial medications such as hydroxychloroquine were heavily used worldwide during the initial phase of the pandemic. These medications produce a QT interval prolongation by blocking the rapidly activating delayed rectifier potassium current.[81] These agents are not being used in current practice as recent guidelines recommend against the use of these medications for COVID-19 infections. [82]

Cardiovascular Medications

Angiotensin-Converting Enzymes Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs)

Overexpression of ACE2 receptors by ACEIs/ARBs therapy has led to speculation that patients on these medications are at a higher risk of worse outcomes with COVID-19 infection. However, there is no evidence to support any association between ACEIs and COVID-19 severity.[83-85] In a large case-control study that included 6,272 patients with

COVID-19, the use of ACEIs/ARBs was not associated with an increased COVID-19 risk or worse prognosis.[83] Similarly, a study of 12,594 patients demonstrated no significant association between the use of ACEIs, ARBs, β-blockers, calcium-channel blockers, or thiazide diuretics and increased severity of COVID-19 infection.[86] Furthermore, some studies suggested possible benefits of ACEIs in COVID-19 patients. A large multi-centered retrospective study has illustrated that the in-hospital use of ACEIs/ARBs was associated with lower mortality among COVID-19 patients.[87] Another study has reported lower levels of inflammatory markers in patients with COVID-19 and hypertension receiving ACEIs/ARBs compared with those treated with non- ACEIs/ARBs medications.[88] Therefore, ACEIs/ARBs should not be stopped in COVID-19 patients.[89]

Beta-Adrenergic Blockers

Although the effect of beta-blockers has not been studied on the COVID-19 clinical course, several theories suggest that beta-blockers might be beneficial in this patient population. Beta-blockers may decrease the ACE2 level and subsequently decreases the cellular entry of SARS-CoV-2 via negative regulation on the juxtaglomerular cells in the kidney and reducing the activity of the RAAS pathway.[90] Some beta-adrenergic blockers down-regulate CD147, which was suggested as a route for infection to the cells.[91] Beta-adrenergic blockers have been shown to decrease proinflammatory cytokines expression such as IL-1β, IL-6, TNFα, and IFNγ.[92-94] This could produce an action similar to tocilizumab which is thought to help in COVID 19 by decreasing mucus through the inhibition of the IL-6 receptor.[95]

NLRP3 is an inflammasome that is thought to be a major component in the pathophysiology of COVID-19 complications and a clinical trial targeting the inhibition of NLRP3 using Colchicine is already registered.[96] Interestingly, carvedilol has been shown to inhibit NLRP3 inflammasome[97]. Furthermore, studies have shown that beta-adrenergic blockers might reduce mortality in respiratory failure, ARDS and septic shock.[98-100] Prospective and retrospective studies are warranted to identify whether beta-blockers intervene positively with the COVID-19 clinical course.

Antiplatelet Therapy

Antiplatelet therapy is a cornerstone in the management of ACS during the acute phase and for the prevention of stent thrombosis. Nonsteroidal anti-inflammatory drugs (NSAIDs) were reported to be associated with worse outcomes in patients with community-acquired pneumonia.[101] However, there is no evidence of harmful effects of NSAIDs in COVID-19 patients. Similarly, there is no evidence for a beneficial role of antiplatelet therapy in thromboprophylaxis or anti-inflammatory action in COVID-19 patients.[102] A study has illustrated that pre-COVID-19 diagnosis aspirin use was associated with lower mortality.[103] Therefore, it is reasonable to resume or initiate antiplatelets if indicated in patients with coronary artery disease.

Statins

Studies from China have reported elevated levels of hepatic transaminase and creatine with COVID-19.[31,104] It is reasonable, if initiating statins in COVID-19, to monitor the liver function and creatine kinase levels at baseline and periodically thereafter. Statins should be held temporarily in patients with a significant increase in liver enzyme or rhabdomyolysis.[105] Another concern is the concomitant use of IL-6 receptor antibodies such as tocilizumab. IL6 receptor antibodies may lower statin concentrations by reversing cytochrome P450 suppression.[106]

Digoxin

A study has suggested that digoxin has antiviral activity against SARS-CoV-2 infection.[107] The study illustrated significant inhibition of viral RNA, copy number, and viral protein expression by digoxin when administered at the post-entry stage. Another study showed that digoxin can inhibit cytokine storm.[108] These data suggest that digoxin should be prioritized in COVID-19 for the management of atrial arrhythmias. However, close monitoring is paramount due to the narrow therapeutic index with multiple drug interactions, and unpredictable serum concentrations of digoxin.

Diuretics

Diuresis is not generally contraindicated in COVID-19 patients. However, acute kidney injury is frequently diagnosed in these patients and studies showed that COVID-19 severity has been associated with lower serum concentrations of electrolytes.[109] Therefore, diuresis should be used cautiously with close monitoring of electrolytes and creatinine.

Ivabradine

Ivabradine is a heart failure medication used in patients in sinus rhythms with ejection fractions of 35 percent or lower, and resting heart rates ≥70 beats per minute despite a maximum tolerable dose of beta-blockers. There are no reported complications or concerns for ivabradine use with

COVID-19 patients.

Conclusion

The COVID-19 pandemic has significantly impacted the care of patients with cardiovascular diseases. SARS-CoV-2 infection can cause a wide range of cardiovascular complications, primarily through viral myocarditis. Cardiovascular disease has a major role in COVID-19 morbidity and mortality. Some of the approved medications for COVID-19 should be used cautiously in patients with cardiac disease due to direct cardiovascular adverse events. Cardiovascular medications including ACEIs are generally safe in COVID-19 and might provide a beneficial impact on the clinical course in these patients.

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One in Eight Women Experience Postpartum Depression

Up to 80% of all new moms experience some level of baby blues after birth, but postpartum depression is more serious and can last for months or years.

Why talking to your patients is critical:

1. South Dakota mothers who are younger, unmarried, have less education and lower household income, and/or are American Indian are at even greater risk for postpartum depression.*
2. Diabetes, hypertension, depression, or emotional abuse during pregnancy can lead to higher rates of postpartum depression.*
3. Postpartum visits that include discussions about healthy eating, exercise, family spacing, contraception, support programs, and treatment options can make a huge difference that will lead to healthier moms and families.

What you can do to help:

- Screen your patients for postpartum depression
- Discuss risk factors and treatment options
- Encourage family support
- Refer them to programs such as WIC and Bright Start Home Visiting

Let's work together to make South Dakota moms and families healthier.

For more information, visit
ForBabySakeSD.com/postpartum-depression

*For the full 2018 SD PRAMS report: doh.sd.gov/statistics/prams.aspx

for baby's sake
Healthier moms + Healthier babies

Post COVID-19 Large Atrial Thrombus Found Incidentally

Fouad Khalil, MBBCh; Muhammad Hamza Saad Shaukat, MD; Swaminathan Perinkulam Sathyanarayanan, MD; and Adam Stys, MD

Abstract

Background: Coronavirus disease 2019 (COVID-19) has become a leading cause of morbidity and mortality worldwide. One of the major complications of COVID-19 infection is the hypercoagulability state. Cardiac thrombi and venous thromboembolism (VTE) have been documented with severe COVID-19 infection. We present a case of large right atrial (RA) thrombus in transit incidentally diagnosed following a mild COVID-19 in a previously vaccinated patient.

Case Summary: An 85-year-old male presented to the emergency department two weeks following resolution of a mild COVID-19 infection due to an incidentally discovered large RA thrombus. Computed tomography with angiography of the chest was positive for acute pulmonary thromboembolic disease with large clot burden and findings consistent with right heart strain. The patient remained hemodynamically stable and was successfully managed with anticoagulation.

Conclusion: RA thrombi and VTE can occur in patients with mild COVID-19 infection and in the setting of full COVID-19 vaccination. Echocardiography is a useful imaging modality in this patient population.

Introduction

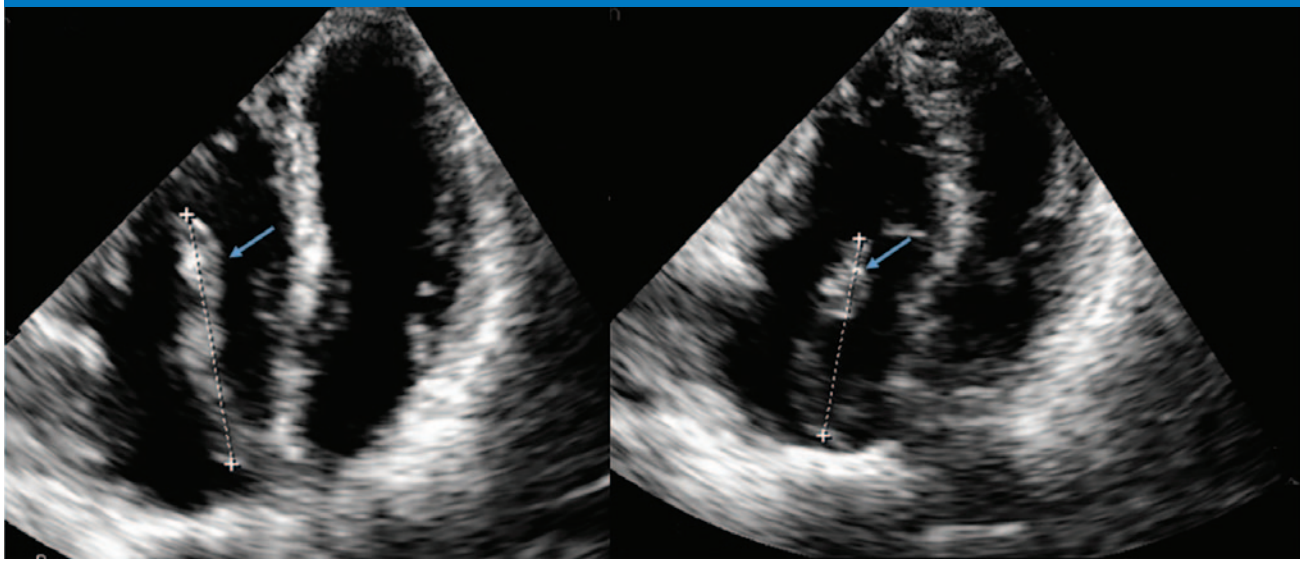
Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) in 2020. Since then, COVID-19 has been one of leading causes of morbidity and mortality worldwide. Several studies have reported the development of hypercoagulability in COVID-19 patients. Right atrial (RA) thrombi and venous thromboembolism (VTE) were previously reported in the setting of severe COVID-19 infection. The main reported risk factors for VTE were ICU admission, increased D-dimer, increased activated partial thromboplastin time and elevated factor VIII activity.

We report a case of an 85-year-old male with incidentally discovered RA thrombus in transit on transthoracic echocardiography (TTE) following a mild COVID-19 infection.

Case Presentation

An 85-year-old male with history of localized adenocarcinoma of the colon status post resection presented to his primary care provider (PCP) clinic with dizziness and fatigue. The patient tested positive for COVID-19 three weeks prior to presentation and received outpatient monoclonal antibodies (casirivimab/imdevimab) therapy. Of note, the patient had completed 2 doses of Pfizer-BioNTech (BNT162b2) (Pfizer, Inc; Philadelphia, Pennsylvania) according to the reference guidelines seven months prior to presentation. His COVID-19 disease course was limited with a few days of intermittent dry cough. He was completely asymptomatic for two weeks before the onset of dizziness and fatigue. In the clinic, his vital signs were found to be normal. His complete blood count, metabolic panel and chest X-ray were unremarkable. Therefore, he was reassured, and his complaints were attributed to post-COVID symptoms. Two days later, he underwent surveillance TTE for follow-up of a previously diagnosed moderate mitral valve regurgitation which revealed a large mobile echodensity in right atrium prolapsing across tricuspid valve (figure 1). He was sent to the emergency department (ED) due to high risk for pulmonary embolism (PE). In the ED, he reported mild dizziness and fatigue. He was normotensive with a heart rate of 76/min, afebrile, had respiratory rate of 18/min and oxygen saturation (SpO2) 96 percent on ambient air. Physical exam was remarkable for diffuse crackles over bilateral lung fields. Electrocardiogram (EKG) showed normal sinus rhythm with left anterior fascicular block that was present on previous EKGs (Figure 2). Labs were notable for elevated troponin at 0.30 ng/ml (reference <0.03

Figure 1. TTE shows a large mobile echodensity in right atrium prolapsing across tricuspid valve (arrows).



ng/ml) and brain natriuretic peptide of 653 pg/ml (reference <300 pg/ml).

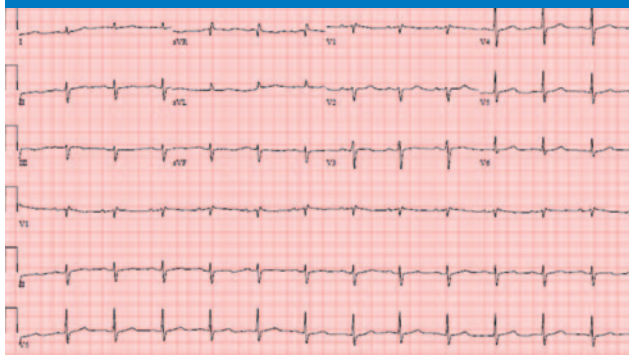
Computed tomography (CT) with angiography of the chest was positive for acute pulmonary thromboembolic disease with large clot burden and findings consistent with right heart strain. (Figure 3). Lower extremity doppler revealed non-occlusive deep vein thrombosis in the left femoral and popliteal veins. Vascular surgery team recommended conservative therapy given the hemodynamic stability of the patient. The patient was started on heparin infusion. Due to concerns of possible colon cancer recurrence, CT of abdomen with contrast in addition to carcinoembryonic antigen (CEA) were obtained and were found to be negative for local recurrence or cancer metastasis.

TTE performed on hospital day three showed resolution of RA thrombus. The patient was switched to apixaban. His dizziness and fatigue resolved and he remained hemodynamically stable throughout his hospital stay. He was discharged home in a stable condition after four days of hospitalization. The patient was seen in oncology clinic two months after discharge for his biannual routine follow up. He was doing well at that time and was instructed to continue apixaban for a total of six months.

Discussion

Previous case reports have described RA thrombi in COVID-19 patients.[1-3] However, most of the reported cases had severe COVID-19 infection with respiratory compromise requiring hospitalization. We describe an incidentally found large RA thrombus complicated by PE after a mild

Figure 2. EKG shows normal sinus rhythm with left anterior fascicular block.

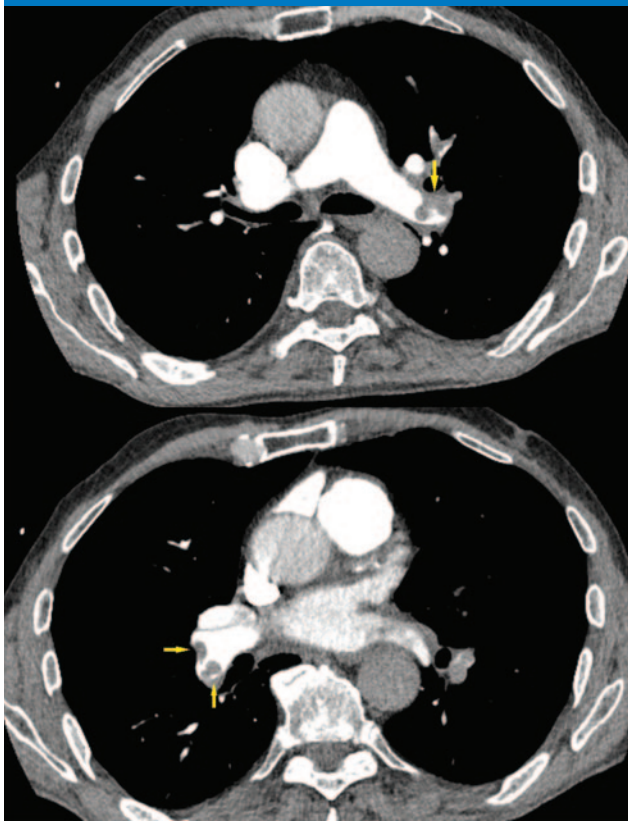


COVID-19 infection in a vaccinated patient.

The exact mechanism of VTE in COVID-19 patients is not completely delineated. However, many risk factors have been identified for the hypercoagulability state in this patient population. The increased prothrombotic factors such as factor VIII, fibrinogen, and neutrophil extracellular traps in addition to immobility are some of these factors.[4] Diffuse lymphocytic endothelial injury and apoptosis due to direct viral infection have been suggested as possible mechanisms as well.[5]

A meta-analysis reported VTE incidence of 14.7 percent in COVID-19 patients.[6] Risk factors reported in the study were ICU admission, increased activated partial thromboplastin time, elevated D-dimer, elevated plasma factor VIII activity, lymphopenia, and mechanical ventilation.[7,8] Interestingly, VTE has been reported with COVID-19 deaths at autopsy despite VTE prophylaxis.[9] However, a

Figure3. CTA shows saddle embolus involving the distal pulmonary artery extending into left upper and lower lobe pulmonary arteries along with bilateral segmental and subsegmental emboli (arrows).



growing body of evidence suggests improved survival in COVID-19 patients who received anticoagulation.[10,11] The dose of anticoagulation is still controversial. Two clinical trials demonstrated better outcomes with therapeutic dose anticoagulation compared to prophylactic dose in non-critically ill patients.[12,13] Conversely, other trials failed to demonstrate major differences in outcomes with therapeutic versus prophylactic doses of anticoagulation.[14,15] Therefore, anticoagulation dosing should be individualized according to the provider's assessment of the risks and benefits.

Although successful thrombolysis has been reported in COVID-19 patients with right heart thrombi, we opted to manage conservatively with therapeutic anticoagulation due to the stable presentation of our patient.[2,16]

Conclusion

Occurrence of RA thrombi and VTE is not limited to patients with severe COVID-19 infection. Providers should be aware of the possibility of cardiac thrombi and VTE even in the setting of mild COVID-19 infection and full vaccination. Echocardiography is a useful imaging modality in this patient population.

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Looking back on 10 years of the Sanford Heart Hospital

with Bridget O'Brien-Johnson, MSN, executive director

An exciting path led Bridget O'Brien-Johnson to leadership. The wife and mother of three has been with the Sanford Heart Hospital since its beginning. Now, the hospital is celebrating 10 years of bringing compassionate heart and vascular care to the Midwest – with O'Brien-Johnson as executive director.

"My parents were the ones who influenced me to want to work in health care – and at Sanford Health. My father was a surgeon at Sanford Health for 35 years, and my mom was a Sanford Health nurse," said O'Brien-Johnson.

She continued, "I saw my mom raise six girls, and even though her passion was her children, she didn't want to give up being a nurse. Her decision to be both a mom and nurse motivated me to do the same."

After completing nursing school at Creighton University in Omaha, Nebraska, the Sioux Falls native came home to begin her career as a cardiology unit nurse at Sanford Health.

"The whole time I was a nurse I worked in some area of cardiology," she explained. "But I immediately felt a passion for taking care of those who take care of patients. That is when I decided to move into a leadership role, and after seven years of nursing, I became a director."

Right as O'Brien-Johnson became the director of the cardiology unit, Sanford Health was beginning to discuss building a new, state-of-the-art heart hospital in Sioux Falls.

"I was involved in the creation of the Sanford Heart Hospital since the very beginning, from early planning to the announcement and all the way to when we opened the doors 10 years ago," said O'Brien-Johnson.

Attached directly to the Sanford USD Medical Center, the Sanford Heart Hospital ensures patients in and around South Dakota have access to all heart services under one roof. A team of more than 750 experienced heart experts deliver care in cardiology, electrophysiology, cardiovascular surgery, interventional cardiology, nuclear medicine, thoracic surgery, vascular care, rehabilitation and other specialties.

"The physicians who I have the opportunity to work with are incredibly motivated to learn and provide our community with the latest and greatest," explained O'Brien-Johnson. "It seems like every year or so we're celebrating a new technology, and it's so exciting."

A year and a half ago, Bridget was promoted to executive director of Heart and Vascular, a position that allows her to utilize her strengths and spearhead the care experience for both her team and patients.

"My proudest moments over the last decade are always when my team reaches milestones – when we performed the first cardiac PET stress test, or when the team celebrated reaching 500 TAVR procedures," she said. "I am extremely proud anytime a team member is promoted, accepted to graduate school or achieves a lifelong goal."

Though ten years have passed, this is only the beginning for the Sanford Heart team.

"My vision is to continue bringing innovative care models and talented physicians and staff to our community. Hopefully, we can keep the program growing and advancing into new areas of heart care that we aren't offering our patients yet."

Why South Dakota is Ready for a Perineal Clinic: A Research-Based Proposal and Review

Caleb R. Wenz, MD; and Matthew A. Barker, MD

Abstract

Perineal trauma is a significant complication of childbirth that can drastically influence an individual's quality of life. Pain, infection, fecal incontinence, and many other adverse outcomes can impact and endanger a woman's life following perineal injury. Early identification, referral and multi-disciplinary care are vital in the correct management of these injuries. The purpose of this manuscript is to discuss the prevalence and etiology of perineal trauma, explain the management of perineal injury and to highlight the important role a perineal clinic would play in South Dakota, especially rural areas, which could improve pelvic floor function and quality of life for these women.

Introduction/Background

Perineal trauma is a serious, and often chronic, complication during delivery that has significantly increased in clinical recognition since the early 2000s.[1] Medical advancements over the last century have dramatically improved care during pregnancy and childbirth. However, research shows that up to 87 percent of mothers may experience a complication within the first eight weeks after delivery.[2] Perineal trauma is an important complication to consider when women present with pain or pelvic floor dysfunction postpartum. Pelvic floor dysfunction is an umbrella term used to describe the manifestation of certain clinical problems due to the inability to correctly coordinate pelvic floor muscles from a variety of etiologies.[3] Uncovering the etiology of pain is complicated by the fact that 42 percent of women without perineal trauma experience pain immediately following a vaginal delivery. The prevalence of pain in this population is reduced to 28 percent and 10 percent at eight and 12 weeks postpartum, respectively.[4] This regression helps delineate the cause of pain, but a delay in diagnosis may drastically worsen outcomes. Women who are otherwise healthy, but who sustain obstetric anal sphincter injuries (OASIS), can face both short- and long-term complications. These complications include anal incontinence, pelvic floor dysfunction, pain, infection, dyspareunia, and sexual dysfunction. OASIS includes both third- and fourth-degree perineal trauma as classified by Goh (Table 1).[5] Risk factors for sustaining OASIS and other complications are summarized in (Table 2).[4-9]

Table 1. Classification of perineal trauma.[5]

First degree	Laceration of the vaginal epithelium or perineal skin only
Second degree	Involvement of the perineal muscles but not the anal sphincter
Third degree	Disruption of the anal sphincter muscles
3a	<50% thickness of external sphincter torn
3b	>50% thickness of external sphincter torn
3c	Internal sphincter also torn
Fourth degree	A third-degree tear with disruption of the anal epithelium as well

Table 2. Risk factors for OASIS.[4-9]

Maternal risk factors	Primiparity Age >27 Asian and African race/ethnicity Maternal diabetes Infibulation
Delivery risk factors	Operative vaginal delivery Vacuum Forceps Vacuum + forceps Episiotomy Midline Mediolateral Epidural Second stage labor >1 hr Shoulder dystocia Vaginal birth after cesarean (VBAC) Water birth Oxytocin augmentation
Infant risk factors	Birth weight > 4000 gm Malpresentation Post maturity Fetal distress Occiput posterior position

Perineal trauma during delivery can lead to muscle and nerve damage that may cause functional problems in women. Mechanical (e.g. muscle/anal sphincter damage) and neuropathic (e.g. injury of the pudendal nerve) are the two different mechanisms behind anal incontinence post-partum.[10,11] Normally, the anal sphincter is in a constant state of contraction to maintain continence. The recto-anal inhibitory reflex (RAIR) is controlled by the autonomic nervous system. It causes transient relaxation of the internal anal sphincter, when the rectum is distended by stool, to allow for a bowel movement. A recto-anal contractile reflex (RACR) causes a brief contraction of the external anal sphincter at the same time to preserve continence until it is appropriate to have a bowel movement. The external anal sphincter has somatic innervation via the pudendal nerve that allows for voluntary control of defecation for the prolongation of continence.[12] The neurological damage is believed to be cumulative and worsen with subsequent pregnancies. Damage to either the sphincter itself or the pudendal innervation can compromise the ability of this loop to maintain continence.[13] Due to the detrimental complications of perineal trauma (e.g. urinary, bowel, and sexual dysfunction), a perineal clinic must be established for women to recognize and address these injuries.

Evaluation

Complete evaluation of perineal trauma involves a detailed physical examination, a thorough understanding of the pelvic, genitourinary and anal/rectal anatomy, different imaging modalities and standardized questionnaires may be used to assess physical, mental, emotional and sexual health/wellbeing. A physical exam by all obstetric providers in the immediate postpartum period is vital for the evaluation of acute perineal trauma after a vaginal delivery. First, the area should be visually inspected to evaluate for injury. A visual assessment should begin anteriorly, beginning with the peri-urethral area and moving laterally and inferiorly. The entire vulva, vaginal vault, anterior, posterior and lateral vaginal walls, perineal body and anal sphincter should be examined.[14] A bimanual exam can help with this assessment, and a lighted speculum may aid in visualization if any injuries are suspected. While assessing for anal trauma, it is important to understand that the external anal sphincter is more striated and will appear more red in color in comparison to the paler smooth muscle of the internal sphincter.[15] The differentiation between the internal and external sphincters is necessary for grading the injury, planning the repair and preparing/counseling for possible future complications. This thorough examination can quickly assess for injury in all of the previously mentioned areas to expedite repair and allow for earlier, and more comfortable, bonding between mother and infant.

After the immediate post-partum period, a referral to the perineal clinic should be made for all patients with third and fourth degree lacerations to be assessed by one to three weeks postpartum. Additional evaluations can be performed at this time to assess for complications (e.g. generalized pain, dyspareunia, anal/urinary incontinence, other defecatory dysfunction, prolapse, bleeding, and infection) and to initiate treatment and adjuvant therapies. The evaluation should begin with a thorough history to understand the timeline of symptoms. Physicians should then expand on the physical exam described previously. After visual inspection, a Q tip exam (i.e. Lightly stroking the vulva and vagina with a Q tip) to test sensation and allodynia should be performed prior to placement of the speculum or a digital exam to reduce unnecessary pain and discomfort for the patient while evaluating internal structures, including pelvic floor muscles.[14]

Assessment of the pelvic floor muscles is essential after perineal injury to evaluate strength and possible muscle/nerve damage due to birth trauma. A simple way to evaluate specific areas of the pelvic floor (e.g. levator ani) is to picture a clock face overlying the vagina. The examiner can then insert a gloved index finger one inch (or to the first knuckle) and palpate the pubococcygeus from 7 to 11 o'clock on the examiner's left and 1 to 5 o'clock on the right. The iliococcygeus muscle can be assessed by inserting your finger further, to the second/third knuckle, and palpating in a swiping motion from 4 to 8 o'clock. While keeping your finger at the same depth, palpating at the 10 and 2 o'clock position will allow you to assess the obturator internus muscle. Finally, inserting the finger as deeply as possible to the 5 and 7 o'clock positions will help evaluate the coccygeus muscle.[14] Finishing the internal vaginal/pelvic floor evaluation with a bimanual examination is helpful to further assess for hematomas, masses, tenderness, pelvic floor strength and pelvic organ prolapse (e.g. cystocele, rectocele, uterovaginal, etc.). This examination method provides a simple technique that can help guide rural practitioners while assessing for correct healing or complications during follow-up in the patients' home communities.

The exam is not complete without anal sphincter inspection and a digital rectal examination. While having your index finger in the anal canal, place your thumb over the perineum and vagina to palpate the anal sphincter between

your fingers. Then ask the woman to contract around your index finger. If the sphincter is not intact, a gap will be felt anteriorly, or there may be an absence of puckering of the skin overlying the defect.[16] This can also help diagnose defecatory dyssynergia in which there is little to no coordination between abdominal and pelvic floor muscles resulting in defecatory dysfunction.[3] An example would be the patient's abdominal muscles contracting for a bowel movement, but the pelvic floor and anal sphincter muscles also contracting when they should normally relax. This would inhibit a bowel movement from occurring and possibly worsen prior perineal injury.

Other modalities may be used to further assess both structural integrity and nerve/muscular functionality. Ultrasound is a common imaging technique used to evaluate female reproductive organs, but it may also be used to diagnose changes in the urinary tract, vagina, perineum and anus. Ultrasound can be used to scan the bladder which can assist in diagnosis of urinary retention. Another resource is endoanal ultrasound to detect the presence and severity of an inadequately repaired/unrepaired anal sphincter defect. This imaging modality can be useful in visualizing both internal and external anal sphincters, assessing the extent of injury, and possibly altering management.[13] In the presence of a thorough physical exam, the use of endo-anal ultrasound is typically unnecessary and could increase the likelihood of developing or exacerbating acute perineal pain.[17] Physiologic dysfunction of the anal sphincter muscles and rectal tone can be assessed using anorectal manometry.[18] Nerve conduction studies can also be used to look at the pelvic nerves (e.g. pudendal nerve) to assess for disruption in those pathways.[19] Finally, pelvic floor magnetic resonance imaging (MRI) and MR defecography are being utilized more often. MRI is beneficial because it allows views from multiple planes, has excellent soft tissue contrast, delineates anatomic abnormalities, provides real time information on functional status, and avoids radiation.[20] MR defecography utilizes a contrast paste in the rectum to evaluate coordination of contraction, emptying capability and any structural abnormalities that may be impeding normal defecation.[20] Although there are many adjuvant diagnostic modalities that may assist in diagnosis of injuries, a thorough physical exam is the gold standard and most utilized tool for assessment.

In addition to physical exam and the aforementioned assessment tools, it is important to screen women with questionnaires about physical, functional, mental, and sexual well-being. These screenings should be implemented during the entire postpartum course. One study found that 60 percent of women may not have resumed intercourse at six weeks, which is why it is vital to continue these screenings past the six-week postpartum check.[21,22] One initial questionnaire to start with postpartum is the "Impact of Female Chronic Pelvic Pain Questionnaire" (IF-CPPQ). This questionnaire provides an overall assessment on how pain impacts the psychological, sexual, relationship, occupational, and emotional aspects of the patient's life.[23] Pelvic floor disorders and their impact on quality of life may be assessed using the "Pelvic Floor Distress Inventory" (PFDI) and the "Pelvic Floor Impact Questionnaire" (PFIQ).[24] Functional status and incontinence can be evaluated using the "St. Mark's Incontinence Score" and the "Questionnaire for Urinary Incontinence Diagnosis" (QUID).[25,26] Widely utilized assessments for mental health include the "Patient Health Questionnaire-9" (PHQ-9) for depression, "Generalized Anxiety Disorder" (GAD-7) for anxiety, and both may be assessed using the "Edinburgh Postnatal Depression scale" (EPDS).[27,28] Finally, sexual health may be assessed using the "Female Sexual Function Index" (FSFI) and the "Pelvic Organ Prolapse Incontinence Sexual Questionnaire" (PISQ).[29,30] All of these questionnaires can be used to follow patients postpartum, track symptom improvement and guide management.

Management

The management of perineal injury is important in both the short- and long-term intervals to help prevent pelvic floor dysfunction. After the diagnosis of a perineal injury, the most important step is adequate, not necessarily immediate, repair. Research has shown that repair can be delayed for up to eight to 12 hours without detrimental effects for the patient.[31] This time may be used to let the mother and baby bond, gather necessary supplies, and allow for a more experienced provider to be present for the repair. OASIS injuries have been historically repaired using the end-to-end technique by obstetricians and gynecologists, but the overlap repair has typically been used by colorectal surgeons outside of deliveries (Figures 1 and 2, respectively). Studies between the two techniques have not consistently shown differences in long-term outcomes. Therefore, either repair is recommended and should be based on surgeons training and comfortability with the procedure.[9] Due to their efficacy and decreased rate of wound complications, a one-time, intravenous dose of a second-generation cephalosporin is currently recommended for all patients that experience OASIS, as well as NSAIDs for pain relief, and laxatives to

Figure 1. End-to-end repair. Ends of the sphincter muscles are reapproximated and sutured together from the deepest layer to the most superficial layer (i.e. inferior → posterior → superior → anterior).

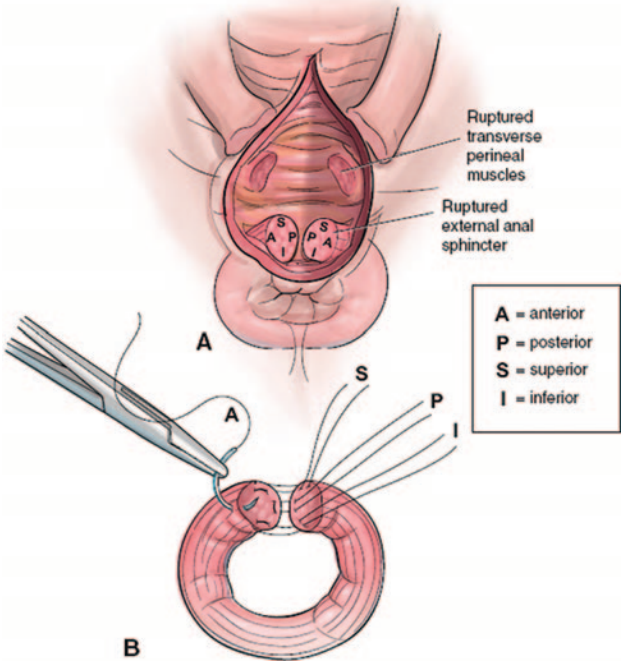

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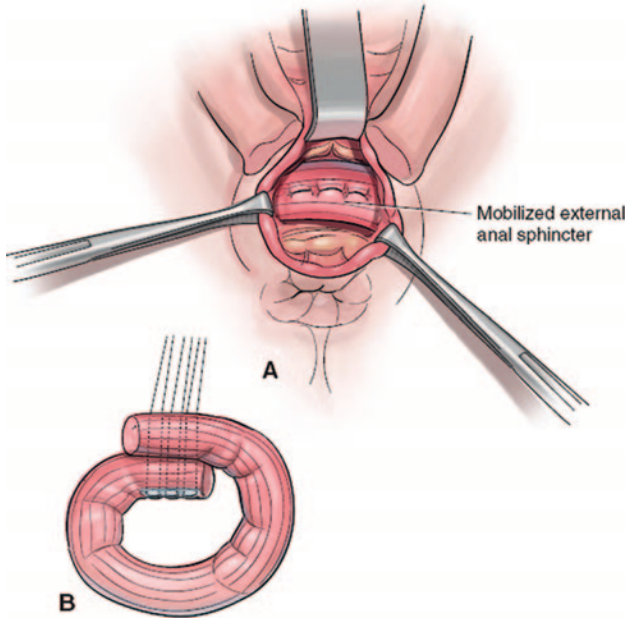
Figure 2. Overlap repair. The sphincter muscle is overlapped by at least 2 cm, superficial and deep edges are reapproximated, and the muscle is sutured together.



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ensure formed, soft bowel movements.[9,31]

Pelvic floor muscle therapy (PFMT) can play a key role in aiding these women get back to their normal daily function. PFMT involves educating patients on pelvic anatomy, pelvic floor exercises (e.g. kegel), manual stretching and dilators for muscle relaxation, biofeedback to assess efficacy of contraction/relaxation and electrical stimulation.[33] One retrospective qualitative study examined the role/effectiveness of early PFMT (within the first month postpartum) vs. standard therapy occurring later. This study found a statistically significant decrease with PFMT in involuntary gas leakage, liquid stool incontinence and urinary stress incontinence.[34,35] Lifestyle modifications, including adequate fluid intake and dietary changes, may be added to optimize this therapy.[36] Given South Dakota's large rural population, more training is necessary so these therapists can offer PFMT throughout the state.

Discussion

As mentioned previously, a clinic held for women with perineal injuries is necessary and would be beneficial for many reasons. The World Health Organization stated that the postnatal period is a critically neglected period of patient care for the mother, as much of the medical attention is directed to the newborn child.[37] By starting a clinic for perineal trauma in South Dakota, we will not only help these women, but we will also raise awareness about third and fourth degree tears, prevent long term complications, and decrease costs. The clinic can help the patient feel more comfortable and provide a safe space to discuss her concerns with multiple healthcare providers trained specifically for perineal care. The multidisciplinary team should include an obstetrician, urogynecologist, colorectal surgeon, pelvic floor physical therapist, psychosexual counselor, primary care provider and a continence nurse.[38,39] The clinic would be one central, all-inclusive visit to limit the referrals and travel from one specialist to another. This is especially important given the large rural population that may need these services but are unable to travel for multiple visits due to distance, socioeconomic factors or other obstacles.[40]

After any perineal injury in the immediate postpartum period, the repair should be completed as soon as an experienced provider is available. Before discharge from the hospital, the patient should be educated on signs of wound complication and proper care, and a physical exam should be completed for baseline function, repair status, and pain. Within one week, the obstetrician's office should contact the patient to assess recovery. A referral should be made to

the perineal clinic for all third and fourth degree tears for a comprehensive assessment so the patient can be seen by two weeks postpartum. The South Dakota perineal clinic would begin as a half day of clinic one to two times per month in Sioux Falls, South Dakota, with the possibility of expansion depending on patient volume. At this visit, a physical exam will be performed, structural and functional status assessed, and a treatment/therapy plan will be advised. Treatment and therapy options may include pelvic floor physical therapy, psychosexual counseling, surgery, and delivery options/risks for future pregnancies. The treatment plan would then be sent back to the referring provider (e.g. Ob/Gyn or Family Practice) for future management of the patient.

One of the most important aspects of this clinic is education and training for the referring providers and institutions. Perineal injury and complications must be incorporated into the prenatal education provided to patients. Although rare, preparing patients for suboptimal outcomes may enhance early recognition of complications, compliance to the treatment plan, and psychological wellbeing if confronted with a chronic complication of perineal injury. Training of the referring providers is also imperative so that patients may continue to receive proper care and treatment once they return to their home communities. The American Academy of Family Physicians (AAFP) created the Advanced Life Support in Obstetrics (ALSO) course that includes a section on third and fourth degree tears.[41] This should be taken and renewed annually by all providers involved with obstetrics and gynecology to ensure training on perineal management is up to date. Resident training/exposure must also be improved so a correct repair can be completed immediately postpartum. A 2002 survey showed that 60 percent of residents had no didactics on episiotomy repair and 59 percent had no formal education on pelvic floor anatomy.[42] More recently, surveys showed that only 20 percent of residents feel comfortable repairing a fourth degree laceration, and approximately 58 percent failed to correctly repair a third degree tear that was observed by an attending.[42] Finally, pelvic floor physical therapy is a vital part of the recovery process. Increased training must be provided to physical therapists across the state, so they are trained in pelvic floor therapy and well equipped to manage these patients. This will allow a patient to remain close to home while receiving the necessary therapy. Proper training and education are vital aspects of perineal injury recovery that will help expand services to patients throughout the entire state of South Dakota.

Conclusion

Perineal trauma is a prevalent injury that affects many patients across South Dakota. A comprehensive perineal clinic, proper training for residents and clinicians, and increased education would allow for increased access to care in rural areas, decreased healthcare costs for patients, and improved quality of life for women.

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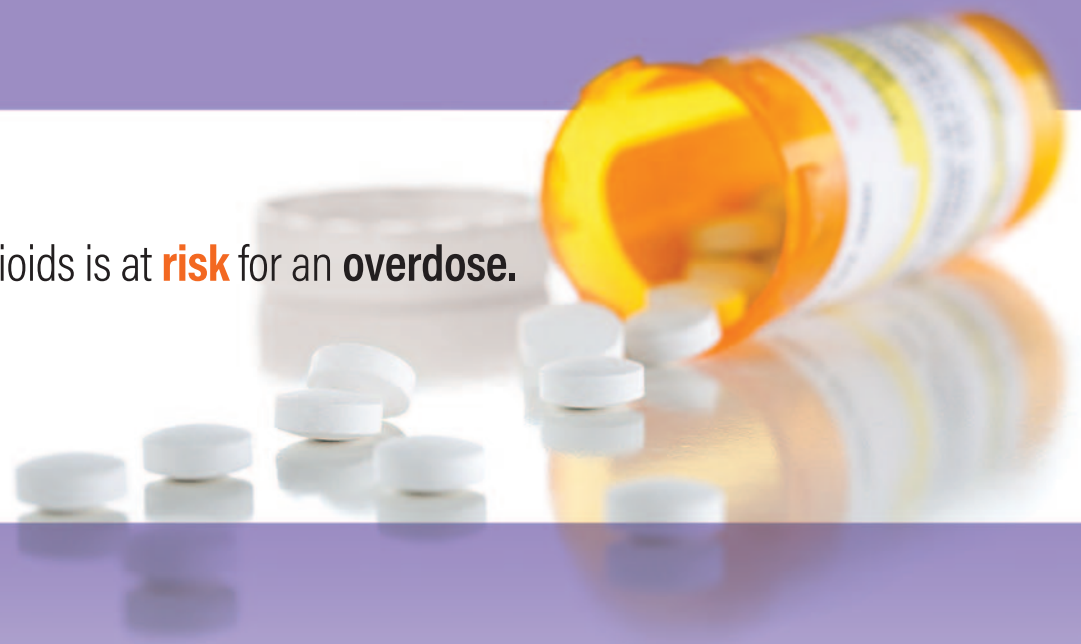
Anyone taking opioids is at **risk** for an **overdose.**



Help your patients recognize the symptoms of an opioid **overdose.**

Most opioid overdoses in South Dakota are *accidental*. If your patients have opioids in their homes, *remind them* of what to look for if an overdose is suspected.

What to watch for:

- Small, constricted "pinpoint pupils"
- Falling asleep or loss of consciousness
- Slow, shallow breathing
- Pale, blue, or cold skin or fingernails
- No response when they rub the middle of the chest with knuckles
- Vomiting, choking, or gurgling sounds

What can be done:

Suggest to patients that they keep naloxone on hand. **It can save a life.** Encourage them to keep their loved ones safe by taking these easy, preventative steps:

- Get naloxone for FREE from any pharmacy
- Order a FREE medication lock box for safe storage
- Order a FREE Dispose Rx packet to safely get rid of unused or expired medication or find a take-back location

Refer your patients and their families to the

Resource Hotline
1-800-920-4343

It's FREE, confidential, and available 24/7

For more about the State Unintentional Drug Overdose Reporting System (SUDORS) data, visit **AvoidOpioidSD.com**

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PRESCRIPTION ADDICTION

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Stroke Nurse Triage: Effects on Time Metrics at a Regional Stroke Center

Stephanie Kazi, MD; John Fanta, MD; Tej Mehta, MD; Katerina DeHaan, MS IV; Jessie Wolf, RN, BSN; and Divyajot Sandhu, MD, MBBS

Abstract

Introduction: Optimization of time metrics in the management of acute stroke is a priority. Nurses with special training in stroke management may contribute to enhanced delivery of care. This study analyzes the effects of initiating a nurse-led stroke triage program at a regional stroke center on time metrics of acute stroke.

Methods: In retrospective review, stroke metrics 25 months prior to the start of the triage program and 23 months after the start of the program were analyzed, including time from arrival to: emergency department assessment, neurologist assessment, head computed tomography (CT) scan, start of tissue plasminogen activator (tPA) administration, and puncture for mechanical thrombectomy.

Results: The study included 1,019 patients presenting with symptoms of acute stroke. Significant decrease was found between means for the time measures of arrival to emergency department (ED) physician assessment (pre-program: 6.2 minutes, post-program: 5.7 minutes, p= 0.0036), and CT start (pre-program: 21.3 minutes, post-program: 19.8 minutes, p= 0.0001). Time from arrival to ED physician assessment and CT start showed an increase in the proportion of cases meeting goal times: ED physician assessment increased from 82 percent to 84.4 percent of cases meeting the goal time (p= 0.3543), and CT start increased from 55.3 percent to 63.2 percent (p= 0.0481) of cases meeting the goal time. Significant increase was found between means for time from arrival to neurologist assessment (pre-program: 11.6 minutes, post-program: 17.1 minutes, p= 0.0015), and the proportion of cases meeting the goal time for arrival to neurologist assessment decreased (88.8 percent pre-program, 75.8 percent post-program, p= <0.0001). No significant differences were found for times from arrival to tPA administration and mechanical thrombectomy, or between Modified Rankin Scores (mRS) at discharge.

Conclusions: Certain time-sensitive metrics of acute stroke care were improved after implementation of the stroke nurse triage program, particularly those related to immediate patient assessment within the ED. Time metrics related to the direct administration of stroke therapies were unaffected, indicating the need for recognition of additional factors affecting timely stroke management. Incorporating specially trained stroke nurses in acute stroke management may be an important component in efforts to improve time metrics of acute stroke.

Introduction

Stroke remains the fifth leading cause of death in the U.S. and continues to be a leading cause of long-term disability.[1,2] A majority of morbidity and mortality associated with stroke is due to acute ischemic stroke (AIS).[3] To reduce the health care impact of AIS, the American Heart Association/American Stroke Association (AHA/ASA) has developed guidelines that lead to improved outcomes in AIS.[4] Included in these guidelines are certain time sensitive metrics including door-to-computed tomography (CT) time within 20 minutes and door-to-needle time within 60 minutes.[5] The presence of effective and efficient management of AIS patients to meet these criteria should be a priority to optimize patient care. With increased availability of endovascular therapy for stroke, initial management has even greater importance in order to maximize potential therapeutic benefit and reduce morbidity and mortality associated with stroke.

Recently there has been interest in the role of stroke-trained nurses in improving AIS care. Studies have shown that nurse-led stroke protocols have resulted in reduced time to initial head CT, improved National Institutes of Health

Stroke Scale (NIHSS) at 24 hours, reduced time from triage to treatment, and improved adherence to stroke management guidelines.[6-8] These results indicate that a nurse with specialized training in stroke may facilitate improved patient outcomes. The stroke nurse can become a manager of a patient's stroke care, taking on some responsibilities of the emergency room physician such as initial assessment, obtaining initial NIHSS, and ensuring timely progression of patient care. Previously, our institution assessed the effects of a nurse-led stroke triage team in improving time metrics of acute stroke management for patients receiving intervention (tissue plasminogen activator (tPA) or mechanical thrombectomy).[9] The current study builds upon this protocol, including increased enrollment of patients and expanded inclusion criteria.

Materials and Methods

Design

This study was a retrospective review of time sensitive outcomes with and without a trained stroke nurse. The stroke nurse triage program was instituted on Feb. 1, 2018, after which a registered nurse (RN) who had received specific training in stroke management was designated to each presenting stroke code. Specific training for the nurses involved NIHSS certification and institutional education on stroke management and treatment options. The stroke nurse remained present with the patient from the emergency department presentation until the completion of immediate stroke related therapy. The stroke RN was responsible for initial assessment, obtaining NIHSS, continued monitoring of the patient, and maintaining timely progression of care. The time metrics of patients presenting to our facility with suspected stroke from Jan. 1, 2016 through Dec. 31, 2019 were recorded in the patients' electronic medical record (EMR). Recorded metrics included time from arrival to: assessment by emergency department physician, assessment by neurologist, CT start, start of tPA administration, and groin puncture. Existing standard nursing protocol in the ED included recording any encounters or events involving the patient in the EMR. For metrics not occurring in the ED, they were recorded by other staff as per standard protocol (i.e. time of groin puncture was recorded by radiology technicians prior to the procedure). Accuracy of initial recorded time metrics was ensured by agreement between the ED RN, stroke RN, emergency medical personnel, and other present ED staff. The stroke coordinator subsequently transferred the EMR data to a stroke registry database, with accuracy ensured via inter-rater reliability checks with an additional abstractor.

Inclusions/Exclusions

All patients over the age of 18 presenting to the facility with suspected stroke between Jan. 1, 2016 through Dec. 31, 2019 were initially included in the study. This included patients 25 months prior to the program institution and 23 months after program institution. Patients who received variables under investigation prior to arrival, such as those who had a CT scan prior to transfer or in whom tPA had already been initiated, were excluded from analysis of that variable. Elapsed time for all variables which had recorded times were examined, without regard to the existence of other elapsed time values.

Outcome Measures

Primary outcome measures included times from arrival to: assessment by ED physician, assessment by a neurologist, CT start, start of tPA administration, and groin puncture, in addition to the proportion of cases meeting target times for each of these metrics. Modified Rankin Score (mRS) at discharge, a measure of post-stroke disability, was a secondary outcome measure. Data were recorded as time, including time-of-arrival, and elapsed times were computed by subtraction.

Statistical Analysis

Statistical analysis was completed using statistical analysis software. T-tests of logarithmic transformed times were used to compare differences in mean metric times and mRS scores between pre- and post-program initiation cases. The proportion of cases meeting goal metric times were compared using a test of independent proportions.

Special Considerations

In some cases, elapsed time values (computed by subtraction) were negative. These were primarily found in events that occurred very shortly after arrival to the ED, and can be attributed to slight differences of recording the time of the event. All elapsed time values -10 minutes to -1 minute were set to 0.

Results

1,019 patients were included in the study, with 293 presenting within the 25 months prior to program initiation and 726 presenting in the 23 months post-program initiation.

Primary Outcomes – Pre- vs. Post-Program Time Metrics

Significant decrease was found between means for the time measures of arrival to ED physician assessment

(pre-program: 6.2 minutes, post-program: 5.7 minutes, p= 0.0036), and CT start (pre-program: 21.3 minutes, post-program: 19.8 minutes, p= 0.0001). Significant increase was found between means for time from arrival to neurologist assessment (pre-program: 11.6 minutes, post-program: 17.1 minutes, p= 0.0015). No significant differences were found for other recorded time metrics between pre- and post-program initiation. Results of comparable time metric means are shown in Table 1.

Time from arrival to ED physician assessment and CT start showed an increase in cases meeting goal times. ED physician assessment increased from 82 percent to 84.4 percent of cases meeting the goal time (p= 0.3543), and CT start increased from 55.3 percent to 63.2 percent (p= 0.0481) of cases meeting the goal time. Neurologist assessment decreased in compliance with goal times, from 88.8 percent pre-program to 75.8 percent post-program (p= <0.0001). Results of proportions of cases meeting target times are shown in Table 2.

Table 1. Results of time metrics: comparison of means.

	Pre-program			Post-program			P-value
Metric - time* from arrival to...	N	Mean	StDev	N	Mean	StDev	
ED physician assessment	289	6.2	7.7	680	5.7	9.8	0.0036
Neurology assessment	251	11.6	16.4	400	17.1	18.9	0.0015
CT start	229	21.3	16.7	397	19.8	16.7	0.0001
tPA start	35	58.2	74.5	46	50.2	23.9	0.9792
Groin puncture	15	99.1	144.4	97	91.4	149.2	0.6603

*Time is recorded in minutes. ED=emergency department. CT=computed tomography. tPA=tissue plasminogen activator.

Table 2. Proportions of cases meeting target times.

		Proportion meeting target time		P-value
Metric - arrival to:	Target time	Pre-program	Post-program	
ED physician assessment	<10 minutes	82.0%	84.4%	0.3543
Neurologist assessment	<25 minutes	88.8%	75.8%	<0.0001
CT start	<20 minutes	55.3%	63.2%	0.0481
tPA start	<60 minutes	80.0%	71.7%	0.3951

ED=emergency department. CT=computed tomography. tPA=tissue plasminogen activator.

Secondary Outcomes - mRS at discharge

No significant difference was found for mean mRS at discharge between patients presenting pre- or post-program (pre-program mean mRS: 2.64, post-program mean mRS: 3.03, p = 0.454).

Discussion

Significant decrease was found after implementation of the stroke nurse triage program for the metrics of arrival to ED physician assessment and arrival to CT start. No significant differences were found for time from arrival to tPA administration or arrival to groin puncture. Both groups achieved average time metrics within the recommendations set by the AHA/ASA: a head CT administered within 20 minutes of patient arrival and tPA administered within 60 minutes of patient arrival.[4] The post-program group demonstrated a significant increase in the percentage of cases that received a CT scan within the recommended time (55.3 percent pre-program vs. 63.2 percent post-program, p= 0.0481). There was no difference in the secondary outcome of mRS, a measure of post-stroke disability that assesses the level of dependence in daily activities on a scale from 0 (no symptoms) to 6 (dead).[10]

Interestingly, there was a significant increase in time to initial assessment by a neurologist for the post-program patients. It should be noted that this time metric records in-person assessment of the patient by a neurologist and does not account for preliminary reports received by the neurologist over the phone or assessment by neurology nurse practitioners. Considering the mean time from arrival to neurologist assessment was shorter than the mean time from arrival to CT start in the pre-program cases, but was longer in the post-program cases (11.6 minutes to neurologist assessment and 21.3 minutes to CT start in pre-program cases compared to 18.9 minutes to neurologist assessment and 16.7 minutes to CT start in post-program cases), the reduction in the average time for a patient to receive a CT scan upon arrival could have contributed to a different order of patient evaluation in which the neurologist more frequently assessed the patient following the CT scan rather than before.

Given the decreased average time from arrival to ED physician assessment, it is plausible that the transfer of tasks formerly under the responsibility of ED physicians to the stroke nurses, such as initial patient assessment and obtaining NIHSS, contributed to streamlined ED operations. Involvement of stroke nurses in acute stroke management may serve as a beneficial use of available personnel, particularly in busy ED settings or areas lacking a stroke neurologist. While a reduction in time to ED physician assessment and CT start was observed with the stroke nurse program, this did not translate to significantly reduced times to administration of interventions, such as tPA or mechanical

thrombectomy, or a difference in outcome as per mRS. This suggests that involvement of the stroke nurses was related to quicker aspects of initial stroke patient assessment, however there existed additional external factors related to administration of therapies that were unaffected.

There was an increase in patients seen in the post-program group, with 726 patients presenting in the post-program group compared to 293 patients in the pre-program group. This aligns with an annual increase in stroke patients seen at our institution, possibly attributed to community education of seeking stroke treatment quickly and protocols to transfer patients quickly from outlying facilities.

Designing protocols to improve outcomes in patients with AIS requires careful coordination between referring facilities, emergency medical services, and the staff at the accepting facility to promptly identify and treat stroke patients. These results suggest involvement of stroke nurses in acute stroke management may contribute to the improvement of certain time-sensitive metrics in stroke care. Other nurse-led stroke initiatives have had mixed results with some demonstrating benefit and others no significant difference.[11,12] A well-trained stroke nurse may be able to provide greater standardization of stroke-care and serve as an important liaison between emergency physicians, neurologists, and interventionalists. The stroke nurse may also serve as a leader in quality improvement initiatives as stroke care guidelines evolve. We recognize stroke nurses as beneficial members of stroke teams and suggest this model may be an important use of resources as stroke care evolves in the future.

Conclusions

Certain time-sensitive metrics of acute stroke care were improved after implementation of the stroke nurse triage program, particularly those related to immediate patient assessment within the ED. Time metrics related to the direct administration of stroke therapies (tPA or mechanical thrombectomy) were unaffected, indicating the need for recognition of additional factors affecting timely stroke management. While the approach to improving time metrics of acute stroke care must be multifaceted, specially trained stroke nurses in the acute management may be a valuable component to quality improvement efforts.

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COPD Assessment Test: A Review of Extant Literature

Muhammad Waleed, MD; Muhammad Soban Arif Maan; Muhammad Danial Siddiqui; Muhammad Umer Siddiqui; Imran Khalek; and Seemal Naseem

Abstract

Chronic obstructive pulmonary disease (COPD) is a major health burden worldwide. Reasons for poor management include lack of awareness regarding COPD among healthcare providers and patients, insufficient use of diagnostic tests (such as spirometry), poor treatment decisions. Another major issue is poor doctor-patient communication which can lead to inaccurate assessment of a patient's clinical picture. The COPD Assessment Test (CAT) is a clinical tool which provides a quantitative measure of the severity of a patient's symptoms and their pulmonary health status. It is a brief patient-filled questionnaire that only takes a few minutes to fill out. This has the potential to help bridge deficiencies in the clinical history that may be left by any communication gap between the patient and the physician. Various studies have investigated the effectiveness of CAT in clinical settings. Herein we review these studies to examine the sensitivity, validity and reliability of the CAT as a clinical diagnostic and assessment tool in light of the existing literature.

Introduction

The 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report defines chronic obstructive pulmonary disease (COPD) as a "common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases."[1] It is a major cause of morbidity and mortality worldwide. With approximately 3.2 million people dying of COPD in 2015, it ranked third among age-standardized death rates for both genders globally.[2] WHO estimates indicate that, unless decisive measures are taken, it will become the third leading cause of mortality all over the world by the year 2030.[3] Alarmingly, researchers have estimated that around 50-90 percent of COPD patients remain undiagnosed.[4] A key reason for this is a lack of awareness regarding COPD among healthcare professionals. A survey of American family physicians, physician assistants and nurse practitioners found that fewer than half of the survey participants knew about or utilized COPD diagnosis and management guidelines.[5] This lack of awareness regarding COPD also extends to patients, who frequently fail to recognize early symptoms and only seek medical help when their symptoms have progressed significantly.[6] Other reasons behind poor COPD diagnosis and management include insufficient use of diagnostic tests (such as spirometry), poor treatment choices and lack of patient counselling regarding the potential of consistent treatment to significantly improve the quality of life.

Another major problem that gets overlooked is the communication gap that may exist between the patient and his/her physician. Patients often find it difficult to properly and accurately convey their symptoms to the clinician, which can lead to misdiagnosis and/or inaccurate assessment of disease severity. This issue points towards the need for some kind of clinical tool that would enable the clinician to efficiently and accurately quantify the patient's claimed symptoms and their severity.[7] Such tools are already in existence. However, a problem with many of them is that they take a very long time to fill out which makes them unsuitable for use in an outpatient setting. Popular questionnaires include Saint George Respiratory Questionnaire (SGRQ), COPD Clinical Questionnaire (CCQ), Chronic Respiratory Disease Questionnaire (CRQ) and COPD Assessment Test (CAT). Out of these, CAT is the shortest and has the simplest scoring method.[8,9]

The COPD Assessment Test (CAT) questionnaire (Figure 1) is a short, precise and specific clinical tool. It was developed with consultation from patients and is designed to be completed by patients within a few minutes.[9] The questionnaire comprises 8 questions, with a score ranging from 0 (no impairment) to 5 (maximal impairment) for each question. The overall score is an added sum of all the

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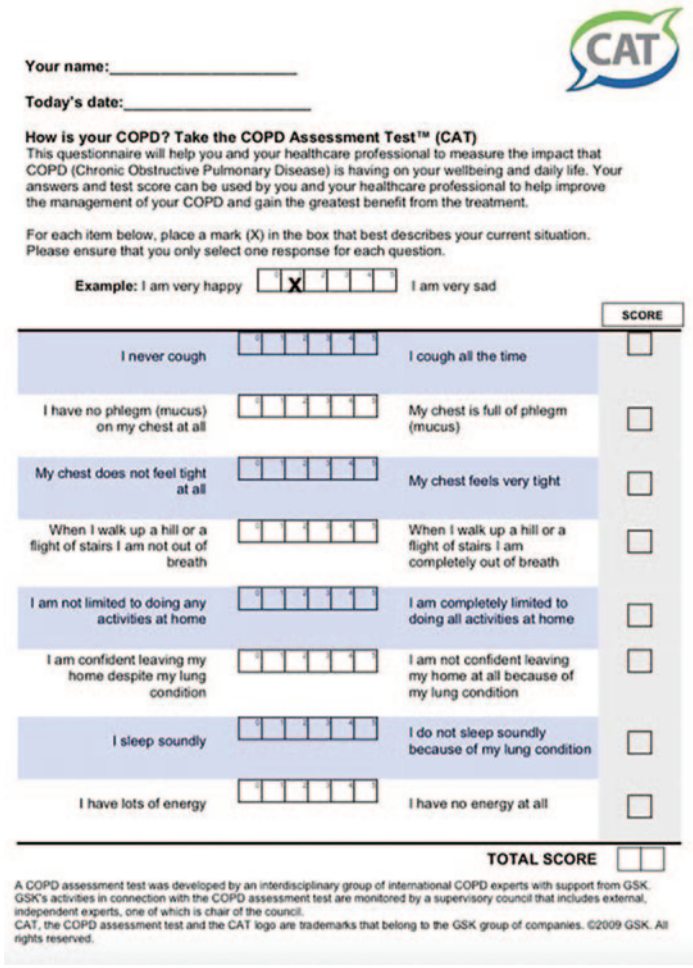
Figure 1. The COPD Assessment Test (CAT) questionnaire.[29]



Your name:_____

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How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional to measure the impact that COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers and test score can be used by you and your healthcare professional to help improve the management of your COPD and gain the greatest benefit from the treatment.

For each item below, place a mark (X) in the box that best describes your current situation. Please ensure that you only select one response for each question.

Example: I am very happy [X] I am very sad

		SCORE
I never cough	I cough all the time	
I have no phlegm (mucus) on my chest at all	My chest is full of phlegm (mucus)	
My chest does not feel tight at all	My chest feels very tight	
When I walk up a hill or a flight of stairs I am not out of breath	When I walk up a hill or a flight of stairs I am completely out of breath	
I am not limited to doing any activities at home	I am completely limited to doing all activities at home	
I am confident leaving my home despite my lung condition	I am not confident leaving my home at all because of my lung condition	
I sleep soundly	I do not sleep soundly because of my lung condition	
I have lots of energy	I have no energy at all	
	TOTAL SCORE	

A COPD assessment test was developed by an interdisciplinary group of international COPD experts with support from GSK. GSK's activities in connection with the COPD assessment test are monitored by a supervisory council that includes external, independent experts, one of which is chair of the council.

Intellectual property rights in the COPD Assessment Test are owned by the GSK Group of Companies

individual scores for various questions, ranging from 0-40. Each question addresses a particular indicator of disease severity. These include severity of cough, amount of phlegm produced, chest tightness, limitation of daily activities, breathlessness when climbing stairs, sleep quality, energy level and the degree of comfort while leaving home with underlying illness (COPD). The total score indicates the overall severity of COPD symptoms at that particular clinic visit according to the patient; the higher the total score, the more severe the patient's symptoms.[7]

The aim of this paper is to review the existing literature for studies that have investigated the sensitivity, validity and reliability of the CAT in clinical settings.

The utility of CAT questionnaire in assessing the severity of COPD has been established in various studies done in different demographic settings. The initial study to develop the CAT questionnaire (conducted in six countries, including U.S. and various European countries) examined 21 variables and with the help of Rasch and psychometric analyses, "identified eight items fitting a unidimensional model to form the CAT."[10] CAT exhibited true interval scaling properties as pointed out by quality of fit to a Rasch unidimensional model. Internal consistency test data from 6 countries demonstrated that the CAT is a reliable instrument for assessing the overall severity of COPD globally.[10] In two other studies conducted in Spain and Iran, Cronbach's alpha coefficient came out to be 0.86 and 0.73 respectively. These findings again signify the high internal consistency of CAT and demonstrate its applicability for worldwide use.[11,12] Furthermore, multiple studies conducted in Europe have shown little variability across countries.[11,12] CAT has proven to be sensitive to intra-patient and inter-patient pulmonary health status changes over the course of time.[7] Herein we shall examine the CAT questionnaire's relation with spirometric indices, the well-known quality of life assessment tool Saint George Respiratory Questionnaire (SGRQ), Modified Medical Research Council (mMRC) dyspnea scale, patient mortality, prior episodes of exacerbation, changes in pulmonary health status over time and the risk of future exacerbation(s).

CAT and FEV1%

COPD is a complex disease that impacts health and quality of life on multiple levels. While spirometric indices such as FEV1% (forced expiratory volume for 1 second expressed as a percentage of forced vital capacity, FVC) provide a somewhat one-dimensional assessment of COPD severity in relation to airflow obstruction, the CAT is a much more comprehensive assessment tool that assesses the overall impact of COPD on a patient's health and quality of life. A study involving 105 patients in Iran found a significant correlation between various GOLD stages (based on FEV1%) (see Table 1) and CAT score categories ($p<0.001$). An inverse relationship was found

Table 1. Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging chronic obstructive pulmonary disease, based on presence of airflow obstruction (FEV1/FVC < 0.70) and its severity as gauged by % predicted FEV1.[1]

In cases where the FEV1 to FVC ratio is less than 0.70:

GOLD stage	Airflow obstruction severity	FEV1
I	Mild	≥ 80% predicted
II	Moderate	50-79% predicted
III	Severe	30-49% predicted
IV	Very severe	< 30% predicted

between CAT and FEV1% groups.[13] Dal Negro and colleagues also found a significant negative correlation between spirometric indices and CAT scores in a study on 681 Italian patients. This pattern was particularly significant for CAT and FEV1% ($p<0.001$ and $r=-0.21$).[7] This documentation of a strong inverse relationship between CAT scores and spirometric indices is noteworthy, since it suggests that CAT can be used as an alternative to spirometry in places where the latter is not available. [14]

Tu et al. found CAT and concomitant FEV1% to have significant negative correlation at the time of exacerbation and seven days after therapy ($r = -0.683$, the 7th day after therapy $r = -0.591$, both $P < 0.001$).[15] A study on 377 patients assessed the construct validity of CAT by comparing it with GOLD stages (classified by FEV1%). CAT was found to have a bimodal distribution, with GOLD I and II bundled together on one hand and GOLD III and IV on the other.[12] In a survey conducted by primary care practitioners in Netherlands, Italy, Germany, France, Belgium, United Kingdom and Spain, a weak negative correlation was found between CAT scores and FEV1% predicted value.[16]

The reliability and consistency of CAT questionnaire are further evidenced by the fact that confounding factors such as age, gender, body size, educational status and Body Mass Index (BMI) have no correlation with CAT scores.[7]

CAT and Saint George Respiratory Questionnaire

Improvement in quality of life is an important goal in COPD management. Other quality of life assessment tools such as the Saint George Respiratory Questionnaire (SGRQ) are quite capable of assessing the severity of COPD in a patient and have established utility in clinical trials. However, some major hurdles hinder SGRQ's use in clinical practice. These hurdles include its complexity, time-consuming nature and the complicated spreadsheets required for calculation of scores. Compared to SGRQ's 50 questions, the CAT questionnaire is much simpler, with only eight short questions. In a study conducted on 90 consecutive COPD patients, the SGRQ took 578 seconds whereas the CAT took 107 seconds to complete on average.[17] Stahl et al found that 10 percent of the patients found SGRQ difficult to complete.[18] The CAT has shown good positive correlation with SGRQ in several validity studies. The first CAT validation study showed a positive correlation with SGRQ ($r=0.8$).[10] Ringbaek et al found a positive correlation of similar magnitude between CAT and SGRQ ($r=0.73$) ($p < 0.001$).[17] Furthermore, a strong positive correlation ($r=0.8$) was found between CAT and SGRQ in 1817 COPD patients (FEV1%=56.7) in another study.[16] A study done on 77 Iranian patients to test the validity of CAT questionnaire in COPD patients in Iran also found a significant correlation between CAT and SGRQ scores ($r=0.666$, $P=0.000$).[11] In a study done on 101 patients in Crete, Greece, Tsiligianni et al reported a lower magnitude of positive correlation between scores on CAT and SGRQ ($r=0.65$).[19] Another study, in addition to establishing a high correlation between CAT and SGRQ scores at a particular time ($r=0.82$), also demonstrated a significant correlation between change in CAT scores and change in the total and domain scores of SGRQ over time in stable patients (r ranging from 0.44 - 0.63, $p<0.001$).[12]

CAT and mMRC Dyspnea Scale

Modified Medical Research Council (mMRC) dyspnea scale and CAT have been recommended by GOLD guidelines for the assessment of COPD symptoms.[20] The GOLD Report suggests that it is unnecessary to use more than one symptom scale in assessing patients' COPD status.[20] If one of these scales is to be used, both need to be comparable for COPD status assessment in patients. Hence, it is important to assess the correlation between CAT and the mMRC dyspnea scale. There is ample evidence in literature regarding the correlation between these two scales. In a cohort of 6,437 COPD patients, CAT scores were found to be significantly correlated (Spearman correlation analysis $r=0.579$, $P <0.001$) with mMRC dyspnea scores.[21] In an another study on 681 patients, CAT score was found to have a significant positive correlation with mMRC dyspnea scale score ($p < 0.001$ $r = 0.62$).[7] A study on 219 Spanish patients demonstrated a clear grading in CAT scores with respect to scores on the mMRC dyspnea scale.[12] In a cohort of 1817 European patients, there was a significant difference in mean CAT score at different mMRC dyspnea grades.[22] Positive spearman correlation (0.605, $P<0.01$) was found in another study of 90 COPD patients.[19]

Dyspnea is the most common and disturbing symptom in patients with COPD.[21] mMRC dyspnea scale categorizes patients based solely on dyspnea whereas the CAT is a multi-dimensional tool that utilizes 8 items of health status to classify patients. In a cohort of 257 patients, mMRC score exhibited wide range of correlation with CAT variables ($r = 0.290 \sim 0.731$; $p < 0.0001$). Amongst the eight variables on the CAT, dyspnea had the strongest correlation with mMRC scores ($r = 0.731$, $p < 0.001$). On the other hand, sputum production in CAT had the weakest

correlation with mMRC scores (r = 0.290, p < 0.001).[20] The 2011 GOLD report suggests categorization of COPD patients into high and low symptom groups. For this purpose, it recommends cutoffs at CAT score of 10 and mMRC dyspnea score of 2.[20] However, some researchers propose that a CAT score of 10 corresponds to an mMRC dyspnea score of 1 rather than 2.[23,20] Given that the CAT is a short and simple tool to assess COPD health status and correlates well with mMRC dyspnea scale, it can prove to be a highly useful addition to the arsenal of physicians treating COPD patients.

CAT and Mortality

Unlike the mMRC dyspnea scale, the CAT questionnaire's relationship to all-cause mortality is not well-established in the existing literature.[24] In an observational cohort of 768 patients, several parameters pointed out CAT's ability to predict all-cause mortality. Patients who died (n=73) had higher average CAT scores (14 vs. 11, P=0.022). ROC analysis in this study demonstrated that higher CAT scores were associated with higher mortality (C-statistic =0.589).[24] Moreover, CAT scores ≥17 proved to be as sensitive as MRC dyspnea scores ≥2 in predicting all-cause mortality. [24] These cutoffs are different than the cutoffs proposed by GOLD 2011 guidelines (as mentioned earlier). In another study done on 285 COPD patients, incremental increases in CAT scores were associated with increases in mortality. A hazard ratio of 1.02 (1.01-1.04, p<0.01) for a single point increase and a hazard ratio of 1.24 (1.05-1.37, p<0.01) for every 8-point increase in CAT scores were seen in this study.[25] In both these studies, CAT predicted all-cause mortality but was inferior to mMRC dyspnea scale for this purpose.

CAT and COPD Exacerbation

The CAT, as a quality of life assessment tool, has an established efficacy in predicting past, current and future exacerbations of COPD. Negro et al. found a significant positive correlation (p<0.001) between the use of steroids and antibiotics (indicators of COPD exacerbation) in the past 12 months and the CAT score at the present time (r=0.19 and r=0.16, respectively).[7] Mackay et al. found that in a population of 161 patients with COPD, frequent exacerbators (2 or more exacerbations per year) had higher mean CAT scores compared to infrequent exacerbators (less than 2 exacerbations per year) (19.5 +/- 6.6 vs. 16.8 +/- 8.0 respectively, P = 0.025).[26] Interestingly, Tu et al. also reported that patients with frequent exacerbations had higher mean CAT scores on exacerbation (24.74 ± 7.21) compared to those with infrequent exacerbations (20.62 ± 5.75); this difference was statistically significant (p<0.001).[15]

CAT questionnaire was initially developed following cross-sectional analysis of patients experiencing COPD exacerbation. However, the ability of this questionnaire to detect changes in pulmonary function status over time (i.e. sensitivity to change) was not established in that first study. Several studies thereafter studied the change in CAT scores during and after exacerbation episodes. Mackay et al found a significant rise in CAT scores from the average baseline value of 19.4 +/- 6.8 to 24.1 +/- 7.3 (p<0.001) during an episode of exacerbation.[26] Importantly, the magnitude of change in CAT scores during exacerbation was not affected by baseline patient characteristics.[26]

The time taken by CAT score to return to baseline after COPD exacerbation episodes was "significantly related" with time to recovery according to symptom diary cards (rho=0.42, p=0.012).[26] Jones et al. investigated the change in CAT scores over a period of 14 days in patient-judged "responders" and "non-responders" following an episode of COPD exacerbation. They reported that the change in CAT scores in responders turned out to be -2.8 +/- 4.6 units while that in non-responders was found to be 0.0 +/- 5.6 units; this difference was statistically significant (p=0.03). This highlights the ability of CAT scoring to differentiate between responders and non-responders to therapy in the first 14 days following a COPD exacerbation. This may help clinicians to make treatment decisions based on the patient's response to therapy.[23] Tu et al. conducted a study on 78 patients with COPD exacerbation and found a significant difference between CAT scores at exacerbation (23.19 ± 7.00) and after seven days of therapy following exacerbation (12.83 ± 5.82).[15] In another study done on 681 Italian patients to validate the role of CAT in assessing pulmonary function status, Negro et al. found the questionnaire to be sensitive to changes in respiratory function. Interestingly, CAT proved to be sensitive to both intra-patient and inter-patient pulmonary health status changes over the course of time.[7]

In addition to predicting exacerbations of COPD prior to its administration, CAT proved to effectively predict the future risk of COPD exacerbation. This supports the use of CAT as an assistive tool to facilitate healthcare providers in identifying patients at increased risk of exacerbation. Based on the hypothesis that health status at one particular point can prove to be a premonitory sign for exacerbation risk of COPD in the future, CAT questionnaires' potential in

predicting exacerbation risk of COPD in the six months following its administration was assessed. In a study conducted in China, Korea, Australia and Taiwan on 545 patients, the relation of baseline CAT scores and the time to first COPD exacerbation, any exacerbation and moderate-severe exacerbation, was assessed. With increasing CAT scores, including both categorized and uncategorized scores, the time to first exacerbation decreased and the risk for any exacerbation and the incidence of moderate to severe COPD exacerbation (requiring steroids and antibiotics) increased ($p<0.001$ for all three variables evaluated).[27] Furthermore, in patients with cardiovascular comorbidity, CAT proved to provide predictions of same magnitude as the general patient population. Previously, Hurst and Colleagues pointed out that the strongest predictor of COPD exacerbation in the future is history of exacerbation in the past year.[7] Meanwhile, CAT has been shown to be predictive of time to first exacerbation, any exacerbation and moderate-severe exacerbation, unlike the GOLD criteria. In alignment with this, Miravitlles et al. established that with a cut-off score of 13.5, CAT proved to be a significant predictor of a composite event (event related to COPD exacerbation) in the future. A significant increase in the probability of a patient experiencing a composite event (hazard ratio: 1.396, 95 percent CI: 1.076–1.812) was found at the cut-off CAT score of 13.5. In addition to this, the CAT score of >13.5 and exacerbation in previous year (AUC=0.864, 95 percent CI: 0.829-0.899, P=0.001) had more discriminatory power in predicting risk of future composite event than that of exacerbation in previous year alone (AUC=0.609, 95 percent CI: 0.559-0.658; P=0.001).[28] This encourages physicians to identify patents at risk of exacerbation by following patients' history of previous exacerbation and also risk stratify patients further based on their CAT scores at a particular visit.[27]

Conclusion

It can be reasonably concluded that the CAT questionnaire is a powerful, reliable and efficient tool that can help provide an objective assessment of a patient's symptoms within minutes. In addition to being sensitive to changes in pulmonary status over time in patients admitted for COPD exacerbations, it has also proven to be able to predict the risk of future exacerbations. The strong negative correlation between CAT scores and spirometric indices means that the CAT has the potential to be a cheap and effective alternative in places where spirometry is not available. Although not as accurate as the mMRC dyspnea scale in this regard, CAT can still be useful tool for predicting all-cause mortality. While the CAT is not meant to replace a thorough clinical history or diagnostic testing, it can potentially be a part of a multi-pronged approach towards the care of COPD patients worldwide. It can contribute to improved doctor-patient communication, better COPD status assessment and more favorable health outcomes.

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Infant With Acute Bilateral Pneumothorax During Air Transport

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Abstract

In rural settings, medically complicated patients may require air transport to facilities that are capable of providing higher levels of care. Extra consideration must be given to pulmonary pathologies when considering this mode of transport. Altitude changes impact both air pressure and volume as described by Boyle's law. These changes can complicate the care of these patients in several ways. We present a case of patient with respiratory failure secondary to viral infection who developed acute bilateral pneumothorax (PTX) while mechanically ventilated during a transport on a fixed-wing aircraft. In this article we outline the unique risks of air travel on the development and progression of PTX as well as the unique challenges with diagnosis and treatment during air transport.

Introduction

Respiratory failure requiring mechanical ventilation is a common indication for air transport, particularly in rural areas without access to higher levels of care.[1] Although necessary, mechanical ventilation can result in complications. These complications consist of volutrauma, traumatic injury to airways, and air leak syndromes including pneumothorax (PTX).[2] PTX is a condition of trapping of air between lung tissue and the chest wall within the intrathoracic space.[3]

Mechanical ventilation is further complicated by the process of air transport and the application of Boyle's law. This law describes the inverse relationship between pressure and the volume of gas; in an unpressurized cabin mid-flight, as altitude increases, air pressure decreases, which causes a fixed volume of gas to expand.[1,4] During air medical transport, these changes in air volume become significant when applied to conditions of air trapping such as mucus plugging in the lung or PTX. Physical examination to diagnose and assess a patient who has developed a complication mid-flight is complicated by the noise and movement of the environment.

We report a pediatric case during a fixed-wing air medical transport where the patient developed acute bilateral PTX while mechanically ventilated. Given the dynamic environment of air transport, the diagnosis and treatment approaches were constrained. Immediate recognition and intervention were required for successful transport and ultimate recovery for the patient.

Case Report

A 7-week-old male infant with no prior medical history presented with several days of symptoms consisting of fever, cough, congestion, and rhinorrhea. He was admitted to the local hospital and intubated for hypoxia and increased work of breathing. Given the severity of disease without a local pediatric intensive care unit (PICU) availability, the referral facility contacted the fixed-wing air medical transport team and requested patient transport to a PICU 200 miles away.

Prior to transport, there was significant respiratory acidosis (pCO_2 77 mmHg) with elevated peak pressures (Peak inspiratory pressures >32 mmHg) despite multiple ventilator maneuvers. Ultimately, achieved appropriate chest rise and improvement of the pCO_2 by tolerating peak pressures between 30 mm Hg and 40 mm Hg (with plateau pressure < 30 mm Hg).

Approximately 45 minutes into the fixed-wing transport, the patient had an acute decompensation during a nebulized bronchodilator treatment. His oxygen saturation rapidly dropped below 60 percent and end-tidal CO_2 ($EtCO_2$) was lost. Heart rate initially increased but then rapidly decreased concurrently with hypoxia. Blood pressure also precipitously dropped. On exam, the patient had poor bilateral chest rise with visible venous distension of his neck

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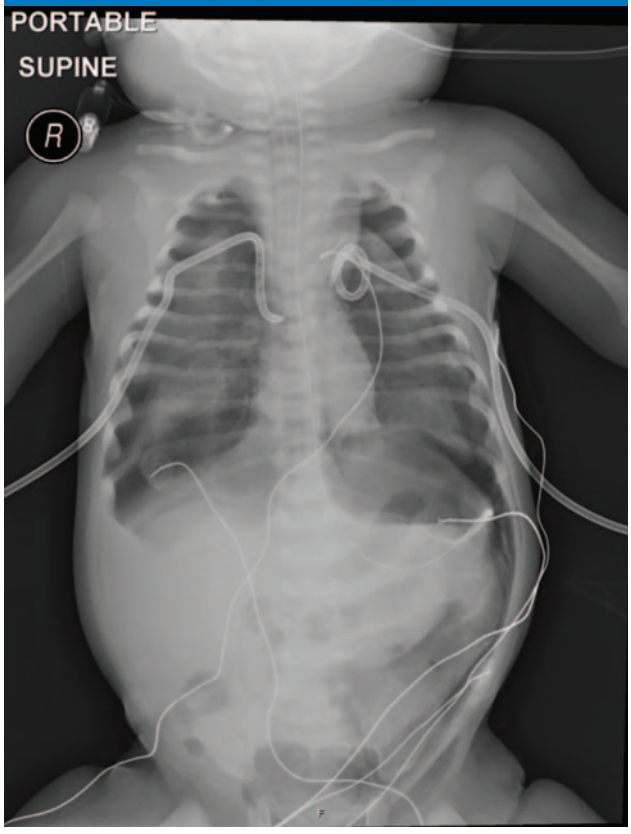
veins. Central pulses were weak. Due to aircraft noise, auscultation was impossible.

Given the constellation of clinical signs and history, a presumptive diagnosis of bilateral PTX was made. Immediate interventions included 100 percent FiO_2 (fraction of inspired oxygen) through bag mask ventilation, sedation boluses, fluid boluses, and emergently needle decompression of the chest bilaterally. The provider chose not to place chest tubes due to the need for a quick response and the difficult nature of preforming procedures on an aircraft including motion of the aircraft and working in a confined space.

Upon landing, the patient was transported by ambulance to the local PICU with continuation of repeated needle decompression as needed, each with air evacuation and improvement in symptoms. Physician to physician communication occurred in route and the receiving PICU was prepared with chest tube trays available in the patient room. Bilateral chest tubes placed immediately on arrival with rapid improvement in symptoms before confirmation by plain film (Figure 1).

Figure 1. Bilateral chest tubes placed immediately on arrival with rapid improvement in symptoms before confirmation by plain film.



During hospitalization, a comprehensive viral panel revealed that the patient's respiratory failure was from Human Metapneumovirus. This virus is a significant cause of respiratory infections in susceptible populations such as children, immunocompromised patients, and the elderly. Symptoms of Human Metapneumovirus infection range from mild cough and rhinorrhea to bronchiolitis, pneumonia and respiratory failure.[5] He was extubated on day 13 of hospitalization and discharged home on hospital day 20 on room air with complete recovery.

Discussion

This patient acutely developed unexpected bilateral PTX during transport. Given the critical nature of the patient, rapid diagnosis was vital for survival. Due to the noise of the aircraft, the diagnosis was made without the use of auscultation. Prompt intervention with needle decompression without chest tube placement during transport followed by emergent chest tube placement immediately on arrival to receiving hospital resulted in a positive outcome for the patient.

A PTX occurs due to a pathologic change in extrapulmonary pressure. The visceral pleura on the lungs and parietal pleura on the inside of the chest wall are typically held in close contact due to an overall negative pressure within the intrathoracic space.[6,7] It is this negative intrathoracic pressure that is responsible for proper expansion of the lungs during respiration. Introducing air (*pnumo-*) into this intrathoracic (*-thorax*) space reverses the negative pressure holding the visceral pleura, and thus lung, to the chest wall. The intrathoracic space, now with increased pressure, can no longer hold the lung open with the result being the partial or complete collapse of the lung. Without being properly inflated, there are regions with low ventilation to perfusion ratios potentially causing hypoxia and hypercarbia.[7]

The incidence of primary spontaneous PTX has been reported as 7.4-18 per 100,000 in men and 6 per 100,000 in women. The incidence in children, however, remains unclear at this time. Case series reviewed by Robinson et al. 2009 suggest that the incidence is low but with male preponderance in this population.[8] A 2015 article by da Silva et al. performed a study on the incidence, risk factors, and other outcomes of mechanically ventilated children. The article describes a 3 percent incidence of iatrogenic PTX. The most frequent cause of iatrogenic injury was from invasive thoracic procedures such as central venous catheter placement. The article goes on to describe how this finding

is three-fold higher than other reports from the Agency for Health Research and Quality (AHRQ) and other pediatric studies. However, the incidence of iatrogenic PTX in children is still not well known as projections are drawn from overall population data without distinguishing pediatric intensive care patients or neonates.[9] The incidence of PTX in commercial flights is rare. As reviewed by Hu et al. 2013, an observational study discussing the incidence of medical emergencies during flight in patients with lung diseases and a survey of 11,920 medical emergencies on commercial airlines, yielded no incidences of pneumothorax during commercial air travel.[10]

PTX is classified by its etiology, which can be either spontaneous or traumatic. [3,7] A primary spontaneous PTX occurs in the absence of underlying lung disease. Often, the primary spontaneous PTX is due to the rupture of weak points on the outer surface of the lung known as "blebs." Additionally, there can be secondary spontaneous pneumothoraces, which result as a complication from lung disease, such as COPD or asthma.[11] The other classification is traumatic, which can be the result of non-iatrogenic insults, such as blunt force traumas or penetrating wounds. The current case represents a case of iatrogenic PTX, which can be caused by medical procedures and treatments, including pleural biopsy, central venous line placement, and mechanical ventilation.[9,12] With iatrogenic PTX from mechanical ventilation, high tidal volumes cause barotrauma which rupture alveolae, ultimately leading to a PTX.[12] Due to the persistent hypercarbia in the presented case, a higher peak inspiratory pressure was required. This potentially worsened barotrauma. Additionally, poor lung compliance from the viral process likely contributed to the development of the PTX.

In addition to classifications, there are two types pneumothoraces: classical and tension.[3,7] Both are the result of free air in the intrathoracic space. The critical difference between the classic and tension type is that in a tension PTX the trapped extrapulmonary air increases in both volume and pressure with each inhalation. This trapped air compresses lung tissue, preventing its ability to oxygenate or ventilate. Furthermore, the intrathoracic air also compresses the large venous structures feeding the heart, the superior vena cava, and inferior vena cava. In doing so, venous return (preload) declines, and the patient experiences tachycardia and hypotension due to low cardiac output. Typically, the tension PTX in a non-intubated patient is the result of the perforated lung or thoracic wall acting as one-way air valve inflating the intrathoracic space during the negative pressure inhalation phase.

Most diagnoses of PTX can be made with auscultation and anterior-posterior plain film X-ray, though smaller sized or more complex pneumothoraces may require a Computed Tomography scan.[7,13] Since the inciting event for a PTX introduces air to the intrathoracic space, the treatment options revolve around removing this air thus restoring the negative pressure gradient.[1,6,7,14-16] On the more conservative end of treatment, the body is left to reabsorb the air itself. As eloquently reviewed in Arshad et. al 2016, gas trapped within the intercostal space is reabsorbed into the capillaries within the pleura.[17] This is due to the net total partial pressures of gases being higher in the trapped air relative to capillary blood which facilitates reabsorption.[7,18] Delivery of higher concentrations of oxygen to the patient increases this gradient further, speeding the process of intrathoracic air reabsorption.[18] A "small PTX" is classified as less than 20 percent or less than 3 cm of apex dehiscence or partial dehiscence with few symptoms, whereas a "large PTX" is greater than 20 percent or greater than 3 cm of apex dehiscence or complete dehiscence.[7] The observation approach is most often used for primary spontaneous pneumothoraces as these are usually non-life threatening. If the PTX is larger in volume complicated by lung disease as in a secondary spontaneous, or the patient's vitals are unstable as in a tension type treatment will consist of more actively venting the trapped air via a thoracostomy.[15] Most of the time, this is done via a needle or chest tube. While there is some debate as to using needle vs tube thoracostomy, the decision often comes down to external factors such as a facility's capabilities, the provider's experience level, patient risks of complications, and time constraints.[19,20] Of note, patients with suspected tension PTX should always be immediately treated with the quicker and less complex needle decompression due to the high probability of cardiopulmonary collapse.[21] For more severe cases that are not resolving despite chest tube placement, surgical options are used to repair the air leak and fix the lung visceral pleura to the chest wall.[7] This can be done via thoracotomy or video-assisted thoracoscopic surgery (VATS).

At flight altitude, the occurrence of a PTX can be complicated by the effects of Boyle's law, first described by Robert Boyle in 1662.[22] Boyle's law demonstrates the inverse relationship between gas pressure and gas volume at a constant temperature. As a formula, it is represented by $P_1V_1 = P_2V_2$, where P is pressure and V is a volume of gas. In the

setting of air medical transport, as an aircraft increases in altitude, the surrounding air pressure decreases. This change in pressure can have negative consequences in the context of pulmonary air trapping and pneumothoraces. In the relationship described by Boyle's law, trapped air volume begins to expand as altitude increases. For patients requiring air medical transport, Boyle's law becomes an important consideration depending on the pathophysiology of their condition. A 2013 study demonstrated the effect of Boyle's law in artificial models of pneumothoraces. This study showed a linear rate of volume change in accordance with Boyle's Law of 1.3 percent-1.5 percent per 500 feet elevation change, leading to a 12.6-16.2 percent increase in gas volume at 5,000 feet.[4] The patient in the current case report was being transported by fixed wing transport (airplane). Fixed-wing aircraft are most often pressurized to offset the low pressure at altitude; however, this typically does not bring the cabin pressure to equal ground level air pressure. A study evaluating commercial airline travel reports that commercial airlines typically operating at 40,000 feet are usually pressurized to 585 mmHg rather than the 760 mmHg found at sea level.[20] For the patient presented, the air medical transport aircraft operates at 20,000 feet above sea level with the cabin pressure set to what would be seen at 3,200 ft (660 mmHg). However, the destination medical facility for this case sits at 1,650 feet above sea level making for an effective altitude pressure differences between the cabin (at 3,200 feet) and ground level (at 1,650 feet) of 1,550 feet. According to the 2013 study modeling the artificial PTX at altitude, this height would correspond to a volume increase of approximately 4.5 percent.[4] Though this volume change is small, it still may have been contributory to the barotrauma or volutrauma leading to the patient's rapid and severe deterioration.

Boyle's law complicates the course of air transported patients with respiratory compromise in several ways. Firstly, in conditions such as reactive airway disease or mucus plugging where air is trapped within the alveoli of the lung, expanding air can induce hyperexpansion of the walls of the alveoli resulting in barotrauma which increases the likelihood of alveolar rupture and subsequent PTX. Secondly, in addition to air trapping within the lungs, air trapping in the intrathoracic space from a PTX can also expand. This air trapping has particular relevance in small non-tension type PTX noted prior to transport. Once intrathoracic air expands due to a lower pressure environment during transport, this classic PTX can convert to a tension type compressing vital structures. Finally, in mechanically ventilated patients, the delivery of air in ventilators calibrated to sea-level do not always adequately compensate for the increased volume of air at higher altitudes. In 2015, the Air Force Research Laboratory released an article evaluating the performance of three different models of portable ventilators. The results showed two of the three models did not have compensatory mechanisms to address increases in altitude. Additionally, they report two of the models had significantly increased tidal volumes at higher altitudes.[17] The altered ventilation volumes could increase in the risk of iatrogenic injury in these patients.[2]

Although the patient was at higher risk for PTX due to his underlying pathology, there were no indications of trapped air causing trouble at the beginning of the transport. It was not until 45 minutes into the flight that the patient developed sudden signs and symptoms consistent with a tension PTX. Specifically, there was rapid onset of hypoxia, loss of chest rise, hypercarbia, and low cardiac output. Additionally, prominent jugular venous distension was seen, a finding uncommon in pediatrics, as well as a rapid redness of the face. It was assumed that the SVC was being compressed as a result of a tension PTX. Confirmation by auscultation or chest radiography was not possible due to the dynamic environment of the aircraft. However, the flight team was convinced by the presentation, and that without immediate reversal the patient's condition would have likely progressed to cardiopulmonary arrest.

In the cases of necessary air transport , resolution the PTX via needle or tube thoracotomy before transport is recommended.[16] A retrospective case-series study of PTX in unpressurized rotor wing air medical transport, presented by Braude et al 2014 concluded that there was a relatively small amount of risk when transporting a patient with a mild PTX.[1] In the study, there were few instances where the patient's respiratory status deteriorated mid-flight. Of these few cases, all were adequately treated in-flight with emergent needle decompression. In the current case of the infant in respiratory distress, PTX was not suspected before flight, removing the question of preflight venting. However, similar to the results from Braude 2014, the rapid in-air deterioration our patient experienced from suspected tension PTX was successfully managed with needle decompression aboard the fixed wing. The same article goes on to describe the mixed efficacy of needle thoracotomy for temporary management of PTX in air medical transport. However, they argue that the complications for both patient and provider staff are higher in tube thoracostomy

compared to temporary needle thoracostomy during air medical transport. This study supports the idea that tube thoracostomy may be safely deferred during air medical transport in suspected mild PTX, which goes against the routine placement of tube thoracostomy, thus saving time for travel and sparing potential complications for patients.[1]

An article from Teichman et al. 2007 described international air evacuation states in patients with hypoxic conditions which should include supplemental oxygen and ventilation; however, pilots can also perform low-altitude flight paths to prevent deconditioning in this setting. The article goes on to recommend that patients with pulmonary conditions should defer evacuation until the patient stabilizes at the local facility. In addition to ensuring stability of airway, breathing, and circulation, the article states thorough preflight checklist evaluations are performed to identify any contraindication to aeromedical evacuation. A chest radiograph is performed to rule out the presence of PTX as it is listed as a relative contraindication to aeromedical evacuation.[23] In the case presented, no PTX or other contraindications were identified at the outside facility and thus air medical transport was warranted. Despite the risks we outline in the discussion of air transport and the effect of Boyle's law, we did not encounter any scenarios that mechanical ventilation alone would disqualify a person for air transport.

Multiple organizations have released guidelines on air travel after a PTX. Bunch et al. 2013 examined current guidelines and performed a review of literature surrounding commercial flight in the setting of PTX. The authors concluded that there was considerable variation in the recommendations and an overall lack of evidence from different organizations such as the British Thoracic Society, British Thoracic Surgery, and Aerospace Medical Association. Interestingly, no published guidelines are currently available from the American Medical Association or American College of Chest Physicians. The review showed only two prospective and two retrospective studies supplemented with several smaller case studies, case series, topic reviews and society guidelines. The study concludes there is too little data on the matter and calls for additional information to be gathered before absolute evidence-based recommendations can be created. However, they did note that most articles seemed to have loose agreement on a 14-day delay for air travel following radiographic resolution of the PTX.[24]

Conclusion

Emergent medical flight transport will continue be a necessary lifesaving component of any medical system that serves rural areas or smaller medical facilities. In this case report, we outline an instance of the pulmonary complications that can result from the relationship between air pressure and gas volume described by Boyle's law. Our patient did not have a recoginzed PTX before getting on the medical flight. A review of the literature did not reveal a larger discussion directly relating to defering emergent air transport due to the risk of developing a PTX at altitude. Any decision to delay air transport must be weighed against the consequences of delaying arrival to an intensive care center. While it is important for the medical community to continue to develop guidelines to reduce risk, we feel the valuable lesson from this case is having an actionable plan and prepared staff in place for such medical emergences.

For the primary care provider who rarely sends patients by air medical transport we would offer a takeaway message to give special consideration to possibility of pneumothorax before trauma patients or those with high-risk respiratory conditions are sent by air medical transport. If a seemingly benign pneumothorax is present, consider that it could convert to a tension pneumothorax in air. A pneumothorax detected before flight can be treated with traditional tube thoracotomy provided time permits and the provider has maintained the skill. If either of these conditions cannot be met, needle thoracotomy is an acceptable alternative.

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A Case of Pituitary Macroadenoma Presenting as Aseptic Meningitis

Brendan Wechsler, MS IV; Stephanie Kazi, MD; and Nessim N. Amin, MD

Abstract

Pituitary adenomas are a common brain tumor that are frequently asymptomatic but may initially present with vision deficits or very rarely as meningitis thought to be due to cerebrospinal fluid leakage. In this case report we discuss the initial presentation of a pituitary macroadenoma as aseptic meningitis, particularly in the absence of an identifiable cerebrospinal fluid leak. We also discuss the workup and diagnostic challenges associated with this atypical presentation, including findings on imaging and pertinent laboratory results.

Background

Pituitary adenomas are a common brain lesion, with an overall prevalence of 16.7 percent, and are often designated as microadenomas (smaller than 1 cm) or macroadenomas (larger than 1 cm).[1] While frequently asymptomatic, the most common presenting symptoms are headache or vision changes due to mass effect. Other presenting symptoms may include those due to increased hormone production in functional pituitary adenomas.[1,2] The occurrence of acute aseptic meningitis as the initial presentation of a pituitary adenoma is rare, with only a few reported cases in the literature. The presentation of meningitis due to a pituitary adenoma is thought to be due to mass-effect causing leakage of cerebrospinal fluid (CSF) from erosion of the floor of the sella by the pituitary tumor into the sphenoid sinus or via alterations in CSF pressures and dynamics, often presenting as rhinorrhea.[3]

We report a case of a pituitary macroadenoma that presented initially as aseptic meningitis. The diagnostic workup is discussed, including the challenges of diagnosis with non-specific symptoms in the presence of medical comorbidities.

Case Presentation

A 66-year-old female with a past medical history including type 2 diabetes, chronic kidney disease, chronic obstructive pulmonary disease, hypertension, hyperlipidemia, osteoarthritis, and former tobacco use was admitted due to acute encephalopathy. Earlier in the day, she was observed to be somnolent but responsive when evaluated at a clinic for confusion, subjective fever, and neck pain prior to transfer to the emergency department. She had a reported history of recurrent falls without head trauma, decreased mental status, and persistent headaches over the previous four days. Her history was positive for chronically blurry vision for the past seven years, however no acute changes in vision were reported. On exam, her temperature was 36.1 degrees Celsius, blood pressure was 130/85, pulse was 105 bpm, and respiratory rate was 17. She was oriented only to self, exhibited restless, spontaneous movements of all extremities, and could only follow simple commands. Cranial nerves were intact and no visual field deficits were apparent. Medications on admission included rosuvastatin for hyperlipidemia, docusate as a stool softener, as well as calcium, vitamin D, and vitamin B12 supplements. Of note, she was not taking any medications or supplements containing Biotin. Kidney function on admission was mildly decreased, with a baseline Creatinine ranging between 1.10 and 1.40 mg/dL. The patient had four pregnancies with four live births. She reports regular menstrual cycles when premenopausal, and no issues with lactation but reports no galactorrhea.

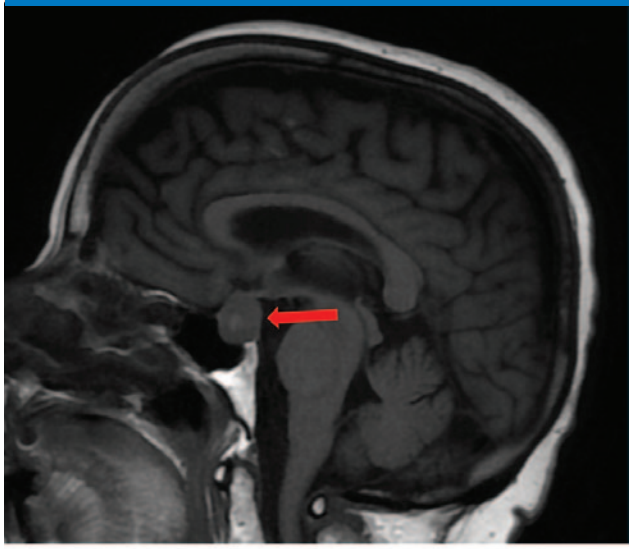
Computed tomography (CT) of the head showed no significant findings and CT of the neck showed chronic degenerative changes with grade 2 anterolisthesis of C2 and C3. Laboratory test results revealed a white blood cell (WBC) count of 8.4K/uL, serum glucose of 103mg/dL, normal electrolyte levels, and elevated inflammatory markers including a C-reactive protein of 133.1mg/L and procalcitonin of 0.19 mg/L. Blood ammonia and lactic acid levels were normal. Urinalysis did not show signs of infection. A lumbar puncture revealed CSF with pleocytosis (WBC count of 15/uL, differential of 5 percent neutrophils, 37 percent lymphocytes, and 58 percent mononuclear cells; red blood cell (RBC) count was 118/uL), markedly elevated

protein (332.9mg/dL), and slightly elevated glucose (78mg/dL). Meningitis and encephalitis panels were negative for bacterial, viral, and fungal pathogens.

CT of the head did not differentiate any intracranial abnormalities. Magnetic resonance imaging (MRI) without contrast of the brain revealed a 1.8 cm lesion within the sella extending into the suprasellar cistern consistent with a macroadenoma. There was a 5 mm focus of bright signal within the central aspect of the mass suggestive of a hemorrhagic focus. Mild to moderate generalized atrophy and a number of bright signal foci were noted diffusely in white matter of both cerebral hemispheres on T2 and fluid-attenuated inversion recovery (FLAIR) images suggestive of chronic small vessel ischemic changes.

Endocrinology evaluation determined the pituitary adenoma to be nonfunctional. Thyroid stimulating hormone, free

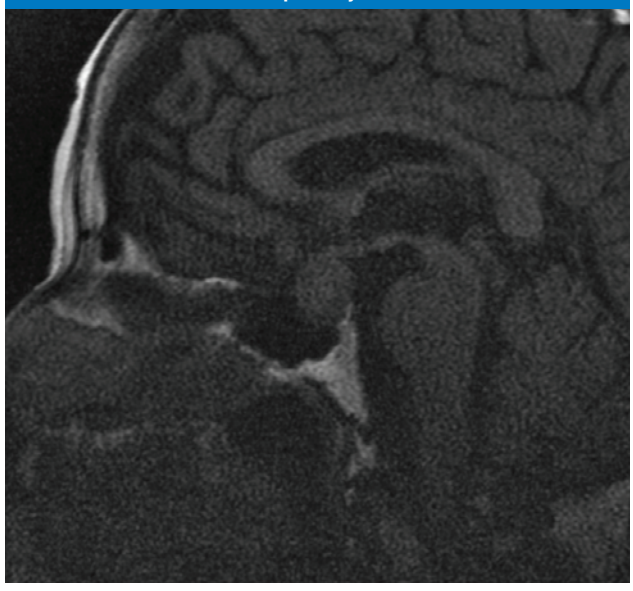
Figure 1. MRI, sagittal T1 FLAIR without contrast depicting a pituitary macroadenoma (red arrow).



T4, adrenocorticotropin releasing hormone (ACTH), serum cortisol, insulin growth factor-1 (IGF-1), and 24-hour urine free cortisol were within the normal ranges. Prolactin was elevated at 66.6 ng/mL, and luteinizing hormone (LH) and follicle stimulating hormone (FSH) were low at <0.1 and 1.3 IU/mL respectively, most consistent with stalk effect from compression of functional pituitary tissue and post-menopausal state. Ophthalmology evaluation was limited due to the patient's inability to participate; however, she appeared perceptive to light in both eyes and anterior segment and dilated fundus exams appeared normal in both eyes with no nerve edema or retinal hemorrhages.

Mentation slowly improved over the following days; she was oriented to person, place, and partially to time (could recall year but not month), able to communicate appropriately, and denied headache or neck pain at discharge. Neurosurgery did not recommend immediate surgical removal of the pituitary adenoma given clinically improved status, absence of visual impairments, the classification of the adenoma as nonfunctional by endocrinology, and extent of patient's comorbidities. Follow-up MRI three months later showed the overall mass size to be stable. There was a new 8 mm area of increased signal on T2-weighted imaging with diminished enhancement suggestive of cystic degeneration. Neurosurgery suggested conservative management and follow-up to monitor for acute changes or neurologic compromise. At ophthalmology follow-up three months later, she continued to endorse headaches and binocular horizontal diplopia, but visual fields and funduscopic examinations remained unremarkable.

Figure 2. Follow-up MRI, Sagittal T1 without contrast depicting stable size of the pituitary macroadenoma.



Discussion

Pituitary adenomas are a common disease process, with an estimated total prevalence of 16.7 percent. These brain tumors are often asymptomatic but can present with headaches or vision changes due to mass effect. Less commonly, they may present with symptoms due to release of excess pituitary hormones. Rarely a patient may present with meningitis as an initial symptom of a pituitary macroadenoma, as depicted in this case.

In this case presentation, the patient underwent a full medical workup including CSF analysis and MRI, which

were consistent with the diagnosis of aseptic meningitis due to a pituitary macroadenoma. Standard imaging techniques for identification of CSF leaks include High-resolution computed tomography (HRCT), Magnetic resonance cisternography using MRI, Radionucleotide cisternography or CT cisternography.[4] In our case, the lack of signs or symptoms of CSF leak such as rhinorrhea, as well as a negative brain MRI effectively ruled out the presence of a CSF leak.

Management of a pituitary macroadenoma often depends on clinical presentation. Surgical resection is recommended with a clinical picture of visual field defects, tumor growth, or hypopituitarism. Patients who do not undergo initial surgical resection may be monitored via surveillance MRI for up to 20 years; Tumor growth in patients not undergoing surgery on initial presentation is expected in approximately 24.1 percent of macroadenomas.[5,6]

This reported case is unusual in that our patient did not experience CSF rhinorrhea throughout the course of the medical workup, whereas similar cases of meningitis due to a macroadenoma typically presented with CSF leaks.[7] With the 5 mm focus of bright signal within the pituitary adenoma suggestive of blood, the differential should also include pituitary apoplexy, which can present with similar nonspecific symptoms such as headache, vomiting, or visual defects. This ailment is a more common presentation with a pituitary adenoma than meningitis, with the reported incidence ranging from 1-26 percent.[8] Imaging such as CT or MRI, as well as a CSF analysis, can help to differentiate these diagnoses. The CSF analysis in a pituitary apoplexy is oftentimes normal, but may present with low glucose, pleocytosis, and elevated protein if necrotic tissue is present within the subarachnoid space.[9]

The patient's prolactin level was 66.6 ng/mL. Caution should be exercised in interpreting serum prolactin concentrations between 20 and 200 ng/mL in the presence of a macroadenoma because of possible artifactually low values due to the "hook effect".[10] This effect occurs when a very high serum prolactin, e.g., 5,000 ng/mL, saturates both the capture and signal antibodies used in immunoradiometric and chemiluminescent assays, preventing the binding of the two in a "sandwich." The result is an apparent prolactin concentration that is only modestly elevated, suggesting that the macroadenoma is clinically nonfunctioning. The artifact can be avoided by repeating the assay using a 1:100 dilution of serum.

Macroprolactinemia is an umbrella term used to describe aggregates of prolactin and antiprolactin antibodies that range in size from approximately 150 to 170 kD. The most common form of native prolactin in serum is 23 kD in size and macroprolactinemia generally appears to be a benign clinical condition. Although these entities are not of clinical significance directly, they are of clinical significance indirectly because they can be misdiagnosed and treated as prolactin hypersecretion.[11] Misdiagnosis can be avoided by asking the laboratory to pretreat the serum with polyethylene glycol to precipitate the macroprolactin before the immunoassay for prolactin.

Prolactin assay may be significantly impacted by high-dose biotin (greater than 5 mg dose) taken within previous 12 hours. A high concentration of biotin may lead to falsely decreased results.[12] These concentrations may be found in patients taking over-the counter supplements with biotin contents higher than nutritional requirements for biotin. Specimens should not be collected until at least 12 hours after the last dose.

In our case, serum prolactin level was repeated six weeks later and came back 62.7 ng/mL (1:10 dilution performed). This is consistent with stalk effect, not a prolactinoma. Macroprolactin was never ordered and the patient was not taking supplements with biotin. LH and FSH were low at less than 0.1 mIU/ml and 1.3 mIU/ml respectively while one would suspect higher levels considering her post-menopausal status. The tumor is therefore impairing the production of gonadotropins.

Conclusions

Aseptic meningitis may be a rare initial presentation of a pituitary macroadenoma. Leakage of CSF into the sphenoid sinus is the commonly recognized pathophysiology behind development of meningitis in the setting of a pituitary adenoma. While this often presents with clear rhinorrhea, it is also possible in its absence, and should nevertheless be considered. Clinicians should also be mindful of the hook effect when ruling out a prolactinoma in the setting of pituitary mass.

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Dry Eye Disease: Advancements and Solutions

Sarah Jungers, PharmD; and Jodi R. Heins, PharmD

Dry eye disease (DED) also known as keratoconjunctivitis sicca is the most common disorder affecting the anterior eye.[1] In the U.S., up to 49 million Americans have dry eyes. The prevalence increases with age and is more common in women than men. Patients with DED commonly present with symptoms that range from mild to severe and often include dryness, red eyes, gritty/burning sensation, and potential for blurred vision.[1] The goal of treatment is to alleviate the dryness of the ocular surface to prevent tissue damage. Treatment can be divided into two different categories, over the counter (OTC) therapy and prescription therapy. First line OTC treatment often includes artificial tears, such as hydroxypropyl methylcellulose or carboxyl methylcellulose. These come in a variety of different formulations and are dosed multiple times daily to maintain the viscosity of the eye.[1] When OTC therapy is not adequate, further evaluation is needed to determine the appropriate prescription therapy.

The two first-line prescription therapy agents are topical cyclosporine and lifitegrast.[2] Of these agents, initial therapy is often determined by cost and insurance coverage. Topical cyclosporine A (CsA) is an anti-inflammatory agent that has been widely used to treat ocular diseases. Topical cyclosporine is a calcineurin inhibitor and immunosuppressant agent that works to inhibit the production and release of interleukin II along with inhibiting interleukin II-induced activation of resting T-lymphocytes. Two different CsA eyedrops have been approved by the U.S. Food and Drug Administration (FDA) for managing dry eyes; Restasis (CsA 0.05%) in 2002 and Cequa (CsA 0.09%) in 2018.

The first approved emulsion agent, Restasis, was found to significantly improve corneal staining and Schirmer's test score (STS) from baseline to six months ($P \leq 0.05$) in two multicenter, randomized phase three trials.[3] The STS is used to measure tear production through the principle of capillary action.[4] A paper test strip is placed into each eye and after five minutes the length of the moistened area of the strip is measured; the rate of travel along the test strip is proportional to the rate of tear production. The STS is measured on a scale of 0-10 mm. A score greater than 10 mm in 5 minutes is considered normal, but a score less than 5 mm in 5 minutes indicates a tear deficiency. About 43 percent of the patients enrolled in the clinical trials experienced adverse effects, mostly limited to ocular effects upon instillation such as burning or pain.

Cequa, an aqueous nanomicellar solution was approved in 2018.[2] Phase 2b/3 clinical studies showed that compared to placebo, Cequa was superior at increasing tear production and improving conjunctival and corneal staining from baseline to four weeks and beyond. Side effects similar to Restasis were observed with administration and no serious adverse effects were reported. Based on clinical studies, both topical cyclosporine products are administered one drop in each eye twice daily, ideally 12 hours apart.[5] Restasis is approved for patients 16 years and older and Cequa is approved for patients 18 years and older. It may take up to six weeks or longer of treatment to achieve noticeable improvements. No head-to-head trials have been done to compare the two products. The most common side effects include a burning sensation of the eyes or eye pain. In rare cases, it has been found to cause headache, urinary tract infection, upper respiratory tract infection, or blepharitis.

Topical 5% solution lifitegrast (Xiidra) functions as a lymphocyte function-associated antigen-1 (LFA-1) antagonist and was approved by the FDA in 2016 for the treatment of DED.[6] Lifitegrast binds to the LFA-1 and blocks the interaction with its cognate ligand intracellular adhesion molecule-1 (ICAM-1) to prevent T-cell activation and migration, which reduces ocular inflammation.

In the phase three study, OPUS-3, participants were randomized to receive twice daily lifitegrast or placebo for 84 days.[6] The primary endpoint evaluated the eye dryness score (EDS), and secondary endpoints evaluated the visual analogue score, safety/tolerability. At day 84, significant improvements in EDS were found in the treatment group vs placebo ($P = 0.0007$). A greater improvement was observed in the lifitegrast group in terms of symptoms

including itching, foreign body sensation, and eye discomfort. Overall, side effects reported were mild to moderate, with no serious adverse events. Based on clinical studies, topical lifitegrast is dosed as one drop in each eye every 12 hours and is approved for use in patients 17 years and older.[6] Adverse reactions common to this product are dysgeusia, application site irritation, and decreased visual acuity. Other reactions are headache, blurred vision, eye discomfort, and sinusitis.

Varenicline (Tyrvaya) is a new agent approved on Oct. 18, 2021, as a nasal spray for the treatment of DED.[7] Varenicline, which also comes as the oral tablet Chantix for smoking cessation, is now approved as a preservative-free prescription nasal spray for dry eye disease. The exact mechanism for intranasal varenicline is unknown but it is thought to work as a cholinergic agonist that binds to cholinergic receptors to activate the trigeminal parasympathetic pathway to stimulate natural tear production. The efficacy and safety of varenicline for DED was established in the ONSET-1, ONSET-2, and MYSTIC clinical studies.[7] All three studies enrolled participants 22 years old and older with a diagnosis of dry eye disease. The studies also looked at a variety of different screening criteria including the Ocular Surface Disease Index, corneal fluorescein staining score (CFS), EDS, and the baseline STS.

ONSET-1 was a phase two study that was followed by a large phase three study, ONSET-2. ONSET-2 evaluated participants that were randomly assigned in a 1:1:1 ratio of treatment with varenicline 0.6 mg/mL, 1.2 mg/mL, or vehicle used in each nostril twice daily for four weeks.[7] The study population included a wide range of patient with dry eye disease from mild to severe symptoms. The primary endpoint focused on the percentage of participants that achieved a 10 mm improvement or more in STS at four weeks. Secondary endpoints focused on the Eye Dryness Score (EDS) from baseline to four weeks and the safety of intranasal varenicline. Overall, the study found a statistically significant increase in the primary endpoint of difference in STS score from baseline to week four ($P < 0.0001$ for both doses). The secondary endpoint on EDS was found not to be significant and 86.5 percent of patients reported some adverse effect within the four-week period. Most commonly reported adverse effects included sneezing, cough, throat irritation, and irritation upon application.

Overall, the results of ONSET-2 remained consistent with the results found in the previous phase two studies ONSET-1 and the MYSTIC trial.[8] Intranasal varenicline was shown to be the first in-class nasal spray used for DED, it showed significant results in patients with a wide range of symptoms within two to four weeks, with minimal side effects.

Based on the clinical trials, intranasal varenicline was approved as a 0.03 mg/actuation spray and is administered as one spray into each nostril twice daily, approximately 12 hours apart.

Although not commonly used, there are several other DED treatments that can be considered for adjunct treatment by an eye specialist. These treatments include: short-term topical glucocorticoids, punctal occlusion to reduce the rate of tear drainage, autologous serum tears, tear stimulation (pilocarpine, cevimeline), Omega-3 fatty acids, oral antioxidants, scleral contact lenses, acupuncture, surgery, or two investigational eye drops, diquafosol and rebamipide.

DED is a prevalent disease that causes discomfort for many people around the world. While treatment options may not provide a permanent solution, relief from symptoms is improving with current therapies. It is exciting to see new treatments and technology being developed to combat this widespread condition.

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Stay informed with InSession, an SDSMA newsletter published during the legislative session. InSession is an up-to-date look at the issues on which the SDSMA is advocating. Watch your email for this weekly legislative update.

Nominations Being Accepted for SDSMA Leadership Positions

The SDSMA Nominating Committee will meet in March to nominate officer candidates for 2022-23 to be voted on by the membership. Those positions include president-elect, vice president, and secretary-treasurer, and AMA delegate. This committee also nominates candidates for three at-large members of the Board of Directors and a Policy Council chairperson from among (or such persons must be) members of the SDSMA Policy Council.

All SDSMA members who have an interest in a leadership position as an officer, AMA delegate, at-large position or Policy Council chair, must submit their name to one of the members of the Nominating Committee listed below by March 2. The Nominating Committee member will present your name at the committee meeting.

Those who have questions about the nominating or election process for SDSMA leadership positions may contact the SDSMA office at 605-336-1965.

Nominating Committee Members

- Benjamin C. Aaker, MD — aakerb@gmail.com
- Jerome W. Bentz, MD — jerome.bentz@avera.org
- Matt Bien, MD — bien@brookings.net
- Lisa B. Brown, MD — lbrosinbrown@mac.com
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Insurers Now Cover At-Home COVID Tests

Insurers and group health plans are now required to cover the cost of over-the-counter, at-home COVID-19 tests beginning Jan. 15, the U.S. Department of Health and Human Services (HHS) recently announced.

The coverage requirement means that most consumers with private health coverage can go online or to a pharmacy or store, buy a test, and either get it paid for up front by their health plan, or get reimbursed for the cost by submitting a claim to their plan. According to the HHS announcement, this requirement incentivizes insurers to cover these costs up front and ensures individuals do not need an order from their health care provider to access the tests.

Legal Brief Highlight: Thinking About Volunteering Medical Services?

Many physicians and other health care providers volunteer their time and skills to give primary and specialty care to patients who lack public or private health insurance and cannot afford care. They might volunteer their time though free clinics and through organized networks started by health departments, hospitals, religious groups and other community organizations.

Addressing the concern of practitioners regarding the risk of liability is one of the challenges to these volunteer efforts. However, there is liability protection for volunteers carrying out medical duties for charitable duties or emergency care.

South Dakota law states that any licensed health care professional providing volunteer services is immune from civil liability in any action that may be brought to court on the basis of an act or omission resulting in damage or injury, as long as the volunteer is acting in good faith and within the scope of the nonprofit organization's duties, and as long as the damage or injury was not caused by gross negligence or willful misconduct. Further, licensed physicians, surgeons and osteopaths who provide care at the scene of an emergency are not liable for any civil damages.

More information is available in the SDSMA legal brief Volunteer Medical Services at sdsma.org. Through the SDSMA Center for Physician Resources, the SDSMA has developed more than 50 legal briefs that are available to members. In addition, the Center develops and delivers programs for members in the areas of practice management, leadership and health and wellness.

COVID-19 Resources

Stay well-informed during the COVID-19 pandemic. Visit SDSMA's resource page at sdsma.org for resources and information, including messaging guidance/talking points for how to approach the topic of vaccination with patients.

COVID-19 Vaccine – Clinical vaccine guidance compiles information from FDA, CDC and other health organizations at sdsma.org.

Booster – CDC guidance states that after the initial 2-dose MRNA vaccine series, booster shot should be after five months (everyone age 12 and above is eligible for Pfizer booster), and everyone age 5 and up is eligible for the 2-dose Pfizer vaccination. After 1-shot J & J vaccine, booster shot should be after two months.

CDC Update – COVID Guidelines for Health Professionals – With the increase in COVID-19 cases due to the omicron variant, the CDC released emergency isolation and quarantine guidelines for health care professionals to assist with staffing shortages. The updated guidance, which differs from that for the general public, advises:

Health care professionals with COVID-19 infection who are well enough and willing to work to return to work as follows:

HCP with mild to moderate illness who are not moderately to severely immunocompromised:

- At least five days have passed since symptoms first appeared (day 0), and
- At least 24 hours have passed since last fever without the use of fever-reducing medications, and
- Symptoms (e.g., cough, shortness of breath) have improved.

HCP who were asymptomatic throughout their infection and are not moderately to severely immunocompromised:

- At least five days have passed since the date of their first positive viral test (day 0).

Healthcare facilities may choose to confirm resolution of infection with a negative antigen test or NAAT. Read the full guidelines at cdc.gov/coronavirus under the Healthcare Workers link for the most up-to-date guidance. CDC also updated its guidance for contingency and crisis management in settings with significant health care worker shortages, which can also be found at cdc.gov. As additional information becomes available, the guidance may change from what is printed at the time of *South Dakota Medicine's* deadline.

Save the Date: 2022 SDSMA Annual Leadership Conference is June 3

The 2022 SDSMA Annual Leadership Conference is Friday, June 3 at the Hilton Garden Inn Downtown Sioux Falls.

With presentations, discussions, networking opportunities and the banquet, the Annual Leadership Conference is a great time to share ideas and learn from fellow members.

Do you have a policy issue you'd like to bring to the SDSMA's attention? Schedule a time to address the SDSMA Policy Council during the Membership Open Forum. Watch sdsma.org for policy submission information to be posted soon.

The Annual Leadership Conference is a benefit of your membership and there is no conference registration fee. Tickets are required for some events and meals, and will be available for purchase at sdsma.org.

PATIENT EDUCATION:

Rural Emergency Medical Systems in Crisis

Matthew Owens, MD

Emergency medical services (EMS) in rural America are in a state of crisis. Difficulty recruiting emergency medical technicians (EMTs) and the financial constraints of EMS agencies are the major causes of this crisis.

The majority of South Dakota is considered a medically underserved area (MUA), indicating too few primary care providers, high infant mortality, high poverty or a high elderly population. Most of the MUAs are also designated as rural or frontier, increasing the likelihood of prolonged transport times to hospital-based medical care. Rural and frontier MUAs are historically served by volunteer EMS services. Seventy three percent of EMS agencies in South Dakota utilize volunteers. In 2016, 32 percent of volunteer agencies reported missing calls due to staff shortages. These conditions have led to a disparity in mortality rate for traumas for rural residents.

An ad hoc group comprised of the University of South Dakota School of Medicine, South Dakota State Medical Association, Northeast and West River Area Health Education Centers (AHEC), Sanford Academic Affairs EMS Outreach, and Community Memorial Hospital in Redfield has received funding through the U.S. Department of Labor, and Substance Abuse and Mental Health Services Administration to combat the EMS crisis in South Dakota and improve health outcomes for rural residents.

For many students, grant money is available to cover costs of the EMT training available at Sanford EMS Outreach. The synchronous online classes can be completed by the student at home, while the hands-on portion may require weekend travel.

In addition, members of the ad hoc group developed the Dakota Responder class curriculum, the goal of which is to train more people. Through a unique collaboration with Agtegra, a farmer-owned grain and agronomy cooperative with more than 6,300 members-owners in eastern North and South Dakota, the Dakota Responder classes will initially be made available to Agtegra employees. Those who attend the classes will be trained to provide emergency care for serious bleeding, opioid overdose, and use of automatic defibrillators. Agtegra employees located in rural areas of the Dakotas are well-positioned to provide life-saving care until EMS personnel arrive on scene.

Ultimately, the goal is to increase the number of trained EMTs to staff rural EMS centers and improve emergency response times. To encourage this endeavor in your community, share this information with your neighbors and contact your legislators and county commissioners to urge their support for local EMS centers where you live.

Matthew Owens, M.D. practices family medicine in Redfield, South Dakota. He is a contributing Prairie Doc® columnist. For free and easy access to the entire Prairie Doc® library, visit www.prairiedoc.org and follow Prairie Doc® on Facebook featuring On Call with the Prairie Doc® a medical Q&A show streaming on Facebook and broadcast on SDPB most Thursdays at 7 p.m. central.

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