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Dear Readers,

We express our deepest gratitude to the authors, reviewers, faculty mentors, our institution's administration and academic departments, and, most importantly, our student staff. It has been an unbelievable learning opportunity and an absolute privilege to work with all of you in the production of this volume.

We joined the Journal in our first year as medical students, overcome with the enthusiasm of its potential. In that year, we witnessed the remarkable effort put forth by Aaron and Devin to bring this Journal back to life. Last year, Katie, Edina, and Dino continued to lay the foundation for making the Journal an integral part of the Wake Forest community. In this past year, we have strived to add to the Journal's legacy, depth, and influence, both within and outside of the Wake Forest community.

Wake Forest Journal of Science and Medicine, volume 3, marks a year in which we received our highest number of submissions and endorsements from reviewers across the nation. We attribute much of this to two important transformations. First, the Journal added positions for graduate students who expanded and inured research in the basic sciences that is displayed in our publication. Second, the Journal developed a new and systematic algorithm to manage the receipt, review, and editing of manuscripts which streamlined our communication with authors and reviewers. With these implementations, we feel confident that the Journal will continue to grow and develop into an even larger publication of highly diverse and novel content.

The following pages are a testament to the remarkable abilities of our colleagues within and beyond this institution. We hope this issue will impart to you intellectual curiosity, new knowledge, and, ultimately, inspiration to provide the best quality of care for patients.

Lauren Edgar, Phillip Kim, and Vahakn Shant Keskinyan
Editors-in-Chief

Perspectives

Lucky 26: When a Cure Comes Too Slowly

Dalane W. Kitzman, M.D.

Twenty-six years ago, as an internal medicine resident, I hugged and waved goodbye to a dear patient of mine. As he was loaded into an ambulance to go to a hospice, I was overwhelmed by conflicting emotions. How could I, a young doctor in training, know that I was doing the right thing in sending this young man, still a teenager, to a hospice to die? He had fought so hard for so long with the terrible disease with which he had been born, cystic fibrosis.

When I first met him several weeks earlier, his chest was grossly ballooned and he was bent completely forward, pounding his back and coughing as hard as possible to clear the tenacious phlegm from his deformed, infected lungs. Reading his chart and talking with him and his mother, it was clear that this had been his existence all his years, a constant struggle to get the phlegm out and breathe air in, and to fight one infection after another.

I often talked with him in the evenings after my work with other patients was done; there was not much else I could do. This was painful. We were not that far apart in age. I shuddered trying to imagine what my life would have been like, growing up constantly in and out of school, disconnected from friends, reliant on my mother and nurses. I was startled when, as he struggled to breathe, he expressed feelings of selfishness, concerned that his needs stole his mother's time from his siblings and had contributed to his father's abandonment of their family. Later, sitting in my car in the parking lot, I wept for him.

Over the coming weeks, I was exhilarated with what appeared to be successes, only to have these hopes dashed by another relapse. One day he looked tired and told me he wasn't sure he wanted to continue fighting. Alarmed, I initially encouraged him to continue treatments, but he repeated his statement several more times. I read more about the disease and realized that most such patients rarely made it to age 30, and death as a teenager was common. The psychiatrist we consulted told me my patient was competent and rational. His mother's eyes glazed when I discussed her son's wish with her, as though this was the day she had always dreaded but had known would come.

Prayerfully, cautiously, I switched gears, tentatively exploring with him this new phase. He alternated between wanting to fight and wanting to give in. I sensed he needed me to tell him he that it was okay to let go. This was not easy. Even my experienced supervising doctor did not seem comfortable in this area. I realized I

From the Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC

Address Correspondence to:
Dalane W. Kitzman, M.D.
Department of Internal Medicine
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157
dkitzman@wakehealth.edu
Phone: 336-716-3274

was on my own. It would have been much easier to help him through this episode, discharge him to home, and when he returned, I would be off on a different assignment, and this difficult situation would be someone else's responsibility.

My heart raced as I made the initial call to the hospice on his behalf. Could they even take a patient this young? Would his insurance cover the cost? All the time I wondered if I were doing the right thing. The nurse at the hospice heard my voice crack and sensed my inner struggle. She shared with me their experience with younger patients and their philosophy of comfort and dignity. She promised me that if my patient changed his mind, she would quickly send him back to the hospital.

I notified the chaplain, whom my patient allowed only a short visit. Later, my patient asked me what I thought about God. He asked, "Is there a heaven?" I told him I felt certain that there was. "Good, that's all I needed to know." Over the next few days, as we concluded his treatments and prepared for his transfer, he said he was looking forward to heaven. No patient had ever said this to me, and hearing it come from someone younger than I made me uneasy. I hoped I was right about heaven.

On the morning of the transfer to hospice, I rose early, dressed slowly, and trudged into the hospital. I fought back tears as I approached my patient's room. To my surprise, he was cheerful and calm. He saw my anxiousness and sought to reassure me. He asked me if I would stay with him until the transporters came, and if I would pray for him. As the transporters moved him to a gurney, I excused myself to the restroom to collect myself. I choked back tears as we wheeled him to the ambulance bay. My last view of him was as he looked me in the eye, put his hand on my shoulder, pointed to the sky, and said calmly, "I'll see you in heaven."

These long-suppressed memories recently came to me vividly as I listened to a lecture on the discovery of the first treatment that had the potential to cure certain patients with cystic fibrosis. Why now, I wondered? Why did this cure not come 26 years earlier? I wondered what my patient, in heaven, was thinking about this development.

Perspectives

Point of Care Ultrasound at Wake Forest Baptist Medical Center: Past, Present, and Future

Joshua Zavitz, D.O., Casey Glass, M.D., David Manthey, M.D., Manoj Pariyadath, M.D.

Over the past two decades, the use of point of care ultrasound (POCUS) has markedly increased across Wake Forest Baptist Medical Center (WFBMC). Initially this technology was developed with bulky machines, used primarily by Radiology, Vascular, Obstetrics and Gynecology (OB/GYN), and Cardiology specialties. With improved engineering and software development, this technology now can be brought to the bedside with a portable device. It has quickly become an integral component of clinical medicine for diagnostic and therapeutic care.

WFBMC has a renowned history of excellence and leadership in medical ultrasound. It was the "father" of neurosonology, Dr. William McKinney, who helped establish the Center for Medical Ultrasound. Dr. McKinney helped organize an educational program for echoencephalography in 1964, arranged the first neurosonology course in 1975, and first published the use of ultrasound to study carotid arteries in 1971. The Center for Medical Ultrasound (CMU) was formed in 1975 under direction of the Dean, Dr. Richard Janeway. A radiology professor, Dr. James Martin, directed the CMU until leadership transitioned to Dr. Frederick Kremkau in 1985. Dr. Kremkau, a Professor of Radiologic Sciences and past president of American Institute of Ultrasound in Medicine (AIUM), conducted extensive research and educational pursuits including ultrasound absorption mechanisms, acoustic properties of tissue, safety of ultrasound, and authored the textbook Sonography Principles and Instruments. Under the direction of Dr. James Johnson, the Center for Applied Learning (CAL) was created to support educational opportunities using simulation, cadavers and ultrasound.

By 2000, other specialties were using and teaching ultrasound. Under the leadership of Dr. Francis Walker, a formal neuromuscular ultrasound program began in 2002, with the goal of improving the diagnosis of neuromuscular disorders. Dr. Walker wrote the first textbook in neuromuscular ultrasound, and our neurologists remain on the cutting edge of ultrasound research internationally. Drs. Stacie Zelman and Bret Nicks introduced POCUS into Emergency Medicine resident education in 2004, initially using it for Focused Assessment with Sonography in Trauma (FAST), aortic imaging, and pregnancy assessment. With the addition of fellowship-trained faculty and a formalized resident ultrasound rotation in the emergency department, POCUS applications expanded and a formal quality assurance process brought consistency to the practice. Under the guidance of Dr. Aarti Sarwal, Critical Care departments are currently formalizing an ultrasound program to improve assessment of critical care patients. Dr. Joshua Nitsche, a maternal–fetal medicine specialist, has enhanced obstetrics care by inventing an ultrasound-guided invasive procedural simulation

From the Department of Emergency Medicine, Wake Forest School of Medicine, Winston-Salem, NC

Address Correspondence To:
Joshua Zavitz, D.O.
Department of Emergency Medicine
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157
jzavitz@wakehealth.edu

trainer to improve hand-eye coordination for performing amniocentesis.

Wake Forest ultrasound courses have become internationally known, with more than 16 continuing medical education courses currently taught each year with participants from over 20 countries. Dr. Charles Tegeler directs a neurovascular course to assist learners in interpreting carotid duplex and transcranial Doppler studies. Dr. Walker and colleagues teach nerve and muscular ultrasound applications to improve diagnoses of neuromuscular disorders. Peripheral vascular ultrasound courses strive to improve diagnosis of peripheral vascular disease. Wake Forest has partnered with Orlando Health in conducting an advanced ultrasound course for obstetrics and gynecology. Institutional faculty have partnered with AIUM to host an annual national Point of Care and Critical Care Ultrasound course.

In 2015, under the direction of Dr. Casey Glass, the medical school incorporated POCUS, utilizing core lecture topics and faculty from multiple disciplines, into all four years of training. It is an effective educational tool to help students apply anatomy and physiology while enhancing their physical exam and ultrasound skill set.

Presently, POCUS has extended clinical applications across other specialties in pediatric and adult patients in office, pre-hospital, surgical, and acute care settings. Endocrinology uses ultrasound for diagnostic and procedural aspects of thyroid evaluation. Physical Medicine and Rehabilitation (PM&R) along with Sports Medicine have benefited from ultrasound evaluations of joints, muscles, and tendons. Anesthesiology uses ultrasound for nerve block procedures in addition to pre- and post-operative cardiac assessments. Emergency Medicine POCUS applications include cardiac, pregnancy, soft tissue, abdominal aorta, FAST, ocular, renal, gallbladder, and thoracic evaluations along with procedural guidance. Urology uses this technology for diagnosis of hydronephrosis and other renal disorders.

POCUS enhances physical exam findings while narrowing a differential diagnosis, and guides therapeutic and resuscitative efforts. Depending on the clinical presentation and findings on the bedside ultrasound, patients may be referred for a more comprehensive examination to be completed by an ultrasound technologist, which is then interpreted by a radiologist. POCUS has improved the competency and safety of ultrasound guided procedures including paracentesis, thoracentesis, pericardiocentesis, amniocentesis, central and peripheral line placement, joint aspiration, fine needle aspirations, biopsies, peripheral nerve blocks, and interventional radiology procedures.

Increased use of and demand for POCUS led to the development of the hospital-wide POCUS committee in 2015, which meets quarterly to discuss quality and assurance, safety, image retention, equipment, and educational topics. This committee currently involves 20 different specialties including Internal Medicine, Hospitalists, Emergency Medicine, Pediatric Surgery, OB/GYN, MFM, Trauma Surgery, PM&R, Neurology, Endocrinology, Urology, Neurology Critical Care, Pulmonary Critical Care, Anesthesiology, Family Medicine, Sports Medicine, Vascular Surgery, Diagnostic Radiology, Interventional Radiology, and Cardiology.

In the fall of 2016 the POCUS Hospital Committee, chaired by Dr. Joshua Zavitz, prepared a multidisciplinary hands-on ultrasound experience designed as an introduction to POCUS applications with a focus on patient care. This inaugural event had eight specialties collaborating to teach WFBMC residents, advanced practitioners, and physicians. The 64 participants, representing nine different specialties, rotated through four different stations. Participants were surveyed before and after the event to assess general awareness of POCUS applications, ultrasound knowledge, and the role of the POCUS committee.

Most participants had minimal experience, were unaware of the hospital POCUS committee, and did not recognize the extent to which POCUS was used in varying specialties. Knowledge assessment questions demonstrated an improvement of 20% in cardiac view identification, 38% in probe identification, 47% in identifying pleura, and 64% in identification of lung sliding. Afterward, 74% believed learning from multiple specialties was excellent, 94% would attend future events, and 88% felt it improved patient care. The greatest barriers to POCUS education were time availability and access to qualified instructors. Courses like these will add to a training process which includes initial induction, supervised training, experience, achieving competency, and continued quality improvement.

The demand for POCUS education is growing and has led to further collaboration and efforts from the POCUS Hospital Committee, including a POCUS elective for senior medical students, and specialty-specific POCUS education events for residency programs at WFBMC. Currently there is an immediate need to centralize POCUS education, especially for those specialties in the infancy of POCUS. In 2017, under the leadership of Dr. Mary Claire O'Brien, the Center for Experiential and Applied Learning (CEAL) was formed with physician and nursing leaders collaborating to improve access to POCUS education. The efforts of the CEAL and POCUS hospital committee will provide opportunity for educational platforms, access to ultrasound machines, POCUS educators, and administration oversight for image retention, training, and competency. This will allow our hospital system to safely and efficiently deliver this technology for our patients. As ultrasound use grows, physicians at WFBMC will continue to champion this technology to improve patient care.

Perspectives

Stress in Faculty and the Impact on Resident Career Intentions

Lisa Cassidy-Vu, M.D., Keli Beck, M.D., Elizabeth Nelson, M.D., Justin B. Moore, Ph.D., M.S.

Abstract

Objectives: To identify stressors in family medicine faculty and determine if female faculty report more stressors than their male counterparts, and to determine if residents perceive differences in stress by sex and by preference for an academic versus private practice career.

Methods: Current family medicine faculty and residents in the North Carolina Area Health Education Consortium (AHEC) database completed separate surveys.

Results: There was a 30% response rate for faculty and 26% response rate for residents. Most faculty (71% male, 63% female) felt successful at their job. Male faculty were 3.5 times as likely to report their job supports work-life balance, and 73% less likely than female counterparts to report stress. Less than half of faculty members felt that stress deters residents from choosing academic careers. Most residents (73%) reported that they were considering entering academia. Compared to unmarried residents, married residents were three times as likely to report being encouraged to pursue an academic career by a male faculty member. Residents encouraged by male faculty were more likely to report an interest in academia.

Conclusions: Despite feeling successful, female faculty report more stress and less work-life balance. Many residents consider a career in academics, but few pursue one. Focusing on ways to decrease female faculty stress may encourage resident career choices into academia.

From the Department of Family and Community Medicine, Wake Forest School of Medicine, Winston-Salem, NC

Address Correspondence to:
Lisa Cassidy-Vu, M.D.
Department of Family and Community Medicine
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157
lcassidy@wakehealth.edu
Phone: 336-716-4942
Fax: 336-716-9126

Introduction

Despite work examining physician burnout and residents' decisions to pursue academic careers,[1-4] little is known about faculty stress and how it affects resident intentions to enter academia. Career choice is influenced by factors beyond interest and skillset[3], including exposure to research, mentorship, individual characteristics, and social situation.[4] The Association of American Medical Colleges (AAMC) notes that while nearly half of medical students and residents are female, only 38% choose an academic career and 21% achieve the rank of professor.[5] We assessed job satisfaction, stress, and perception of work-life balance in faculty and resident physicians in two concurrent studies to 1) identify stressors in faculty and determine if female faculty report more stressors than their male counterparts, and 2) determine whether encouragement by a male or female faculty member is associated with an intention to pursue a career in academic medicine.

Study 1

Methods

We developed an 11-question survey for faculty to assess stressors, job satisfaction, work-life balance, and perception of precepting ability. After Institutional Review Board approval, the regional Area Health Education Center (AHEC) distributed electronic surveys to all AHEC family medicine programs statewide (222 faculty members) via a secure online platform. We used logistic regression to analyze perceptions of support for work-life balance, and perceptions of stress or fatigue, with demographic characteristics and time in academia as independent variables. Responses were dichotomized by the responses of "strongly disagree"/"disagree"/"neutral" vs. "strongly agree"/"agree" or "likely"/"very likely" vs. "maybe"/"unlikely"/"very unlikely." We used Stata 13.1 software (StataCorp, College Station, TX) for all analyses.

Results

The survey elicited 66 responses (30% response rate). The faculty sample is mostly women (53%) who are married (89%). Participants have less than 2 years (20%), 2–5 years (8%), 5-10 (24%) 10–15 (8%) or greater than 15 years (41%) in academia. Seventy-seven percent of faculty report having children. Overall, 70% of faculty reported feeling stressed or fatigued less than 50% of the time, and 62% agreed that their job supports career/life balance.

Male faculty members were 3.5 times as likely to agree that their jobs support work-life balance, after controlling for marital and parental status (Table 1). Male faculty were 73% less likely to report feeling stressed or fatigued than female faculty, after controlling for parental status and years in academia.

Study 2

Methods

We developed a 13-question survey for residents to assess interest in academia, satisfaction with the quality of supervision/teaching, encouragement to enter academia, and perception of stress in faculty. AHEC distributed surveys to 228 residents in all AHEC family medicine programs

Table 1a. Results of logistic regressions predicting perceptions of A) work-life balance* and B) stress or fatigue†.

A) Work-life balance (Y = 1)				
	OR	**SE**	**P≤**	**[95% CI]**
Gender (male = 1)	**3.45**	**1.92**	**0.03**	**1.16, 10.24**
Children (yes = 1)	0.97	0.68	0.96	0.24, 3.83
Married (yes = 1)	0.15	0.18	0.12	0.01, 1.59
*controlled for marital and parental status				

B) Stress or fatigue (Y = 1)				
	OR	**SE**	**P≤**	**[95% CI]**
Gender (male = 1)	**0.27**	**0.18**	**0.05**	**0.07, 0.98**
Children (yes = 1)	3.06	2.60	0.19	0.58, 16.15
Time in academia				
2-5 years	5.03	6.38	0.20	0.42, 60.40
5-10 years	2.00	1.97	0.48	0.29, 13.76
10-15 years	5.19	6.74	0.20	0.41, 66.18
>15 years	2.10	1.93	0.42	0.35, 12.71
†controlled for parental status and years in academia				

Table 1b. Results of logistic regressions predicting perceptions of C & D) intention to pursue an academic career, E) reported encouragement for an academic career (female), and F) reported encouragement for an academic career (male).

C) Intend to pursue an academic career (Y = 1)				
	OR	**SE**	**P≤**	**[95% CI]**
Encouragement from male faculty	**3.63**	**2.37**	**0.05**	**1.01, 13.03**
Gender (male = 1)	1.08	0.67	0.90	0.32, 3.66
Married (yes = 1)	0.39	0.27	0.18	0.10, 1.53

D) Intend to pursue an academic career (Y = 1)				
	OR	**SE**	**P≤**	**[95% CI]**
Encouragement from female faculty	**2.66**	**1.66**	**0.12**	**0.78, 9.01**
Gender (male = 1)	1.09	0.67	0.88	0.33, 3.63
Married (yes = 1)	0.47	0.31	0..25	0.13, 1.70

E) Encouraged by a female faculty member to pursue an academic career (Y = 1)				
	OR	**SE**	**P<**	**[95% CI]**
Gender (male = 1)	1.29	0.70	0.64	0.45, 3.75
Married (yes = 1)	2.30	1.25	0.13	0.79, 6.68

F) Encouraged by a male faculty member to pursue an academic career (Y = 1)				
	OR	**SE**	**P<**	**[95% CI]**
Gender (male = 1)	1.31	0.74	0.63	0.44, 3.94
Married (yes = 1)	2.98	1.66	0.05	1.00, 8.89

statewide. We conducted logistic regression analyses using intention to pursue an academic career and perceptions of encouragement from male/female faculty as dependent variables and demographic characteristics and male/female faculty encouragement for academic careers as independent variables. Data were coded as indicated in Study 1.

Results

The survey elicited 60 responses (26% response rate). The sample is majority female (55%), and married (60%). Residents were in their first (32%), second (33%) or third (33%) post-graduate years (one not reporting). Some residents reported they were likely (8%) or very likely (13%) to enter academia, with 52% uncertain (i.e., "maybe"). Most reported receiving encouragement from female (58%) and male (67%) faculty to pursue academia. No differences in these responses were seen between male and female residents.

Residents were 3.6 times as likely to intend to enter academia if reporting encouragement by a male faculty member, but encouragement by a female faculty member is not a significant predictor (Table 1). Neither gender nor marital status predict reported encouragement by a female faculty member to pursue an academic career, but married residents were 3 times as likely to report encouragement by a male faculty member.

Discussion

Our results suggest that gender differences exist in perceptions of support for work-life balance and stress in faculty members, and differences by marital status in perceived encouragement from male faculty members to pursue academic careers in residents. This encouragement may influence intentions to pursue academics, consistent with previous literature reporting that burnout in academic physicians was associated with work-life imbalance.[8,9,10]

Despite a number of strengths, such as a balanced number of male and female respondents and resident versus faculty respondents, our results are limited by sample size and the self-reported nature of the data. For example, other studies of faculty and residents reported 66.8%[6] and 53%[7] response rates, respectively. Future studies should recruit larger samples to investigate sources of stress and support in faculty and factors influencing career decisions in residents. This could be accomplished through a survey of all North Carolina AHEC-sponsored residency programs (e.g., internal medicine, pediatrics, and psychiatry), or inclusion of neighboring states. Further, our analyses tested 19 possible associations, which introduces the possibility that our results are due to chance.

Work-life balance was a commonly reported stressor faced by faculty, more often for women. Striving for success at home and at work leads to greater fatigue and a lesser sense of well-being among women.[11,12] That male faculty tend to encourage more married residents to pursue academics may also enhance burnout by creating a work/home imbalance, and this effect might be more pronounced in female faculty. Our sample, however is too small to test this concept.

While a number of residents reported considering a career in academics, more than half had not decided. Given that residents were more likely to report an interest if encouraged by male faculty, coupled by more female faculty reporting stress than their male counterparts, residents may observe stressors in their female preceptors and opt for a non-academic position. We did not assess issues such as perception of lifestyle flexibility in private practice versus academia, effect of time spent with faculty, or effects of the seniority of the faculty member, since full professors and chairs are usually men.[13,14] We also did not assess reasons for career decisions of residents. Similarly, we did not consider the variation in types of academic positions available and whether residents in this survey were from large university affiliated programs or smaller community programs. These differences in programs and inherent stressors could also factor into resident decisions regarding career path. Further research could identify those reasons, which may explain the discrepancy between those interested in an academic career and those who pursue one.

Efforts to support female faculty and reduce their stressors and encourage more female residents to pursue academia could be enhanced, including individualized mentoring programs for early career faculty who may struggle to establish work-life balance. Additional strategies could include provision of onsite childcare, full-time benefits for part-time positions, and flexible promotion timetables.[15] Future studies should investigate sources of stress in female faculty and their influence on residents' career choices.

Disclosures:

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Perspectives

Clinical Documentation in the Age of the EHR: An Overview of Challenges and Potential Solutions

Joseph Cristiano, M.D.

From the Department of Internal Medicine, Wake Forest School of Medicine, Winston Salem, NC

Address Correspondence To:
Joseph Cristiano, M.D.
Department of Internal Medicine
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, NC, 27157
jcristia@wakehealth.edu

Written documentation by physicians has existed in some form since the early twentieth century[1]. Despite the rapidly evolving landscape of healthcare delivery, including the adoption of the electronic health record (EHR), a physician's unique duty in clinical documentation remains the same as it was decades ago: synthesize complex clinical data concisely and express clinical reasoning effectively. To quote the American College of Physicians, physician documentation should consist of "concise, history-rich notes that reflect the information gathered to develop an impression, a diagnostic and/or treatment plan and recommended follow-up."

The EHR, as the primary tool for physician documentation, has both positive and negative effects. A widely-acknowledged benefit is that electronic notes are more legible, and as a result, reduce concerns about patient safety. Interoperability between different EHRs facilitate a much more readily available and complete database of clinical information across the spectrum of healthcare settings. Electronic prescribing, clinical decision aids, safety alerts, and other tools built into the EHR improve patient safety and quality of care.[2]

The EHR is also having an impact on the quality of physician documentation. Contrary to what many hoped for, the EHR increasingly threatens the physician's ability to efficiently render high-quality clinical documentation. Accordingly, there is growing evidence in the medical literature that electronic charting diminishes the effectiveness of physician notes as a communication tool.[3,4]

EHRs today emphasize entry of data in a highly-structured format rather than facilitating documentation that captures the patient's story and physician's thought process. Completing standardized check-boxes, drop-down menus, and automatic importation of data are typical. These overly structured notes increase the volume of distracting information, creating "note bloat," and impair cogent and concise documentation.

At the same time, other functions have been added within the EHR for physicians. These include updating problem lists, linking orders to appropriate ICD-10 codes to support billing, and complying with meaningful use and best practice advisories. Overall, the EHR is requiring more time away from the bedside,[5-8] reducing the time physicians can spend with their patients rendering care. A recent time-motion study demonstrated that outpatient physicians spend twice as much time interfacing with the EHR and doing office work than with patients. Another study in Switzerland suggests that hospitalized patients are seeing their physicians less as a result of

completing EHR duties and that physicians spend less time at the bedside.[9] Lastly, in a 2013 study, emergency physicians captured approximately 4,000 clicks per shift, resulting in 43 percent of their time spent on data entry.[10] This increasing focus on the EHR rather than the actual patient is now widely recognized as the phenomenon of the "iPatient." Complicating the situation, there is growing evidence that the excessive amount of time spent in non-clinical work is a major factor in physician burnout.[6]

Additionally, as healthcare evolves more deeply into a model of value-based care, physician documentation is increasingly deconstructed to fit highly specific coding criteria. These data are extrapolated and utilized for downstream evaluation of performance, efficiency, and quality metrics. This situation imposes additional demands on physicians to provide supporting data in their documentation to satisfy coding requirements. The American Health Information Management Association (AHIMA) describes this difference in documentation to satisfy coding as opposed to documentation strictly for clinical care as the "physician-coder chasm."[11] AHIMA states, "physicians are not taught how to complete the documentation to accurately assign codes, and physician billing does not require a high degree of specificity."

Despite growing recognition of these complex challenges, most medical schools in the U.S. are not better preparing students for written documentation in the EHR environment.[3,12-16] Yet these same physicians in training are increasingly tasked with more and more clinical documentation responsibilities. In 2011, a survey of resident physicians found that documentation was one of the most frequent skills of first-month residents, yet with the least amount of attending physician supervision.[17]

For more experienced physicians, there is early evidence that they, too, may suffer from diminished effectiveness in written documentation in the electronic form.[3,14,18] Considering these factors, how can physicians adapt? Fortunately, there are a number of strategies that can potentially help.

Medical students need an up-to-date curriculum for EHR utilization and documentation; however, there are only a few U.S. programs that provide such training, and an urgent need remains. The scope of curricular need is broad, but a few examples follow to illustrate the EHR skills needed in the modern-day patient encounter and subsequent clinical documentation.

First, the curriculum needs to prepare learners to balance the reality of data-gathering from the EHR with conventional data-gathering from the patient during the visit. It is crucial that despite the abundance of information available in the EHR, trainees remain patient-centered and use an open-ended interview approach without focusing just on the data gathered electronically. Rather, teaching learners effective strategies for verifying important EHR data with patients could free up time for deeper history-taking and allow more time for exam maneuvers and shared decision-making. There is much literature suggesting that the doctor-patient relationship is evolving in the technology era, and a thoughtful curriculum to maintain a humanistic relationship is needed.

Second, this training would also include instruction for effective communication in clinical documentation within the EHR. Currently, many medical schools still train pre-clinical student's foundational skills in written documentation outside of the context of the EHR platform. Today's learners need to be trained to document electronically with the proper use of EHR tools including "copy-and-paste" functions, note templating, data importation, and "smart phases." These tools need to be framed in the broader context of their ability to effectively communicate and also as they relate to the cognitive processing of information for clinical reasoning. Medical students need to be prepared to provide accurate, relevant, and up-to-date documentation that minimizes "note bloat" and "copy forward" as these are distracting, low value, or irrelevant.

EHR training for advanced trainees and faculty physicians also needs to adequately prepare them to satisfy the increasingly complex non-clinical expectations of their documentation. Best practice processes are needed to guide institutions regionally and nationally. Physician leaders need to work alongside stakeholders from compliance, quality, billing and coding to identify the highest need

areas of need for training, keeping in mind physicians' other responsibilities. This training needs to be concise, iterative, and consistent, and needs to ensure that the physician's principal focus for documentation remains centered on communicating around clinical care.

Point of care resources also need to be arrayed to simplify documentation expectations for busy physicians. Best practices need to assure that physicians have clinical documentation improvement (CDI) resources available in healthcare institutions. CDI is well-established as an advanced discipline of nursing, in which nurses with clinical experience are cross trained in medical coding, quality improvement, and compliance.[11] These specialists can assist physicians at the point-of-care to make documentation more clear and complete. Physician buy-in, however, for such assistance is slow; perhaps such specialists could be further integrated into the multi-disciplinary care team to leverage their resources. Accordingly, the medical literature suggests that a team-based approach may mitigate overall physician burnout.[6] Further incorporation of CDI into the multi-disciplinary care team could potentially diffuse or reduce the documentation demands placed on physicians.

Moving forward, policymakers and healthcare leaders need to work in collaboration to develop processes that reduce the workload burden on physicians, who are increasingly at risk of burnout from the modern-day EHR while simultaneously developing point-of-care resources. Additionally, EHR vendors need to continue to make electronic charting tasks less cumbersome for physicians.

Inevitably, the complexities and expectations of documentation will continue to grow. In response, healthcare and IT leaders and physicians must acknowledge the importance of responding to these changes taking place with strategies to adapt. To prepare our physicians of tomorrow, enhanced awareness is urgently needed among all stakeholders to foster a collaborative and a team-based approach to the EHR and documentation.

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Clinical Review

Risk Factors for Neonatal Abstinence Syndrome among Opiate-Dependent Pregnant Women: A Systematic Review

Cody McLeod BS[1], Aaron M. Smith, M.D.[2], Mary Marquette, M.D.[2], Jessica Coker, M.D.[3], Zachary N. Stowe, M.D.[4]

Abstract

Neonatal Abstinence Syndrome (NAS) refers to a set of symptoms seen in infants of mothers who were dependent on certain substances during pregnancy. This systematic review of the literature aims to identify and analyze potential risk factors for NAS among opioid-dependent pregnant women. Applicable literature was searched between January 1990 and June 2015. While a total of 189 articles were initially reviewed, 29 publications met inclusion criteria. Extracted data was focused primarily on study design, maternal exposures (i.e., tobacco and psychotropic medication), and the respective dose relationships between opiate replacement therapies and NAS incidence, peak NAS scores, and length of hospital stay. Although results of these studies varied, several suggested relationships emerged. Infants of buprenorphine-maintained mothers had less severe, and a lower incidence of, NAS than methadone-maintained mothers. Breastfeeding appeared to reduce the severity of NAS. While the use of psychotropic medications such as benzodiazepines was associated with an increased length of stay for neonates and peak NAS scores, maternal dose of methadone or buprenorphine was not correlated with risk or severity of NAS. With better understanding and improvement of medication-assisted treatment and enhanced implementation of existing medical and psychological treatments, incidence and severity of NAS can be improved.

[1] University of Arkansas for Medical Sciences College of Medicine, Little Rock, AR

[2] University of Arkansas for Medical Sciences, Little Rock, AR

[3] Department of Psychiatry, University of Arkansas for Medical Sciences, Little Rock, AR

[4] Department of Psychiatry, University of Wisconsin School of Medicine and Public Health, Madison, WI

Address Correspondence To:
Cody McLeod
University of Arkansas for Medical Sciences College of Medicine
4301 W Markham St.
Little Rock, AR 72205
cmcleod@uams.edu

Introduction

In 2014, an estimated 1.9 million Americans were abusing prescription opioids and half a million were addicted to heroin.[1] That year, 18,893 deaths were related to overdoses of prescription pain relievers, and another 10,574 to overdoses with heroin.[2] Furthermore, while the number of heroin-related poisonings increased by 12.4% from 1999 to 2002, the number of prescription opioid poisonings increased by 91.2% in that same period, and continues to increase.[3] Opioid use and dependence have become growing concerns for women's health over the past two decades. Women had a 5-fold increase in prescription opioid-related deaths from 1999 to 2010. On average, one woman is admitted to the emergency department for prescription opioid abuse complications every three minutes.[4] Considering that approximately 51% of all pregnancies are unintended,[5] potential effects of opioid use on the developing fetus, specifically NAS, is a serious concern.

NAS is considered as a group of withdrawal symptoms—including tremors, convulsions, sweating, vomiting, diarrhea, and a high-pitched cry—observed in mothers of newborns who have been taking psychoactive substances, primarily

opioids.[6] NAS is commonly diagnosed using a scoring system, with the modified Finnegan scale being the most popular.[7] This scale requires the scorer, usually a nurse trained in the procedure, to rate 21 symptoms of withdrawal every four hours. A score greater than 4 is considered a positive diagnosis. An infant scoring greater than 8 usually requires pharmacologic treatment, commonly opioid replacement with morphine. Cases of NAS have risen markedly, from 1.1 per 1,000 births in 2000 to about 5.8 cases per 1,000 births in 2009.[8]

The concomitant rise in NAS incidence and prescription opioid use poses a substantial financial burden on the healthcare system. A recent study of 10,327 NAS cases from 2004-2013 found an 8-fold increase (0.6% to 4%) in the proportion of neonatal intensive care unit (NICU) admissions due to NAS, with the average number of NICU days increasing from 13 to 19.[8] Another study reported a 10-fold increase in NAS (0.4 to 4.4 discharges per 1,000 births) in 6 Florida hospitals from 1995 to 2011. Maternal opiate use was primarily illicit (55%), with 41.3% receiving medication-assisted treatment (MAT) for addiction, 21.5% for chronic pain, and 10.3% for unknown reasons.[9] One Florida hospital reported that it spent $4 million treating NAS from 2009 to 2011.[9]

Because of concomitant use, and reporting bias associated with illegal drug use, the relative contributions of prescription versus non-prescription opioids to the symptoms of NAS are difficult to determine. However, over half of women who deliver a child with NAS are using opiates illicitly. The longer half-lives and regular dosing schedules of medications used for MAT prevent spikes in blood levels and are thought to lead to better outcomes for both mothers and infants.[10] Although MAT with methadone reduces severity of NAS, recent studies suggest that buprenorphine treatment may reduce severity still further.[7]

Nonetheless, many questions remain regarding why some infants are more susceptible to NAS than others, since only half of opioid-exposed infants require treatment.[10,11] Improved characterization of these vulnerable infants can assist providers in identifying at-risk pregnancies before delivery and allow clinicians to target these mothers with preventative measures, including counseling, support, and possibly MAT. The American College of Obstetrics and Gynecology has addressed these issues with their recent guideline changes which advocate screening for substance use disorders among all pregnant women, as well as patient education and safe prescribing practices.[12] These preventive screenings and treatments could further improve detection of risk factors contributing to NAS before delivery. However, although these screenings allow identification of high-risk pregnancies, the challenge of improving neonatal outcomes through effective medical treatment and addressing psychosocial issues and barriers to care remain.

To better address the clinical problem of NAS, this systematic literature review aims to identify and analyze potential modifiable risk factors for NAS, most notably maintenance medications, providing clinicians with further insight into this complex issue. Moreover, this review may help clinicians better understand and use the available literature to improve their clinical decision-making and, thus, patient care.

Data Sources and Methods of Study Selection

For this systematic review, publications were obtained from MEDLINE, PubMed, and clinicaltrials.gov databases. Searches included all publications between January 1990 and June 2015. Key terms searched included "neonatal abstinence (or withdrawal) syndrome," "pregnancy," "risk factors (or characteristics)," "perinatal outcome," "drugs of abuse," "buprenorphine," "methadone," or "opiate." Reviews and publications not in English as well as those that did not discuss maternal characteristics, lacked a clear NAS diagnosis, or had a sample size less than 15 were excluded. The type of study, sample size, method of NAS diagnosis, and inclusion of a urine drug screen (UDS) were extracted from each selected study. Maternal characteristics such as age, race or ethnicity, socioeconomic or educational status, marital status, additional medical and/or psychiatric diagnosis, and planned versus unplanned pregnancy were added, if discussed. Maternal use of additional psychoactive substances including benzodiazepines, tobacco, marijuana, cocaine, alcohol, and any MAT medications were also included if applicable. Neonatal characteristics such as gestational age,

birth weight, and breastfeeding status were also extracted. MOOSE guidelines for systematic reviews of observational studies were used for this review.[13]

Tabulation, Integration, and Results

We identified a total of 189 potential studies. Of these, 160 publications met exclusion criteria. Of the excluded articles, 71 were reviews, 38 did not address proper demographics, 25 were not in English, 25 presented duplicated data, 24 did not represent a clear NAS diagnosis, and nine had inadequate sample size. Therefore, 29 publications were included in the final systematic analysis, which included a total of 6,564 mother-infant dyads.

Methadone versus Buprenorphine

Eight of the studies compare the perinatal outcomes of methadone- and buprenorphine-maintained women. The overall incidence of NAS ranged from 11.9% to 84.6%.[14,15] The incidence of NAS between the 2 groups was not statistically significant for five studies[7,14-17] Two of the eight studies found a significant increase in NAS among methadone-exposed infants versus buprenorphine-exposed infants.[18,19] However, after controlling for heroin use late in pregnancy, this significance was lost in one of the two studies, with methadone-maintained mothers being more likely to have taken heroin compared to buprenorphine-maintained mothers ($p = 0.004$).[18] The remaining study found methadone-exposed infants were more likely to have NAS treatment compared to buprenorphine-exposed infants (56.9% vs 47.4%, respectively), but this was not reported as a statistically significant difference.[12]

Although differences in NAS incidence are difficult to assess between buprenorphine and methadone, the available literature clearly establishes buprenorphine as superior when reviewing factors of severity. This is exemplified by one randomized trial of opiate-dependent women that compared buprenorphine and methadone outcomes, where buprenorphine-exposed infants had lower peak NAS scores (11.0 vs 12.8, $p = 0.04$), shorter duration of NAS treatment (9.9 days vs 4.1, $p < 0.003$) and shorter duration of hospital stay (17.5 days vs 10, $p < 0.0091$), requiring lower cumulative doses of morphine (10.4 mg vs 1.1, $p < 0.0091$) compared to methadone-exposed infants.[7] Additional studies agree that buprenorphine-exposed infants had shorter treatment durations and/or length of hospital stay.[14,16, 17,19] Peak NAS scores for buprenorphine-exposed infants were similar or higher than those of methadone in 2 studies.[15,19] In both, however, the length of stay was still shorter with buprenorphine, suggesting that differences in NAS scores more likely represent subjectivity in evaluating scores and not a true difference in severity.

In addition, when looking at the 2 groups combined, treatment for NAS was predicted by greater infant birth weight ($p = 0.009$) and more cigarettes smoked 24 hours before delivery ($p = 0.03$).[20] The use of other psychotropic medications alone, including benzodiazepines, did not statistically increase risk for NAS.[18] Use of psychotropic drugs concomitant with opiate maintenance treatment, however, increases length of hospital stay and total dose of morphine required for treatment.[16,17,20] Breastfeeding data were included in only one study, which noted that breastfeeding was associated with reduced length of stay (beta of -0.176, $p=0.05$).[11]

Buprenorphine

There is only 1 study in the reviewed literature examining perinatal outcomes in buprenorphine-exposed women alone. A prospective study of 54 buprenorphine-maintained pregnant women (58 infants) evaluated infant urine concentrations of buprenorphine and its metabolite, norbuprenorphine, in correlation to NAS treatment and length of stay. The incidence of NAS treatment was 66%, and highest urinary norbuprenorphine concentrations across the first three days of infants' life correlated with both an increased length of hospital stay and duration of morphine treatment ($p < 0.005$ and $p < 0.008$, respectively). However, when looking at urinary buprenorphine concentrations independently of norbuprenorphine concentrations, there was no significant correlation with length of stay or duration of treatment.[21] These results suggest that norbuprenorphine is predictive of infant length of hospital stay and duration of morphine treatment, while urine buprenorphine alone is not. The authors suggest that, while fetal concentrations of norbuprenorphine accumulate proportionally to

maternal concentrations, buprenorphine concentrations do not seem to accumulate in a consistent or proportionate manner. Even though this study established an association between the concentration of a buprenorphine metabolite, norbuprenorphine, and NAS, the study did not report a dose-dependent relationship between maternal oral dosage of buprenorphine and NAS.

Methadone

Twenty studies evaluated NAS factors after prenatal methadone exposure. The incidence of NAS in these studies ranges from 27% to 74%. Seven publications reported a dose-dependent relationship with risk for NAS (i.e., higher doses of methadone increased incidence of NAS).[10,22-27] Furthermore, this dose-dependent relationship remained significant after accounting for concomitant heroin use during pregnancy.[22] The remaining 8 papers that evaluated this factor did not find a dose-dependent relationship in risk for NAS.[28-35]

When looking at other factors needed to treat NAS, higher doses of maternal methadone were associated with longer hospitalizations of the infant and larger doses of morphine to treat NAS.[22,33] Additionally, concomitant uses of other psychotropic substances such as benzodiazepines and polysubstance use were associated with increased lengths of stay and more infants requiring NAS treatment, respectively.[6,30,33] In one study, an odds ratio of 1.7 was attributed to benzodiazepine use and NAS.[10]

There is no consensus with regard to smoking status and its effects on NAS risk or severity in methadone-exposed infants. In a large Australian study, mothers who were heavier smokers with concomitant methadone use were more likely to have infants with NAS ($p < 0.001$).[36] In addition, among a subset of infants who were born full-term ($n = 19$), mothers smoking 20 or more cigarettes per day had infants with higher NAS peak scores ($p = 0.039$);[37] however, many other studies have reported no association between maternal smoking status and NAS incidence or severity.[26,27,30,31,33,36,37]

Incidence and Severity

There was a wide range of incidence of NAS between the studies examined. Anywhere from 1/3 to 2/3 of infants with opiate exposure required treatment for NAS. Consistent associations with risk of NAS were lacking among the studies, underscoring the remaining question of why some infants develop NAS when others do not. The diagnosis of NAS is subjective; this subjectivity was potentially reduced when rating scales were assessed by skilled raters.

Studies comparing risk of NAS between methadone and buprenorphine disagree; most studies found no significant differences between the two groups. Thus, a conclusion regarding incidence of NAS between the two drugs cannot be made on the basis of current evidence. However, multiple studies did find less severe NAS and shorter duration of NAS treatment with buprenorphine compared to methadone, suggesting buprenorphine may be superior regarding overall infant outcomes.[14,16,17]

Maternal Dosage

Maternal dose of opiate replacement was consistently evaluated in most studies mentioned above; however, results regarding correlations of risk and/or severity of NAS with maternal dosage are difficult to establish. While around half of the studies found a significant correlation, the remaining half did not. Both methadone and buprenorphine cross the placenta and are present in infant urine and cord blood at birth.[27] Methadone crosses the placenta with possible regulation by p-glycoprotein with serum ratios of infant/mother at 0.36-0.41. Methadone concentration in the placenta was correlated with maternal dose ($r = 0.685$, $p = 0.001$). A metabolite of methadone known as 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) is a possible surrogate marker of methadone use found in placental tissue. Concentrations of EDDP were related to reduced head circumference ($r = -0.579$, $p = 0.009$), and EDDP/methadone ratios were positively related to NAS peak score ($r = 0.513$, $p = 0.030$).[27] Buprenorphine has a similar ability to cross the placenta (ratio from 0.14-0.47).[38] However, p-glycoprotein is not involved in buprenorphine transfer and differing serum protein levels in maternal and fetal circuits have been implicated as a modulating factor for transfer.[39] Buprenorphine metabolites are in the placental tissue as well, indicating that the placenta may offer some protection by metabolizing or sequestering the drug.[31] Variability in any factors affecting placental passage can alter the *in utero*

exposure of opioids, and this may help to explain variability in outcomes seen in studies in this review. Differences in maternal or placental metabolism or efflux mechanisms, or differences in fetal metabolic ability, are ways in which this process could be modulated.

However, buprenorphine does not show a conclusive dose-dependent relationship with NAS. In a single study, higher urinary concentrations of buprenorphine were associated with longer length of stay and duration of morphine treatment among infants diagnosed with NAS,[21] although additional studies are needed to confirm these results.

Tobacco Exposure

The negative effects of prenatal tobacco exposure have been explored, with overwhelmingly consistent results including low birth weight.[40] While 17% of pregnant women in the US use tobacco,[41] participants in these studies had greater percentages of tobacco use, ranging from 70–99%. Nonetheless, evidence was conflicting regarding risk of NAS and severity of NAS with concomitant tobacco exposure. Most prospective studies found no associated risk of NAS incidence or severity of NAS with tobacco exposure. Methodologic differences in accounting for tobacco exposure do not account for these differences, as many studies used maternal self-report measures and did not stratify based on quantity of cigarettes per day. Gray et al. used qualitative measures by examining meconium levels of nicotine/cotinine, finding no correlation with NAS.[31] Nicotine-exposed infants have greater excitation of the central nervous system (CNS) similar to symptoms consistent with NAS, perhaps complicating the clinical picture.[42] One study noted that NAS peak scores were about 4 points higher for mothers who smoked over 10 cigarettes per day compared to those who smoked less than 10; however, there were fewer than 20 women in each group, making the results less conclusive.[39] Currently, most of the data suggest that tobacco exposure does not increase risk of the incidence or severity of NAS, although more data are needed to support this conclusion.

Additional Psychotropics

Other psychotropics (such as benzodiazepines, illicit substances, and selective serotonin uptake inhibitors) taken by the mother have been proposed as contributing factors to presentation of NAS. Similar to previous factors, the relationship between NAS and concomitant use of psychotropics is difficult to establish in the literature. In several studies, benzodiazepines were associated with increased length of hospitalization among infants with buprenorphine or methadone exposure and subsequent NAS.[10,11,17] There is reasonable concern for the potential of overlap in symptoms of benzodiazepine and opioid withdrawal.[43] Dysfunction of the central and autonomic nervous systems and the gastrointestinal system, occurs with both; thus, it is difficult to discern how many NAS symptoms can be attributable to a given opioid. Nonetheless, concomitant benzodiazepine use should be noted by clinicians as a potential factor that can worsen NAS symptoms.

Use of additional illicit opioids such as heroin is an obvious associated risk of NAS, severity of NAS, and length of hospitalization. Unfortunately, most publications did not evaluate concomitant drug use as a potential confounder. This is undoubtedly because of the difficulty of measuring exposure to illicit substances. Further research aimed at parsing out how these factors contribute to NAS would be valuable. Including urine specimens in datasets would enable future evaluations of this factor.

Breastfeeding in general reduces agitation, facial grimacing, crying, and heart rate in infants.[44] Abdel-Latif et al. reported that mothers who breastfed were more likely to have better prenatal care and less likely to participate in other behaviors that may increase NAS severity, such as benzodiazepine and polydrug use. The soothing effect of maternal contact on an agitated infant can undeniably reduce symptoms associated with NAS.[45]

Other studies have suggested that the small quantities of opioid delivered to the infant through breast milk may ameliorate some NAS symptoms. However, Wajnar-Horton et al showed that only 2.07–3.51% of the maternal dose of methadone was available to the infant after taking into account excretion into breast milk and bioavailability which is not high enough to reduce NAS symptoms.[46] The concept does seem valid, but further data would be helpful to corroborate these results.

Limitations of the Current Review

This review does have some limitations. First, search terms are necessarily limiting and despite our best efforts, some studies may have been unintentionally excluded. Second, due to a wide range of variables and methodologic techniques among the studies included, only those pertinent to the study were included. Variance in incidence of NAS could be attributed to the potential that healthcare providers miss a NAS diagnosis, to variability in NAS treatment, and to the use of three different rating scales, including Finnegan, Modified Finnegan, and Lipsitz. In studies on opioid-maintained women, clinicians may be more apt to look for signs of NAS. In addition, unobserved factors that lead to CNS agitation or something mimicking CNS agitation may also lead to over-diagnosis of NAS in some instances. The lack of urinary drug screens in many studies is also a limiting factor, since this is another opportunity for confounding data to be missed.

Conclusion

Although NAS has been reported in the medical literature for decades, many questions remain as to why some infants of opioid-using mothers receive a diagnosis and others do not. Some studies have found statistically significant links between certain factors, whereas others have not. Nonetheless, it appears that infants of mothers maintained on buprenorphine had reduced severity of NAS compared to infants of mothers maintained on methadone; furthermore, the available literature suggests a lower incidence of NAS associated with buprenorphine, although this is not conclusive or supported universally by the data. Additionally, concomitant use of tobacco or benzodiazepines increases the length of stay of neonates with NAS, and their peak NAS scores. Breastfeeding has a soothing effect on infants, leading to reduced symptoms of NAS and reduced agitation in general. Yet there is no clear suggestion that the maternal dose of methadone or buprenorphine correlates with the risk or severity of NAS.

The incidence of NAS is quite unpredictable; further research is needed to better identify pregnancies that may be at risk. Many variables identified in the literature to date offer surprisingly little insight, suggesting that NAS may result, in large part, from deeper influences at play. *In vivo* factors such as variations in pharmacokinetic and pharmacodynamic actions of opioids and psychotropics, and in maternal, placental and fetal hormones, need to be further explored. In addition to further research, patient and clinician education are fundamental in making the judgments necessary to prevent NAS and improve care for infants who have it.

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Challenge Cases

A Young Man with Hearing Loss, Blurred Vision, and Diplopia

Patrick Kuhlman, M.D.[1], Cane Hoffman, M.D.[2], Meagan Lewis, Au.D.[3], Vinay Bhatia, M.D.[2], Timothy Martin, M.D.[4], Roy Strowd, M.D.[1,5,6]

Case presentation

A 22-year-old black man presented to the outpatient internal medicine clinic with hearing loss and blurred vision.

The patient and his mother reported that hearing loss began in his left ear about a year ago and progressed to involve the right ear a few months thereafter, leading to loss of all conversational hearing. He also had ataxia, frequent falls, blurred vision, and daily headaches.

Audiometry 6 months prior showed conversational deafness bilaterally with pure tone average not recordable on the left and 60 dB (moderate to severe hearing loss) on the right. Further diagnostics were not completed because the patient said he lacked insurance coverage as defined by the patient. The patient's twin sister is healthy. His symptoms caused him to stop attending college courses. He takes no medications, works at a grocery store, and played football and wrestled in high school. The review of other systems was negative.

On examination, the patient was a young, well-developed black man in no acute distress, with a blood pressure of 123/58 mmHg, heart rate of 77 bpm, and respiratory rate of 18. Gross auditory acuity was absent, requiring written words to communicate. Bilateral tympanic membranes lacked any abnormalities. Cardiopulmonary and abdominal examinations were negative for evident pathology. No gross deformity of major joints was observed, and tone was good. The patient could move from the chair to exam table without assistance. Finger-to-nose and heel-to-shin testing were negative for dysmetria. Great toe position sense was intact. His gait was unsteady, wide-based, and ataxic, and he could not perform a tandem walk. A undilated fundoscopic exam revealed optic disc swelling bilaterally. No skin abnormalities noted.

Laboratory results included a normal complete blood count and basic metabolic panel. The patient was negative for HIV antibodies and rheumatoid factor screen, and had an erythrocyte sedimentation rate of 8.

A neuroophthalmology consultation was obtained. The examination showed visual acuities of 20/50 in the right eye, and 20/100 in the left eye. There was no anisocoria or relative afferent pupillary defect. Confrontation perimetry was full to counting fingers in both eyes. Ocular motility showed esotropia with bilateral abduction deficit. However, the most striking finding was severe papilledema, with grade 4 optic disc swelling in both eyes (Figure 1).

[1] Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC

[2] Department of Radiology, Wake Forest School of Medicine, Winston-Salem, NC

[3] Department of Audiology, Wake Forest School of Medicine, Winston-Salem, NC

[4] Department of Ophthalmology, Wake Forest School of Medicine, Winston-Salem, NC

[5] Department of Neurology, Wake Forest School of Medicine, Winston-Salem, NC

[6] Translational Sciences Institute, Wake Forest School of Medicine, Winston-Salem, NC

Address Correspondence To:
Patrick Kuhlman, M.D.
Department of Internal Medicine
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem NC 27157
pkuhlman@wakehealth.edu

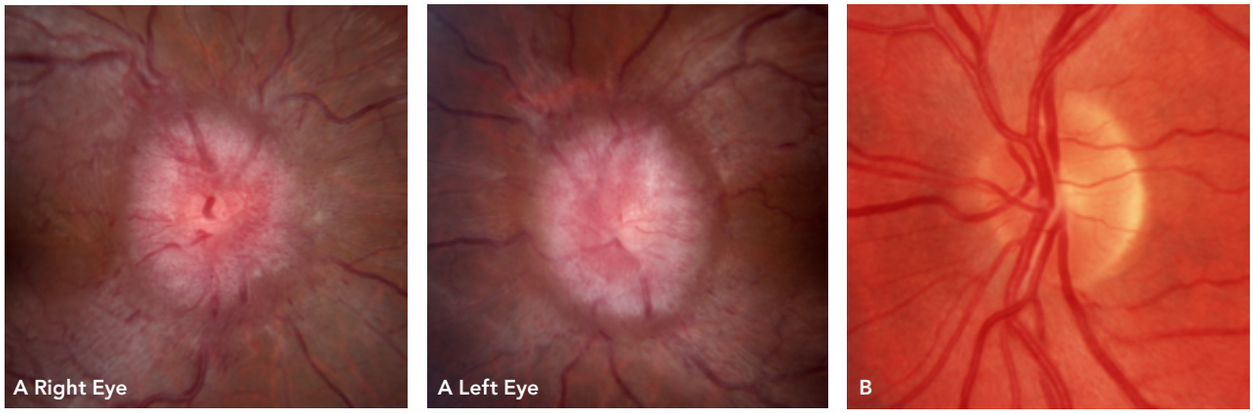

Figure 1. A) Patient's fundoscopic examination. B) A normal fundoscopic examination

These findings of severe bilateral papilledema and bilateral cranial nerve VI palsies in this patient with progressive hearing loss were consistent with elevated intracranial pressure. Neuro-imaging was obtained with MRI brain with gadolinium (Figures 2–3).

Challenge Questions

Q1: Based on the patient's history, physical exam, and diagnostic testing, what diagnosis best explains this constellation?

A. Normal pressure hydrocephalus
B. Idiopathic intracranial hypertension (Pseudotumor cerebri)
C. Neurofibromatosis type 2
D. Glioblastoma
E. Ménière's disease

Q2: The patient's ataxia, frequent falls, papilledema, and headaches are most likely to benefit from which of the following?

A. Ventriculoperitoneal shunt
B. Acetazolamide
C. Meclizine
D. Lumbar puncture
E. Salt restriction

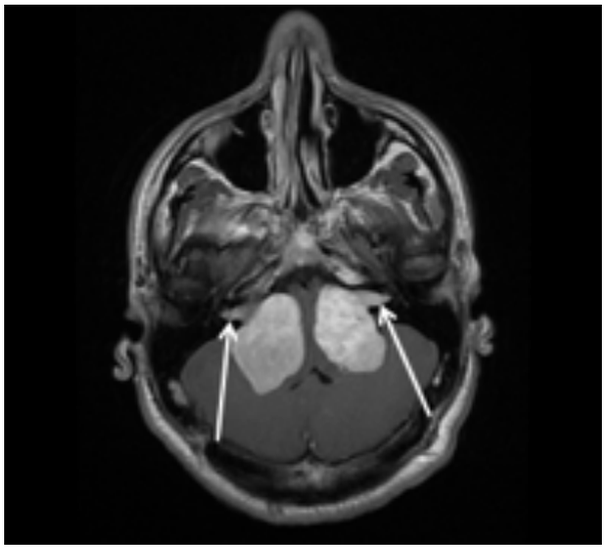

Figure 2. T1 Flair post-contrast MRI at the level of the cerebellum, with arrows indicating bilateral vestibular schwannomas extending into the bilateral internal auditory canals.

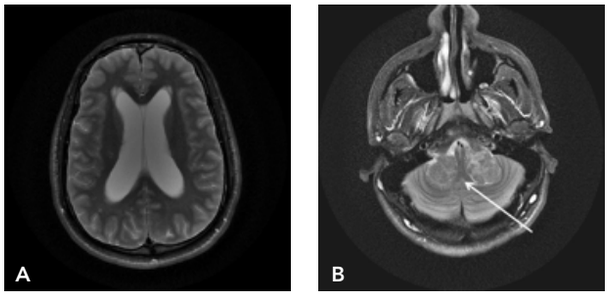

Figure 3. A) Axial T2 fat saturated MRI at the level of the lateral ventricle (left). B) Axial T2 fat saturated MRI at the level of the inferior 4th ventricle, with arrow revealing near-complete obliteration of the 4th ventricle (right).

Challenge questions: answers and explanations

The correct answer to Q1 is C.

All choices listed can explain one or more aspects of the patient's presentation; however, only neurofibromatosis type 2 (NF2) fully explains the range of symptoms. Normal pressure hydrocephalus may lead to symptoms of gait difficulty, often with urinary incontinence and cognitive dysfunction. Idiopathic intracranial hypertension can lead to papilledema and headache, but is not associated with an underlying mass lesion (i.e. pseudo-tumor). Glioblastoma typically presents as a ring-enhancing lesion within the brain parenchyma; this diagnosis was not supported by this patient's radiographic imaging, showing bilateral enhancing lesions at the cerebellopontine (CP) angle. Such lesions can be remembered with the mnemonic "AMEN" (Acoustic neuroma/vestibular schwannoma, Meningioma, Epidermoid, and facial Neuroma). Ménière's disease can cause vestibular symptoms, typically vertiginous, with hearing loss and tinnitus, but typically presents with unilateral symptoms often occurring in episodes. Bilateral vestibular schwannomas are diagnostic of NF2.[1]

The correct answer to Q2 is A.

This patient had symptoms of elevated intracranial pressure (headaches, blurry vision), signs of secondary end organ damage (papilledema), and imaging evidence of obstructive hydrocephalus at the level of the fourth ventricle. This is a medical and surgical emergency and prompted immediate neurosurgical evaluation and cerebrospinal fluid diversion via ventriculoperitoneal shunting.

Discussion

We asked experts in neuro-oncology, neuroophthalmology, audiometry, and radiology to comment on the pathophysiology and clinical course of a patient with NF2, and specifically about the fundoscopic examination, audiology considerations, and the pertinent radiographic findings of this case.

Patrick Kuhlman, M.D. (PGY-3, Internal Medicine), Roy Strowd, M.D. (Neuro-oncology)

NF2 affects fewer than 200,000 people worldwide. It is characterized by development of benign tumors of the nervous system, including vestibular schwannomas, meningiomas (cranial and spinal), spinal ependymomas, and other peripheral nerve schwannomas (cranial, spinal, and cutaneous).[2] One mnemonic to recall the cardinal features of NF2 is "MISME" (Multiple Inherited Schwannomas, Meningiomas, and Ependymomas). The average age of onset of symptoms ranges from 18–24 years, with nearly all affected individuals developing bilateral vestibular schwannomas by age 30 years.[3] Diagnosis is considered "definite" in patients with bilateral vestibular schwannomas or a first-degree family member under 30 years of age with NF2 plus unilateral vestibular schwannomas, or any two of the following disorders: meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular cataract.[1]

NF2 results from the loss of function of the tumor suppressor gene, NF2, located on chromosome 22q11.2.[3,4] The NF2 gene encodes the tumor suppressor protein, *merlin*, which is thought to be involved in membrane stabilization and regulation of cellular growth pathways.[1,5] While genetic in its origin, only half of cases are inherited, with 50-60% of patients having no family history of NF2 and harboring *de novo* mutations.[6] Occasionally, non-germline NF2 mutations will be acquired later in embryogenesis (termed mosaic NF2).

Timothy Martin, M.D. (Neuroophthalmology)

Unlike the classic ophthalmic findings in NF1 (Lisch nodules, retinal astrocytomas), NF2 lacks characteristic primary ocular findings, though early cataract does occur. However, as in this case, the intracranial manifestations of NF2 may be evident during ocular examination. This patient demonstrated severe papilledema, a secondary effect of the intracranial tumors causing hydrocephalus (Figure 1). He also had bilateral sixth nerve palsies, which can be a component of elevated intracranial pressure from any cause. In this case, they could also have been due to direct compression of the sixth cranial nerves by the patient's bilateral acoustic neuromas.

Papilledema from elevated intracranial pressure can cause vision loss or even blindness if the papilledema is acute and severe or present over long periods of time. This patient was certainly at risk for blindness given the severity of his

optic disc swelling, and immediate intervention to lower his intracranial pressure was indicated.

Meagan Lewis, Au.D. (Audiology)
Patients with NF2 may present with a variety of audiometric findings. Some notice decreased hearing in one ear before the other, similar to this patient. Pure tone testing evaluates specific frequencies much like the keys on a piano keyboard. The location of tumor compression along the course of the auditory nerve and the size of the tumor both affect the degree of loss, the frequencies affected, and most importantly, speech discrimination (i.e. the ability to distinguish words). The hallmark of a retrocochlear lesion is poorer speech discrimination ability than is typical of the pure tone audiogram. For example, for this patient, although he could detect sounds (albeit at a higher intensity level) in the right ear, he could not distinguish words. Additional tests, such as acoustic reflex testing and rollover, are done as part of the audiometric battery to screen for such retrocochlear pathology.

The degree to which speech discrimination is affected in NF2 is variable; some individuals are helped with amplification if they retain some ability to discriminate words. That said, nearly all patients with NF2 will eventually progress to profound hearing loss.[7] Some patients have undergone resection of their tumors with preservation of nerve fibers and received cochlear implants.[7] However, if there is no residual auditory nerve function, cochlear implantation is not helpful. Auditory brainstem implants, while an option for some, have shown variable results. Some individuals achieve open set speech discrimination (meaning that they understand words without knowing the choices in advance). However, most gain improved lip-reading abilities, environmental awareness, and closed set speech discrimination (can pick from a list of choices).[8]

Cane Hoffman, M.D. (Radiology, PGY-3), Vinay Bhatia, M.D. (Neuroradiology)
Figure 2: Axial T1 Fluid Attenuated Inversion Recovery (FLAIR) post-contrast sequence reveals bilateral intensely enhanced masses centered at the bilateral CP angles, consistent with bilateral vestibular schwannomas. Enhancement continues into the internal auditory canals bilaterally (arrows). This pattern of tumor enhancement is seen due to origination of the tumor from the vestibulocochlear nerve which courses through the CP angles and continues into the internal auditory canals.

Figure 3: (A) Axial T2 fat saturated MRI at the level of the lateral ventricles reveals dilated lateral ventricles because of obstructed cerebrospinal fluid outflow at the level of the 4th ventricle. (B) Axial T2 fat saturated MRI at the level of the 4th ventricle (arrow) reveals near-complete obliteration of the 4th ventricle. The tip of the arrow should normally point to a bright fluid-filled 4th ventricle on a T2-weighted sequence. Brainstem compression from bilateral vestibular schwannomas occluded drainage from the 4th ventricle through the foramen of Magendie and paired foramina of Luschka, causing obstructive hydrocephalus (Figure 3A).

Figure 4: Sagittal T2 Short Tau Inversion Recovery (STIR) sequence of the cervical spine reveals an intramedullary (within the spinal cord) mixed solid and cystic tumor of the cervical spinal cord most consistent with an ependymoma. A low T2-signal intensity region is consistent with a predominantly solid component (white arrow). High T2-signal regions are consistent with a predominantly cystic tumor versus formation of a central syrinx (blue arrow) due to obstruction of cerebrospinal fluid flow. A small focus of low T2-signal likely represents a "hemosiderin cap." This is suggestive, although not pathognomonic, for an ependymoma (red arrow).

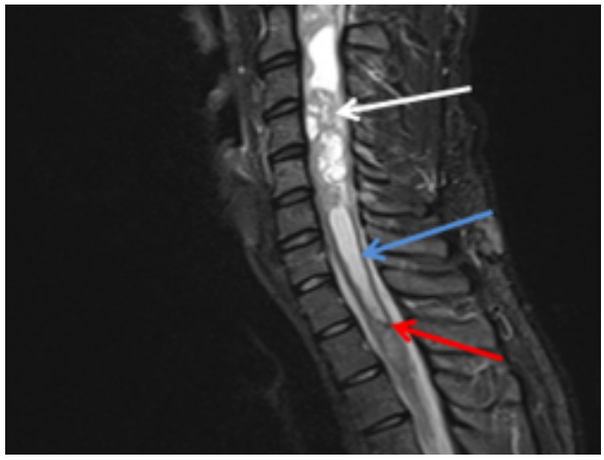

Figure 4. Sagittal T2 STIR MRI revealing multiple lesions of the cervical spine, with solid lesion (white arrow), cystic versus formation of central syrinx (blue arrow), and likely "hemosiderin cap" suggestive of an ependymoma (red arrow).

Patrick Kuhlman, M.D. (PGY-3, Internal Medicine), Roy Strowd, M.D. (Neuro-oncology)

Vestibular schwannomas are the dominant tumor manifestation in many patients with NF2. This case highlights the need for clinical evaluation of young patients presenting with progressive hearing loss, particularly when bilateral. The hearing loss in NF2 manifests as sensorineural hearing loss from cochleovestibular dysfunction.[1,2] Whereas treatment options commonly considered for solitary vestibular schwannomas not associated with NF2 include surgery or radiosurgery, these interventions have less benefit, more frequent complications, and higher failure rates in NF2 patients.[1] Optimal management of vestibular schwannomas includes optimizing function and quality of life, with brainstem compression, hearing decline, and/or facial nerve function typically warranting surgical intervention.[3,9] In the absence of aforementioned alarm symptoms, watchful waiting and close observation may be acceptable. Recently, bevacizumab, a vascular endothelial growth receptor (VEGF) targeted antibody, has shown promise in improving hearing and reducing tumor size in Phase 2 studies.[10]

Ultimately, NF2 possesses a wide range of disease severity, with tumor size and location driving disease prognosis. From the time of diagnosis, patients with NF2 have an 85% survival at 5 years, 67% at 10 years, and 38% at 20 years.[11] This patient presented with signs and symptoms of elevated intracranial pressure, which required prompt and immediate management before definitive evaluation of underlying NF2. His treatment consisted of placement of a ventriculo-peritoneal shunt, cervical-thoracic laminectomy (C1-T2) for resection of the spinal ependymoma resulting in quadriparesis, post-operative functional immobility, and need for tracheotomy, percutaneous endoscopic gastrostomy, and surgical decompression for removal of a vestibular schwannoma on the left side. Left eye corneal perforation developed secondary to peripheral facial nerve paralysis, and the patient underwent multiple hospitalizations for urinary and pulmonary sepsis syndromes. The patient was treated with bevacizumab for 8 months but this was discontinued with evidence of continued radiographic progression. Unfortunately, the patient died suddenly at home of unknown cause approximately 16 months after initial presentation.

Conclusion

This challenge case highlights the importance of clinical prioritization in patients presenting with complex medical problems. The most pressing aspect of this patient's presentation was his elevated intracranial pressure caused by obstructive hydrocephalus, as manifested by blurry vision, diplopia, cranial nerve VI palsies, and severe papilledema. This required emergent management involving radiology (define anatomy), ophthalmology (papilledema confirmation), and neurosurgery (surgical treatment). The tumors were long standing, and grow slowly over time. They are best assessed by a multidisciplinary team, which should optimally include neuro-oncology, neurosurgery, audiology, and physical and occupational therapy, to carefully coordinate approaches to preserve function and quality of life.

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Challenge Cases

Recurrent Altered Mental Status in a Patient Newly Prescribed Methadone

Eliza Szuch[1], Jennifer L. Hannum, M.D.[2], Ihtsham Haq, M.D.[3], Roy E. Strowd, M.D.[3,4,5]

Case Presentation

A 41-year-old male with a history of fibromyalgia on alprazolam and duloxetine, who reported chronic illicit methadone use, initially presented to an outside facility with confusion, dysphasia, paranoia, and short-term memory loss.

The patient reported having recently acquired methadone from a new distributor and had ingested a "larger" dose prior to this episode. Initial work-up was unremarkable except that a urine sample was positive for benzodiazepines and methadone. Symptoms improved over several days. Three weeks later, the patient returned with another episode of acute-onset confusion, combativeness, hallucinations, and gait disturbance developing over <24 hours. Urine drug screen was positive for benzodiazepines and methadone. Over the next several days, the patient developed akinetic mutism, severe rigidity, tremors, and parkinsonism, and was ultimately transferred to Wake Forest Baptist Medical Center in a coma. He required intubation, gastrostomy tube placement, and remained hospitalized for 33 days, followed by 35 days of inpatient rehabilitation.

Investigations and Work-Up

While afebrile at the time of initial transfer to our facility, the patient had a temperature maximum in the 24 hours prior of 103.2°F, blood pressure of 119/74 (mmHg), heart rate of 65 (bpm) and respiratory rate of 19 (breaths/min). On neurologic examination at the time of transfer, the patient could not be aroused to verbal or tactile stimulation and was minimally responsive to painful stimulation. Cranial nerve examination was without focal findings or brainstem dysfunction with intact blink to threat, roving eye movements, intact oculocephalic and corneal reflexes, no facial asymmetry, and intact gag reflex. Motor examination showed withdrawal of all four extremities and was significant for diffuse axial and appendicular rigidity, including the upper and lower extremities bilaterally as well as neck with flexion and extension. Deep tendon reflexes were symmetrically brisk throughout (without clonus) and bilateral extensor plantar responses were present.

An MRI of the brain revealed diffuse, bilateral T2-weighted and FLAIR hyperintensities sparing subcortical U-fibers (Figure 1C and D). Though there was a significant and diffuse corresponding increased signal on diffusion weighted sequences, there was no associated change in the apparent diffusion coefficient sequences (Figure 1A and B), consistent with T2 shine-through.[1]

Laboratory tests found no evidence of systemic infection, inflammation, or explanatory

[1] Wake Forest School of Medicine, Winston-Salem, NC

[2] Department of Emergency Medicine, Wake Forest School of Medicine, Winston-Salem, NC

[3] Department of Neurology, Wake Forest School of Medicine, Winston-Salem, NC

[4] Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC

[5] Translational Sciences Institute, Wake Forest School of Medicine, Winston-Salem, NC

Address Correspondence To:
Roy E. Strowd, M.D.,
Departments of Neurology, Internal Medicine, and the Translational Sciences Institute,
Wake Forest School of Medicine,
Medical Center Boulevard
Winston-Salem, N.C. 27157
Phone: 336-716-2357
Fax 336-716-9489
rstrowd@wakehealth.edu

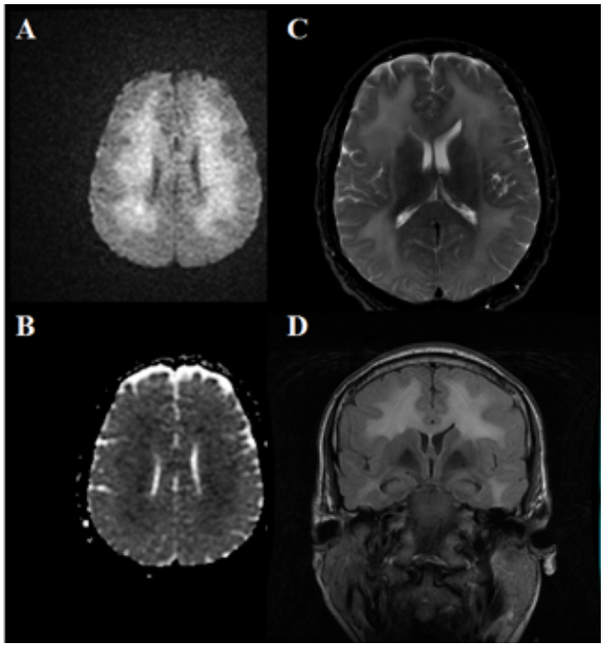

Figure 1. Axial and coronal MRI brain sequences demonstrating increased signal on diffuse weighted sequences in the bilateral subcortical white matter (A) without corresponding increased signal on apparent diffusion coefficient sequences (B) and corresponding mild, diffuse, bilateral, symmetric T2-weighted (C) and FLAIR (D) hyperintensities sparing the subcortical U-fibers and not extending into the cerebellum and brainstem without associated contrast enhancement (not shown).

metabolic disturbance. Lumbar puncture was normal (2 cells/mm^3, protein 45 mg/dL) including bacterial culture, fungal culture, viral polymerase chain reaction (PCR) testing (HSV, VZV, CMV, EBV and enterovirus), venereal disease research laboratory testing, and JC polyoma virus DNA testing. Cerebrospinal (CSF) fluid IgG index was normal without oligoclonal bands. CSF myelin basic protein was 5.2 mcg/L, (reference: 0-4 mcg/L) and tau protein was 748 pg/ml (negative) with 14-3-3 protein interpreted as not supportive of a prion protein disorder. Additional serologic evaluations did not explain the patient's symptoms. This included normal thyroid stimulating hormone, vitamin B12, human immunodeficiency virus testing, rapid plasma reagin testing, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody screen, lupus inhibitor, antibodies to double-stranded DNA, anti-Rho and-La antibodies, thyroglobulin and anti-thyroid peroxidase autoantibodies, very long chain fatty acids for peroxisomal disorders, and arylsulfatase enzyme activity for adult-onset metachromatic leukodystrophy. Tests for both serum and CSF paraneoplastic antibodies (including N-methyl-D-aspartate receptor antibody) found no significant results. There was no history of paint huffing or toluene exposure, and urine heavy metal levels were in the normal range.

Continuous and serial electroencephalography showed no epileptiform abnormalities. CT angiography of the head and neck did not reveal evidence of vasculitis. CT scans of the chest, abdomen, and pelvis revealed an incidental renal mass, which was found to be clear cell renal carcinoma on biopsy. Brain^{18} F-fluorodeoxyglucose positron emission tomography (FDG-PET) demonstrated diffuse and symmetric hypometabolism sparing the temporal lobes and cerebellar vermis. A right frontal brain biopsy showed nonspecific gliosis.

The patient was empirically treated with five successive days of intravenous methylprednisolone without improvement. He subsequently underwent five sessions of plasmapheresis over 10 days without improvement.

Challenge Questions

1. Based on the patient's history and imaging, what white matter pathology best explains this presentation?

A. Progressive multifocal leukoencephalopathy
B. Epileptic encephalopathy
C. Creutzfeldt-Jacob disease
D. Toxic leukoencephalopathy
E. Autoimmune encephalitis or encephalopathy
F. Hypertensive leukoencephalopathy

2. Given the lack of initial symptomatic improvement, the patient's family would like to know if this condition is possibly reversible. Based on your leading diagnosis in Question 1, how would you describe the possibility of reversing this condition?

A. This condition is reversible and he could experience a full neurologic recovery.
B. This condition is reversible, but only if treated early, in which case a good neurologic recovery is possible.
C. This condition is irreversible and he will experience no neurologic recovery.
D. This condition is irreversible; he will continue to decline and has a high likelihood of death.

The correct answer to Q1 is D.

The patient's clinical presentation was of an acute-onset, progressive encephalopathy with cortical (confusion, dysphasia), limbic (hallucinations, memory loss, paranoia), and subcortical (rigidity, tremors) involvement. Though encephalopathy has a broad differential diagnosis, the presence of extrapyramidal signs is a helpful discriminator. These findings signify disruption or damage to basal ganglia circuitry,[2] fibers that are particularly sensitive to toxic or metabolic insults as well as to inflammatory, infectious, degenerative, and vascular pathologies.[3] Possible pathology in our patient included diseases with gray matter predominance (e.g., seizure, Creutzfeldt-Jacob disease, etc.), white matter predominance (e.g., leukoencephalopathy), combined involvement (e.g., acute demyelinating leukoencephalopathy), or normal neuroimaging (e.g., endocrine disorder, infection).

Prior to the MRI scan of the brain, serotonin syndrome and neuroleptic malignant syndrome were considered, given the parkinsonian symptoms of stiffness and rigidity combined with altered mental status and known duloxetine treatment. However, after MRI of the brain revealed a progressive, diffuse leukoencephalopathy, other causes seemed more likely. Alternative pathologies included inflammatory, neoplastic/paraneoplastic, toxic, metabolic, hereditary, vascular and other disorders.

A lack of inflammation on the lumbar puncture (i.e., normal CSF protein, IgG index), absence of associated serologic testing, and lack of response to adequate immunomodulation (i.e., methylprednisolone, plasmapheresis) appeared to rule out an inflammatory cause. Infection was not supported by the lack of pleocytosis, and normal cultures, PCRs, and biopsy. Though the patient had an incidental renal cell carcinoma, there were no associated paraneoplastic antibodies, no evidence of inflammation in the lumbar puncture, and no response to immunomodulatory therapy. Furthermore, renal cell carcinoma has not been widely associated with progressive encephalopathy.[4] The clinical course was inconsistent with a hereditary process, and laboratory testing was unremarkable. Vasculitis was not supported based on the lack of pleocytosis, the diffuse, symmetric involvement on MRI, and the negative CT angiogram and biopsy.

A diagnosis of toxic leukoencephalopathy was made and supported by the antecedent methadone overdose, temporal association of symptom onset, and report of recent "larger" dose of ingestion.

The correct answer to Q2 is A.

The patient initially received a therapeutic trial of 1 g/day intravenous methylprednisolone for 5 days and subsequently received plasmapheresis every other day for a total of 5 sessions without improvement.

Symptomatically, his severe akinetic, rigid parkinsonism was treated with carbidopa-levodopa, bromocriptine, and then baclofen. Clonidine was added for dysautonomia. For activation, the patient was initially tried on amantadine, but was ultimately transitioned to methylphenidate combined with propranolol for intermittent agitation.

The patient's condition gradually improved following discharge, and he returned to functional independence with a normal neurologic exam at four months. He developed symptoms of pseudobulbar affect which gradually improved without specific treatment and all symptomatic medications were withdrawn over one year. At two years, he had returned

to normal with a completely normal neurologic examination and no further symptoms except a self-described reclusive personality and mild difficulty with concentration.

As was the case in this patient, gradual neurologic recovery is common and often reported to be near full recovery.[5] This clinical course is strikingly different from other causes of subacute progressive clinical decline, characterized by irreversible worsening, such as Creutzfeldt-Jacob disease or hypoxic-ischemic injury, or other causes of leukoencephalopathy or ischemic encephalopathy.

Discussion

Methadone-induced leukoencephalopathy is a rare cause of reversible subacute progressive encephalopathy, with several reported cases in children,[6-13] but only limited reports in adults.[5, 14, 15]

Heroin-associated leukoencephalopathy has been frequently described in the literature. While additive agents or impurities have been implicated, studies have failed to demonstrate a clear association.[16] The underlying pathophysiologic mechanisms are unknown. Mitochondrial damage has been suggested based on pathologic evaluation and data from agnetic resonancy spectroscopy (MRS). Similar pathogenesis has been suspected in cases of methadone-induced neurotoxicity. In one case, a reduced N-acetylaspartate level and elevated lactate peaks on MRS were interpreted as suggesting mitochondrial dysfunction. A relative increase in the choline peak was thought to suggest local hypoxia.[14] In another study reporting pathologic evaluation of biopsy specimens, predominantly axonal loss with preserved myelin was observed.[15]

The finding of diffuse subcortical hypometabolism on FDG-PET has not been previously described in the setting of methadone-induced leukoencephalopathy. Substantial alterations in cerebral perfusion and metabolism by FDG-PET have been demonstrated in the setting of heroin-induced leukoencephalopathy.[17] These findings, while nonspecific, indicate changes to cerebral perfusion, glucose metabolism, oxygen consumption, or neuroreceptor density. The significant reductions in this study correlated to regions of white matter hyperintensity and T2 shine-through that did not respect vascular or watershed territories, suggesting an alteration in local cerebral metabolism. This non-invasive tool may be particularly helpful in differentiating between toxic etiologies and central nervous system lymphoma or neoplasm.

While methadone-induced leukoencephalopathy remains rare, clinicians must maintain a high index of suspicion for accurate diagnosis and prognostication. Recent epidemics involving similar medications including Opana® and others raises concern for greater physician awareness of this potential cause of toxic encephalopathy.[18] Other causes of leukoencephalopathy (e.g., hypoxic ischemic injury) have a poorer prognosis. Treatment for this condition remains largely supportive. There are reports of antioxidant therapy as an effective treatment for toxic leukoencephalopathy; however, further investigation is needed to define their role in management. Given the reversibility of methadone-induced toxicity and the poor correlation of MRI imaging abnormalities to ultimate clinical outcome in toxic leukoencephalopathies,[19] clinicians must remain vigilant in reviewing a patient's medication and social history.

Teaching Points

- Methadone overdose is a rare but important cause of toxic leukoencephalopathy
- Clinicians should maintain a high index of suspicion in patients presenting with subacute progressive encephalopathy, parkinsonism, and a history of at-risk exposure
- Differential diagnosis is broad and is aided by MRI imaging, which can be supplemented by CSF and laboratory evaluations to exclude alternative diagnoses
- Treatment remains supportive, with most patients receiving steroids, antioxidant or other therapies
- Symptoms tend to improve over several months, with patients returning to baseline

Disclosures

The authors have no conflicts of interest or disclosures to report.

Authorship

All authors have contributed substantially to this report.

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Original Science

Blood is Blood: Validation of Scapular Capillary Blood Gas Sampling to Determine Serum pH

Jason P. Stopyra, M.D.[1], Christine A. Hall, M.D., M.Sc.[2,3], Jenny K. Potter, BS, EMT[4], Patti J. Kriegel, RT[5], John Gaillard, M.D.[1], William P. Bozeman, M.D.[1]

Abstract

Background: Standard arterial blood gas (ABG) sampling can be difficult in uncooperative patients. Scapular region capillary blood gas (ScapGas) sampling is easily performed in restrained but uncooperative patients, but has not yet been performed in clinical settings when patients have abnormal pH values.

Methods: We conducted a prospective controlled trial of adult emergency department patients who received ABG analysis as part of their clinical care, to determine if the pH measured by analysis of ScapGas samples was comparable to standard ABG samples.

Results: Forty-three patients with matched pairs of ScapGas and standard ABG samples were enrolled. Mean age was 60.4 years, and 67.4% were male. The mean difference in pH was 0.02 (SD 0.04, 95% CI 0.01 – 0.04). pH values agreed within 0.05 in 38/43 cases (88.4%; 95% CI 75.1 – 95.4). Lactate values were also compared in a subgroup of 16 patients; these were also similar, with a mean difference of 0.37 (SD 0.40, 95% CI 0.15 – 0.58).

Conclusions: ScapGas sampling and point-of-care analysis produces pH measurements that agree with standard ABG sampling and analysis to a clinically acceptable degree. This sampling technique may be useful in both hospital and prehospital settings to guide clinical care in combative or uncooperative patients.

[1]Wake Forest School of Medicine

[2]University of British Columbia

[3]University of Calgary

[4]University of North Carolina

[5]Cone Health

Address Correspondence To:
Jason P. Stopyra, M.D.
Deptartment of Emergency
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157
336-713-7050 (office)
336-716-5438 (fax)
jstopyra@wakehealth.edu

Introduction

Arterial blood gas (ABG) analysis provides important clinical information regarding respiratory and metabolic function, and acid/base regulation.[1-3] Its use in the emergency setting is well established for patients who may be extremely ill. ABG sampling, a precise procedure that involves careful insertion of a needle into an artery, requires patient cooperation.[4] This fact may prevent the ability to collect a sample for analysis. Attempting to obtain an ABG from uncooperative or combative patients presents increased risks both for patients and medical personnel.[4]

In the prehospital and emergency department settings, some patients who are unable or unwilling to cooperate with ABG sampling could potentially benefit from the information provided by blood gas analysis. These situations include patients who cannot or refuse to provide information about their history of present illness. Providers who care for these patients are also compromised by the limited amount of information the physical exam can provide. Patients with excited delirium, status epilepticus, closed

head injuries, and polysubstance ingestion may present in such conditions.

Capillary blood gas (CBG) sampling is a validated alternative method to ABG sampling, and is commonly employed in children.[5-7] However, use of traditional CBG sampling sites such as the heel or earlobe has limitations in uncooperative adult patients. The scapular region could be safely accessed for sampling and analysis of critical metabolic parameters in such patients. Measurements of pH from the scapular region agreed with arterial pH in healthy volunteers, but has not yet been measured in the clinical setting across a range of normal and abnormal pH values.[8]

Thus, we performed a prospective controlled trial to determine if measurement of blood gas pH using capillary blood samples from the scapular region (ScapGas) is in clinical agreement with blood gas pH from a standard ABG in emergency department patients with a range of pH values. A secondary objective was to determine if ScapGas lactate levels were in clinical agreement with those derived from standard arterial blood gas samples.

Methods

We compared matched pairs of pH measurements as determined by traditional ABG and ScapGas sampling in adult emergency department patients undergoing ABG sampling for clinical purposes. Enrollment occurred at two academic Emergency Departments with annual clinical volumes of 54,000 and 104,000 patients, respectively. The protocol was approved by each institution's Institutional Review Board. Eligible subjects in the Emergency Department were approached by research staff and completed informed consent after a clinician ordered a standard ABG. In critically ill patients, proxy consent was obtained from an authorized representative by research staff. Exclusion criteria included age less than 18 years, trauma to the scapular region, contraindication to skin puncture (e.g., cellulitis, abscess, contusion, abrasion, laceration or burns), concurrent intravenous bicarbonate infusion, and previous participation in this study.

After informed consent was obtained, ABG and ScapGas samples were obtained within 5 minutes of each other. ScapGas sampling (Figure 1) involved cleansing the skin site and inserting a manual skin lancet into the subcutaneous tissues. The skin around the lancet puncture was repeatedly squeezed to produce approximately 0.5 ml of blood, which was collected into a heparinized capillary tube. ScapGas samples and a portion of the traditional ABG sample were analyzed using a previously validated point-of-care blood analyzer and cartridge that performed blood gas and lactate parameters (i-STAT Handheld Analyzer and CG4+ cartridge,

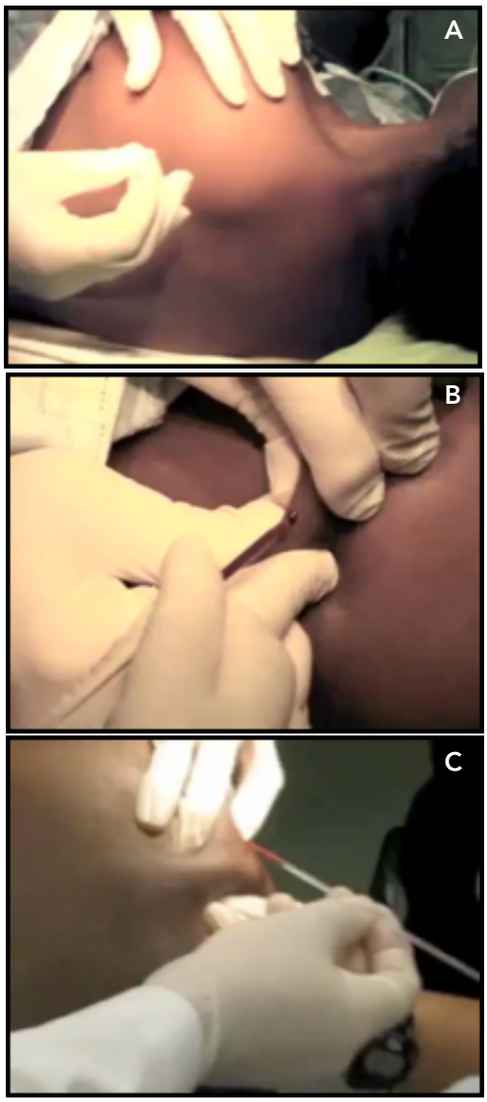

Figure 1. ScapGas sampling technique.
a. Preparation and lancet insertion
b. "Milking" tissues to obtain blood sample
c. Collection of sample in heparinized capillary tube

Abbot Point of Care, Princeton, NJ).[9] The remainder of the standard ABG sample was processed by the hospital laboratory and reported for clinical use in the usual fashion.

Data collection forms included demographic and clinical information, and results of all blood gas sampling. The primary comparison was pH values; a secondary comparison was lactate levels, when available. *A priori* sample size calculations indicated that with a correlation coefficient between the pair elements presumed to be 0.80 or better, at an alpha error of 0.05 and with 80% power to detect disagreement between the pairs, a total of 37 matched pairs would be needed for analysis. Clinically acceptable agreement between pH samples was defined *a priori* as pH results within 0.05 of each other.

Statistical analysis included descriptive statistics using standard spreadsheet software (Microsoft Excel 2010, Microsoft Corporation, Redmond, WA). Wilcoxon matched pairs testing was used to compare pH and lactate values and to calculate the Pearson correlation product-moment coefficients (InStat version 3.10, GraphPad Software, La Jolla CA). A Bland-Altman plot was generated to plot pH values among samples.

Results

A total of 78 subjects were enrolled in the study. ScapGas sampling was not successful in 35 cases. Of these, the capillary tube samples clotted in 9 cases and the sample volume was inadequate for processing in 26 cases. These cases had arterial pH values in a similar range as the other participants. With these exclusions, complete results were available for comparison in 43 subjects.

Patient demographics and clinical characteristics are shown in Table 1. The mean age was 60.4 years (range 22 to 89), and 67.4% were male. The most common clinical indication for ABG testing was respiratory complaints.

Primary Results (pH)

Arterial pH values ranged from 6.99 to 7.63, with a slight skew toward acidosis (Figure 2).

The mean difference between measured pH by traditional ABG and ScapGas sampling was 0.02 and the median difference was 0.01 (standard deviation [SD] 0.04, range -0.04 to 0.15). The 95% confidence interval (95% CI) for the difference ranged from 0.01 to 0.04. The results of both types of sampling are shown in Figure 3. Five of the 43 values (11.6%) were greater than the predefined clinical agreement range of 0.05, leaving 38/43, or 88.4%, within acceptable clinical agreement (95% CI 75.1% – 95.4%). Correlation between the paired ABG and ScapGas samples was excellent (Pearson correlation coefficient of 0.94).

Table 1. Demographic and clinical information

Gender	Male	29
	Female	14
Age (yr)	Min	22
	Max	89
	Mean	60.4
	Std Dev	17.2
Condition	Respiratory	37
	Altered Mental Status	2
	Others*	4

*Others – Sickle Cell (1); Abd Pain (1); Hyperglycemia (1); Syncope/ Hypertension (1)

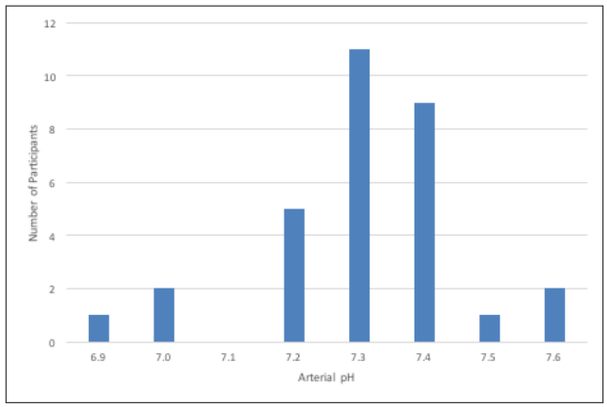

Figure 2. Distribution of arterial pH values in the study population.

Secondary Results (Lactate)

Lactate was not consistently measured due to variations in clinician ordering preference. However, paired samples were available for 16 subjects. The mean difference between lactate measured by traditional ABG and ScapGas was 0.37mmol/L and the median difference was 0.23 mmol/L (SD 0.40, range -0.10 to 1.28, 95% CI 0.15 – 0.58). Correlation between the paired ABG and ScapGas samples was again excellent (Pearson correlation coefficient of 0.95).

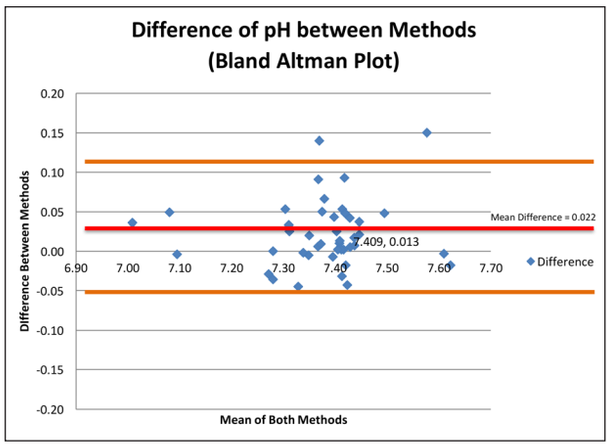

Figure 3. Bland Altman Plot of the pH values in ABG and ScapGas samples. Mean and 95% confidence intervals indicated.

Discussion

Compared to the standard ABG, ScapGas sampling of adults in an emergency room produced pH measurements with clinically acceptable agreement to guide critical resuscitation interventions. This sampling technique allows medical providers to obtain lab values to guide clinical care without compromising their own safety even before attempts at intravenous access are made. This method also mitigates the risk of complications of traditional ABG sampling in patients with altered mental status who cannot provide reliable histories or cooperate with examination.

The scapular area can be easily accessed in restrained or uncooperative patients. This area is large, devoid of major neurovascular bundles, and has the added protection of the bony scapula, which protects the pertinent major organs of the thorax. Sampling can be performed while simultaneously restraining the patient's arms, legs, and head, if necessary.

Rapid assessment of pH or lactate in patients who are resisting efforts to collect blood samples can be very helpful. The patient's acid-base analysis is certainly only part of the patient's evaluation, but an acidotic value would indicate a higher likelihood of significant uncompensated metabolic illness and could assist the clinician in initiating aggressive resuscitative measures. A normal pH may indicate that the patient has just recently developed an altered sensorium and may lead the clinician to take a more conservative "watch and see" approach. In the proper clinical circumstance, an alkalotic pH may indicate the need for anxiolysis. ScapGas collection in the prehospital settings could alert emergency physicians of acid/base status, establish a baseline for future comparison, and reduce door-to-treatment times for patients with altered status who have significant pH derangements.

Previous work in healthy normal volunteers has demonstrated agreement between ScapGas pH and arterial pH, with a mean difference of 0.01 (95% CI -0.01 – 0.00).[8] The present study successfully tested a population of 43 emergency room patients, 18 of whom had an abnormal pH values. It is likely that these values outside of the normal range will more closely apply to patients with altered sensorium.

In our study, the Pearson correlation coefficient was 0.94, reflecting a high degree of correlation between the two tests. More importantly for clinical applications, pH measurements using the ScapGas technique agreed with standard measurements across a broad range of pH values. This makes ScapGas clinically useful without the need for conversion factors or formulas. Thus, providers can quickly obtain and interpret ScapGas values, just as they would traditional arterial pH values.

The predefined range of clinical agreement in terms of pH was defined at 0.05 to reflect a clinically acceptable and narrow margin of error.[4] While five pairs of values fell outside the predefined range of clinical agreement of ± 0.05, three of those had differences of less than 0.10, which is unlikely to have clinical significance that influences treatment. In one alkalotic patient, the arterial pH was 7.50 and the ScapGas pH was 7.65. This difference may have been due to temporal asynchronicity of obtaining the ScapGas and arterial pH, but is unlikely to generate a significant change in treatment approach for severe alkalosis. However, further work may be required to determine the role of ScapGas in patients with extreme alkalosis.

Limitations

ScapGas sampling was unsuccessful in 35 out of 78 patients (44.9%) in this study. This failure rate may have been caused by the novelty of the procedure and lack of familiarity of the equipment; these may improve in time. This testing modality is used in situations with very limited opportunities to obtain

laboratory data. Thus, a success rate over 50% of attempted tests may be quite good when the alternative is a complete lack of laboratory information.

Another important factor that may limit this test modality is its incorporation of glass capillary tubing. Though unlikely, the potential for glass breakage during its use in a population of combative or uncooperative patients may present a danger to staff. It may also limit utility in the prehospital setting during transport in the back of a moving ambulance.

An additional clinical limitation is the use of manual lancets. These produced minimal discomfort and were well tolerated by patients, but produced only a small droplet of blood. The low volume necessitated considerable squeezing of tissues over a 30- to 60-second period to provide an adequate volume for sampling. This requirement could be difficult in a patient who is actively struggling or having a seizure. While this factor does not detract from our results it does suggest that further refinements in the sampling technique or equipment used could enhance the clinical utility of ScapGas measurement in the envisioned scenarios.

Conclusion

Sampling and point-of-care analyses of ScapGas samples from adults in an emergency department produced pH measurements that agreed with standard ABG sampling and analyses to a clinically acceptable degree. This sampling technique may have utility to guide critical resuscitation interventions in combative or uncooperative patients in prehospital or emergency department settings.

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Original Science

Comparison Between Mitral Valve and Concomitant Mitral with Tricuspid Valve Operations: A Retrospective Analysis

Steven T. Leung, MBBS[1], David Luo, M.D.[2], Patrick E. Parrino, M.D.[3]

Abstract

Background: Treatment of tricuspid regurgitation secondary to mitral regurgitation is not uniform. This study compares mortality and morbidity of concomitant mitral/tricuspid valve operations to mitral valve operations alone.

Methods: 153 mitral valve operations were performed. 130 patients (age, 58.2 ± 13.6 years) underwent mitral valve repair only, and 23 patients (age, 70.6 ± 7.7 years) underwent joint mitral and tricuspid valve repairs. Results were compared using Pearson's chi-square and propensity score analyses.

Results: Patients undergoing combined operations were older (ages 58.2 vs. 70.6 years, p<0.001), and more commonly female (73.9% vs. 44.6%, p=0.010). Using Pearson test, combined operations had similar operative mortality (0.0% vs. 1.5%), higher incidence of prolonged ventilation (30.4% vs. 11.5%, p = 0.026), and higher postoperative length of stay (9.7 days vs. 6.4 days, p = 0.0006). No statistically significant differences in rates of major complications (43.5% vs. 16.2%, p = 0.14) or aortic cross-clamp time (114.9 min vs. 119.7 min, p = 0.566) were observed. Propensity score analyses revealed no differences between outcomes measured.

Conclusions: Postoperative mortality and morbidity were similar between groups. Given the decreased quality of life from progressing tricuspid regurgitation, a concomitant procedure is reasonable for selected patients with severe tricuspid regurgitation.

Introduction

Patients considered for operations due to mitral valve disease often have accompanying functional tricuspid regurgitation (TR) at time of presentation. Historically, tricuspid valve repairs were not routinely performed during mitral valve operations, since functional TR was thought to improve after mitral procedures.[1] It was believed that functional TR was strictly caused by left-sided disease processes such as mitral stenosis or mitral regurgitation. However, it has since been established that the main factor causing TR is dilation of the tricuspid annulus secondary to right ventricular dilatation, indicating that an actual anatomic anomaly existed.[2] Therefore, resolution without intervention after mitral valve procedure seems unlikely to occur. In addition, unresolved tricuspid regurgitation at time of mitral operation negatively impacts perioperative survival and outcome.[3]

[1] Department of Surgery, Wake Forest School of Medicine, Winston-Salem, NC

[2] Department of Orthopedic Surgery, Wake Forest School of Medicine, Winston-Salem, NC

[3] Department of Surgery, Ochsner Health System, New Orleans, LA

Address Correspondence To:
Steven T. Leung, MBBS
Department of Surgery
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157
sleung@wakehealth.edu
Phone: 626-991-9820

Notably, one study observed that secondary TR is an ongoing process; during follow-up, TR worsened in 45% of their patients after mitral valve replacement.[4] Multiple studies have also concluded that the severity of tricuspid valve disease is an important prognostic indicator in the survival rates of patients after mitral valve operations. In 2009, Chan et al. concluded that tricuspid valve repair is indicated in severe TR to alleviate heart failure symptoms and prevent progression of disease.[5] Patients who underwent concomitant valvular operations had improved quality of life and fewer complications. Based on these observations, the American College of Cardiology/American Heart Association Guidelines recommend surgical correction of severe TR when patients undergo mitral valve repair or replacement.[6] LaPar et al. concluded that simultaneous mitral plus tricuspid valve operations increased postoperative morbidity and mortality compared to mitral valve surgery alone, even after risk adjustments.[7] However, based on our experience, postoperative mortality and morbidity rates are comparable for both types of surgeries. Therefore, this retrospective study was designed to determine the factor(s) that affect postoperative morbidity and mortality among patients with tricuspid valve disease at the time of mitral valve operation.

Methods

This is a retrospective cohort study of patients treated by a single surgeon at one institution starting from 2004 to 2012. We included patients who had mitral valve surgery only, and patients who had combined mitral and tricuspid valve surgery during the same procedure. Patients who underwent mitral valve replacements were excluded from this study because too few patients underwent mitral valve replacement with tricuspid valve surgery to produce any statistically meaningful data for comparison. All procedures used the bi-caval cannulation technique, and both antegrade and retrograde cardioplegia were used for myocardial protection. Patient preoperative risk for mitral valve repair only was assessed using the Society of Thoracic Surgeons (STS) risk score.

During the study period, 153 mitral valve procedures were performed. Of these, 130 patients (age, 58.2 ± 13.6 years) underwent a mitral valve operation only and 23 patients (age, 70.6 + 7.7) underwent a mitral and tricuspid valve operation. Of the 130 patients who underwent mitral valve surgery only, 18 patients underwent repair only without reconstruction. Eight patients underwent annuloplasty only using the Carpentier-Edwards Physio II annuloplasty ring. The remaining 104 patients underwent reconstruction with annuloplasty. All patients who underwent tricuspid repair had severe TR requiring annuloplasty, which was performed using the Carpentier-Edwards Physio tricuspid annuloplasty ring. This is in concordance with the 2014 American Heart Association/American College of Cardiology valvular disease guidelines, which recommend repair for patients with severe TR who are undergoing left-sided valve surgery.

The primary outcomes of interest were operative mortality and major complications between the two groups. Secondary outcomes were differences in the aortic cross-clamp time and postoperative length of stay. Operative mortality was defined as patient deaths occurring during hospitalization and up to 30 days later, regardless of discharge status. Major complications were defined as: deep sternal wound infection, postoperative stroke, renal failure or hemodialysis, prolonged ventilation, pneumonia, and need for reoperation. Postoperative complications were defined using standard STS definitions, including prolonged ventilation (>24 hours of mechanical ventilation) and renal failure (serum creatinine level increase >2.0 or twice the last preoperative creatinine level).[8]

The Pearson chi-squared test was used to compare variables between groups. In the combined mitral and tricuspid valve group, three outcome variables (operative mortality, stroke, and myocardial infarction) had zero occurrences, and therefore could not be analyzed by the Pearson chi-squared test. Statistical significance was considered for all results with p-values of less than 0.05.

In addition, major differences existed between our two comparison groups that may skew our statistical analyses, such as: different sample sizes (n=130 vs. n=23), age (ages 58.2 vs. 70.6 years), and sex (73.9% vs. 44.6% females). To achieve balance between the two study groups, propensity score matching was used to match a control (mitral valve repair only) with the 23 subjects who also received tricuspid valve repair. The subjects were matched on age, sex, and presence/absence of hypertension, stroke, diabetes mellitus,

and atrial fibrillation. Fisher's exact tests were used for categorical data and Wilcoxon rank sum tests were used for continuous measures. Significance was assumed if the p-value was <0.05.

Results

Table 1 shows all patient characteristics and operative features separated by procedure type. All patients who underwent mitral valve procedure had either a reconstruction only, annuloplasty only, or reconstruction plus annuloplasty. All patients with combined valve procedures had a mitral valve annuloplasty only or reconstruction with annuloplasty and tricuspid valve annuloplasty only. Patients who underwent combined valve procedures were more likely to be elderly, female, and had a higher incidence of urgent operations. They also had higher incidences of hypertension, peripheral arterial disease, stroke, diabetes mellitus, dyslipidemia, atrial fibrillation, NYHA Class IV heart failure, renal failure, hemodialysis, and previous history of coronary artery bypass grafting (CABG). However, the mean ejection fraction and mean pulmonary arterial pressures were similar between the two groups.

Table 1. Patient Demographics

Variable	MV Repair (n=130)	MV Repair + TV Repair (n=23)	p-value
Preoperative			
Patient age	58.2 (13.6)	70.6 (7.7)	<0.001
Female sex	44.60%	73.90%	0.01
Hypertension	58.50%	91.30%	0.003
Peripheral arterial disease	0.80%	4.30%	0.164
Stroke	3.10%	13.00%	0.035
Diabetes mellitus	7.70%	21.70%	0.037
Dyslipidemia	52.30%	60.90%	0.448
Heart failure	34.60%	34.80%	0.988
Atrial fibrillation	26.90%	60.90%	0.001
NYHA Class			
I	16.90%	13.00%	
II	29.20%	30.40%	0.895
III	10.80%	13.00%	
IV	1.50%	4.30%	
Infective endocarditis	6.90%	4.30%	0.645
Previous CABG	5.40%	8.70%	0.534
Previous valve procedure	5.40%	0.00%	0.255
Ejection fraction	0.54 (0.13)	0.49 (0.13)	0.101
Mean PAP, mmHg	35.1 (15.7)	39.2 (14.8)	0.394
STS Predicted Risk of Mortality	0.009 (0.007)	---	
Operative			
MV Repair	100%	100%	
Annuloplasty only	10%	52.2%	
Reconstruction with annuloplasty	87.7%	47.8%	
Reconstruction only	2.3%	0%	
TV repair (Annuloplasty only)	---	100%	
Status			
Elective	96.20%	91.30%	
Urgent	3.80%	8.70%	0.305
Emergency	0.00%	0.00%	
Aortic cross-clamp time, min.	119.7 (36.6)	115.0 (35.3)	0.566

The postoperative outcomes and complications are summarized in Table 2. Overall, the operative mortality was higher in the mitral valve only group; there were no operative mortalities in the combined mitral plus tricuspid valve group. Although more patients in the latter group had major complications, the difference was not statistically significant. Patients with combined valve procedures had a statistically significant increase in prolonged ventilation, and longer lengths of hospital stay. Of note, the total aortic cross-clamp time was statistically insignificant. The p-value could not be calculated for three variables (operative mortality, stroke, and myocardial infarction), since none of these occurred in the mitral valve plus tricuspid valve group. There were also no differences in outcomes after propensity matching in any variables.

Table 3 represents the demographics of our two groups after propensity matching, along with the p-value. The only statistical difference between our two groups after matching is ejection fraction (p=0.039). Table 4 represents variables that were propensity matched, along with the p-value. All variables were not statistically significant between our two groups after propensity matching.

Table 2. Outcomes

Outcomes	MV Repair (n=130)	MV Repair+ TV Repair (n=23)	p-value	MV Repair (n=23), matched	p-value
Operative Mortality	1.5%	0%	>0.99	4%	>0.99
Major Complications	16.2%	30%	0.14	26%	>0.99
Stroke	1.5%	0%	>0.99	0%	>0.99
MI	0.0%	0%	>0.99	0%	>0.99
Pneumonia	1.5%	4%	0.39	9%	>0.99
Prolonged ventilation	11.5%	30%	0.026	22%	0.74
Renal failure	0.8%	4%	0.28	4%	>0.99
Postop LOS, days	6.4 (3.9)	9.7 (7.1)	0.0006	7.4 (4.6)	0.087

Table 3. Propensity Match Demographics

Preoperative	MV Repair (n=130)	MV Repair + TV Repair (n=23)	p-value
Patient age	71.3 (6.7)	70.6 (7.7)	0.73
Female sex	17 (65%)	15 (74%)	0.75
Hypertension	22 (96%)	21 (91%)	>0.99
Peripheral arterial disease	0%	1 (4%)	>0.99
Stroke	0%	0%	>0.99
Diabetes mellitus	4 (17%)	5 (22%)	>0.99
Dyslipidemia	16 (70%)	14 (61%)	0.76
Heart failure	8 (35%)	8 (35%)	>0.99
Atrial fibrillation	13 (57%)	14 (61%)	>0.99
NYHA Class			
I	2 (9%)	3 (13%)	>0.99
II	8 (35%)	7 (30%)	
III	3 (13%)	3 (13%)	
IV	1 (4%)	1 (4%)	
Infective endocarditis	3 (13%)	1 (4%)	
Previous CABG	2 (9%)	0%	0.49
Previous valve procedure	0%	0%	>0.99
Ejection fraction	56.0 (12.0)	49.3 (12.8)	0.039
Mean PAP, mmHg	34.7 (11.7)	39.2 (14.8)	0.50
Operative			
MV Repair	100%	100%	
Annuloplasty only	1 (4%)	12 (52%)	
Reconstruction with annuloplasty	19 (83%)	11 (48%)	
Reconstruction only	3 (13%)		
Status			
Elective	23 (100%)	21 (91%)	0.49
Urgent	0%	2 (9%)	
Emergency	0%	0%	
Aortic cross-clamp time, min.	114.2 (34.2)	115.0 (35.3)	0.91

Table 4. Propensity Match Variables

Variable	MV Repair (n=23)	MV Repair + TV Repair (n=23)	p-value
Patient age	71.3 (6.7)	70.6 (7.7)	0.73
Female sex	65%	74%	0.75
Hypertension	96%	91%	>0.99
AFIB	61%	57%	>0.99
Stroke	9%	13%	>0.99
Diabetes mellitus	17%	22%	>0.99

Discussion

This study examines the postoperative mortality and morbidity of concomitant mitral and tricuspid valve procedures compared to mitral valve procedures alone. Those who underwent combined valve procedures were more likely to be elderly, female, and had a higher incidence of co-morbidities. Other studies have reported similar trends.[9] Concomitant valve procedures did not increase the rate of operative mortality or major complications, comparable to other studies.[10,11] The only statistically significant increases observed were in prolonged ventilation and postoperative length of stay. These results are in stark contrast to those reported by LaPar et al, who reported that simultaneous mitral and tricuspid valve operations are associated with increased morbidity and mortality, even after risk adjustment.[7] In addition, risk factors such as advanced age and urgency of operation strongly influence the risk of morbidity and death. Although our patients who underwent combined mitral and tricuspid valve procedures were older and had a higher incidence of urgent operations, morbidity and deaths did not increase, and no operative mortalities occurred. One possible explanation for these differences is the decreased aortic cross-clamp time among our patients. LaPar et al. reported that their mitral valve and tricuspid valve groups had a mean aortic cross-clamp time of 125.0 minutes in their mitral and tricuspid valve procedures, compared to 103.0 min for the mitral valve-only group. At our institution, mitral valves were repaired with the clamp on, while tricuspid valves were repaired with the clamp off. Increased aortic cross-clamp time might have occurred from performing tricuspid valve repairs with the clamp on. In addition, in the report from LaPar et al., aortic cross-clamp time was directly proportional to both operative mortality and major complications. By performing the tricuspid repair with the clamp off and decreasing the aortic cross-clamp time, ischemia to the myocardium can be minimized, resulting in decreased complications. However, since we had no operative mortalities in our combined group, we could not perform any statistical analyses to address this concept. Future studies with larger sample sizes are needed to conclusively answer this question.

Our patients who had both mitral and tricuspid valve procedures had a statistically significant increase in prolonged ventilation (30.4% vs. 11.5%, p = 0.026) and postoperative length of stay (9.7 days vs. 6.4 days, p = 0.0006). This was expected, as they were older and had more comorbidities at time of operation. Interestingly, rates of other postoperative complications, such as pneumonia and new-onset renal failure, were similar between the two groups. In addition, when we compared our groups using propensity score analysis, there were no differences between them for any outcomes. Given these results, it is reasonable to consider that patients with tricuspid regurgitation secondary to mitral valve disease could undergo concomitant mitral and tricuspid valve procedures. Historically, valvular reoperations have been associated with drastically increased postoperative mortality rates, and medical management of TR was limited and ineffective.[12,13] Although better techniques have resulted over time, risks are still higher than in patients with single valve operations. Furthermore, many patients have mild to moderate TR at time of presentation that can be adequately repaired using ring annuloplasty. As mentioned previously, TR, if not repaired during a mitral valve operation, can steadily progress into more severe regurgitation. Although no studies to date have shown an increase in long-term survival in these situations[4], addressing the tricuspid valve during the initial operation can decrease symptoms of congestive heart failure and improve patients' quality of life.[5] Therefore, we propose that a concomitant valve operation will result in the most benefit in terms of patient safety and quality of life.

Limitations exist in our current study that will require further investigations in the future. The biggest limitation is the small sample size — we examined only operations performed by one surgeon at one medical center. In addition,

more complicated statistical methods could not be used due to a limited sample size. For example, since several variables had zero occurrences, Pearson chi-squared tests could not be performed. Therefore, we cannot determine whether or not decreased operative mortality between our two groups was statistically significant. Furthermore, since we only studied patients treated by a single surgeon, we could not assess differences in surgeon experience and technique. Our study only examined 30-day postoperative mortality and morbidity; long-term follow-up to monitor prolonged survival and improvement in quality of life was not performed. Third, this study looks at valve repairs; due to limited sample size, valve replacements were omitted in the data set. Valve replacements have been associated with longer operative times and increased rates of mortality and morbidity, and thus further studies are warranted to examine the relationship between valve replacement and valve repair. Last, although we speculated that decreased aortic cross-clamp time decreases morbidity and mortality, our study did not find a statistical significance between our groups, most likely due to our small sample size. Thus, an adequately powered study is warranted in the future to test this hypothesis.

Conclusion

In this single-institution study of patients treated by one surgeon, concomitant mitral and tricuspid valve operation did not increase postoperative morbidity and mortality rates in selected patients. More importantly, there was no correlation between advanced age and urgency of operation to adverse outcomes. The only significant increases in postoperative complications were observed in prolonged ventilation time and increased length of stay. Furthermore, when our two groups were matched using propensity score analysis, no statistical significances in any variables were observed. Thus, it would be reasonable to recommend concomitant mitral and tricuspid valve operation for patients with mild or moderate tricuspid regurgitation secondary to mitral valve pathology who are undergoing left-sided valve surgery. However, further research studies will be required to determine the long-term benefits and adverse outcomes for these patients.

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Original Science

Factors that Predict Bullying Experiences among Adolescent Psychiatric Inpatients

Sebastian G. Kaplan, Ph.D.[1], Brittany Simpson, M.A, LMFT, M.B.A.[2], Victoria Wimalarathna, M.Ed.[3], Matthew Hough, DO[1], Elizabeth Mayfield Arnold, Ph.D., LCSW[1]

Abstract

Bullying in school is a significant public health problem. Our study examined the prevalence of school bullying (bully, victim, or both) and the factors that predict these bullying experiences among adolescent psychiatric inpatients. Participants (N=91) were 12–17 years old, included nearly equal numbers of males/females (49.45%/50.55%), were 59.34% white, and mainly high school students (67.03%). We administered the School Climate Bullying Survey (Cornell, 2014) and reviewed participants' medical records. At the bivariate level, we found associations between bully victims and past childhood abuse and being in middle school, those who bullied others and previous psychiatric admissions, and being both a bully and victim with past sexual abuse and being in middle school. At the multivariate level, bullying others was associated with a history of any type of childhood abuse and previous psychiatric admissions. Being a bully and victim was associated with a history of sexual abuse and previous psychiatric admissions. Being a victim only was not associated with any of the variables examined. Results suggest that middle school is a time of heightened risk for youth who are bullied. Youth who are bullied and those who are both perpetrators and victims should be carefully assessed for histories of abuse.

[1] Wake Forest School of Medicine, Department of Psychiatry and Behavioral Medicine, Winston-Salem, NC

[2] Magnolia Center for Counseling and Eating Recovery, Winston-Salem, NNC

[3] Seattle Public Schools

Address Correspondence To:
Sebastian G. Kaplan, Ph.D.
Wake Forest School of Medicine
Department of Psychiatry and Behavioral Medicine
791 Jonestown Rd.
Winston-Salem, NC 27103
sgkaplan@wakehealth.edu
Phone: 336-716-3381
Fax: 336-716-9642

Introduction

School bullying is widely recognized as a significant problem for children and adolescents that can have serious mental health consequences. According to the National Center for Education Statistics,[1] nearly 30% of school age youth reported being bullied at some point during the 2010–2011 school year. A recent U.S. Government Accountability Office Report to Congressional Requestors[2] estimates that 20 to 25% of youth have been bullied and recommends that the issue of civil rights protections for victims be examined. A recent study of high school students documented that 19% of youth reported being victims of bullying, and 16% reported perpetrating bullying at some point in the past month.[3] Recently, incidents of adolescent suicide with links to bullying have garnered national attention.[4] Anecdotal evidence suggests that emergency departments and inpatient psychiatric units have seen an increase in recent years of children who have experienced bullying.[5] Thus, serious concerns exist about the emotional well-being of youth who have been involved in bullying.

Involvement in bullying, either as a victim, perpetrator, or both, is associated with a variety of mental health problems.[6-8] High rates of depression and suicidality are documented among both victims and bullies compared to those uninvolved

in these behaviors.[9,10] A recent meta-analysis suggests that the existing research confirms the associations among peer victimization, bullying, and suicide with cyberbullying have more deleterious effects on suicidal ideation than traditional forms of bullying.[11] Heikkila and colleagues[12] found that in a school-based sample of 2,070 Finnish adolescents, being a bully victim and a perpetrator at age 15 predicted suicidal ideation at a two-year follow-up relative to uninvolved peers. Others reported that involvement in bullying among children between the ages of 4–10 was associated with increased risk of suicide by age 11.[8] In another school-based sample of 1,118 pre-teens, children classified as depressed or anxious were more likely to experience bullying for the first time at six-month follow-up.[13] Being a victim of bullying, as opposed to a perpetrator, may be even more strongly associated with suicidal thoughts among adolescents.[14]

Existing research suggests that differences may exist in terms of who experiences or participates in bullying. Lovegrove and Cornell[3] found that boys are more likely than girls to bully others by physical, verbal, and social means except cyberbullying. Others have noted gender differences in the rates of suicidality among youth involved in bullying, with girls being at particularly higher risk.[15] In the same Finnish sample, boys and girls with externalizing disorders were more likely to be bullies or bully-victims, whereas boys with internalizing disorders and chronic somatic diseases were more likely to be bully victims.[16] Youth with disabilities of any type are also at higher risk of being bullied than youth without disabilities.[17]

Existing research on the backgrounds of youth who are engaged in bullying behaviors suggests that past exposure to maltreatment may play a role in understanding these behaviors. Shields and Cicchetti[18] found that children who have been maltreated, especially those who have experienced physical or sexual abuse, are more likely to bully others. In addition, those who were maltreated were at higher risk for being bullied by others, whether male or female. Bjorkgvist, Oseterman and Berg[19] reported that a history of being hit by an adult was more common among school bullying victims compared to those who had not experienced bullying. Other research indicates that there may be gender differences in these behaviors. In a national survey in England, Meltzer and colleagues[20] found that female bully victims were more likely to report histories of childhood sexual abuse than those without such histories. Males who were bullied were more likely to have been severely beaten during childhood.

Most existing studies on bullying have consisted of samples of students in schools[3,9,14,21,22] and/or of youth in other countries.[8,15,22,23] Little research from the United States has appeared regarding bullying behaviors among youths who are experiencing acute psychiatric distress, such as those admitted to psychiatric inpatient units. Two studies have examined bullying among inpatients: one among Finnish adolescents[15] and one among hospitalized youth in the U.S.[24] In the latter study of suicidal adolescents, youth who were bullies had higher rates of suicidal ideation compared to non-bullies while hospitalized. However, these differences were not seen after six weeks, and bullying behavior increased suicide risk when the behavior occurred. We know of no other U.S. studies that have examined both bullying and bully victimization among adolescent psychiatric inpatients.

Our study attempted to answer the following questions: 1) What is the prevalence of school bullying (bully, bully victim, or both) among adolescents on an inpatient psychiatric unit? and 2) What factors predict school bullying (bully, bully victim, or both) among adolescents on an inpatient psychiatric unit?

Methods

Description of Participants

Participants were 91 adolescents ages 12–17 (M=14.76, SD=1.52) who were patients on an inpatient adolescent psychiatric unit. The sample consisted of nearly equal numbers of males (n=45; 49.45%) and females (n=46; 50.55%). Slightly more than half of participants were white (n= 54, 59.34%), with the remainder identifying as multi-racial (n=12, 13.19%) or black (n=10, 10.99%). The rest of the sample were of other or unknown race (n= 15, 16.48%). Most participants were in high school (n=61, 67.03%), and about one-third were in middle school (n=27, 29.67%). One youth was in elementary school, and the grade in school for two youth was unknown. No data on socio-economic status of participants were collected. A description of the psychiatric

experiences and background of participants is provided in Table 1.

Eligible patients were those on the unit where the study was conducted, enrolled in a traditional public or private school (not including home-schooling or online educational programs), and English-speaking with an English-speaking parent. Youth were excluded if they: 1) were actively psychotic or had a cognitive impairment; 2) had an IQ of 70 or lower based on estimates of cognitive functioning or prior test results; 3) were in the custody of the Department of Social Services; or 4) were under severe psychiatric distress (such as debilitating depression) based on the clinical judgment of the study team (which included the Medical Director of the unit).

Table 1. Description of Participants (N=91)

Variable	N or Mean	% or SD
Primary Axis I Diagnosis at Discharge		
Depression	51	56.04%
Bipolar Disorder/Mood Disorder	17	18.68%
Anxiety Disorder	8	8.79%
Disruptive Behavior Disorder	7	7.69%
Substance Abuse Disorder	3	3.30%
Psychotic Disorder	4	4.40%
Other	1	1.10%
Suicidal at time of admission	77	84.62%
Beck Depression Inventory Mean Score	23.26	SD=12.52
History of abuse	35	38.46%
History of sexual abuse	18	19.78%
History of physical abuse	78	85.71%
History of emotional abuse	12	13.19%
Number of previous psychiatric admissions		
None	64	70.33%
One	14	15.38%
Two	9	9.89%
Three	2	2.20%
Four	1	1.10%
Number of previous suicide attempts		
One	18	19.78%
Two	5	54.95%
Three	2	2.20%
Six	1	1.10%
Mean number of previous suicide attempts	1.54	SD=1.10

Note: All data taken from medical record.

Informed Consent

Parents or legal guardians of eligible participants were approached during the time of the youth's admission or during visits to the unit. A study staff member approached the parent or guardian and provided information about the study. Those parents/guardians who were interested in having their child participate signed the consent form. Youth were then approached about possible participation and were given the option of signing an assent form if they wanted to participate. Youth were told that participation would not impact their treatment, and interviews were conducted on the unit during times when youth would not miss important therapeutic activities.

Measures

Bullying experiences

Self-reported experiences of bullying were assessed using the School Climate Bullying Survey (SCBS),[25] a self-reported measure of adolescents' experiences of bullying and victimization, and of school climate. The SCBS has demonstrated acceptable correspondence with peer and teacher nominations of bullying,[26,27] associations with poor psychosocial outcomes,[26] and concurrent findings with the well-established Olweus Bullying Victimization Questionnaire.[25,28] To assess whether the participant had engaged in bullying behavior, had been a victim of bullying behavior, or had experiences with both behaviors, we used two items from the SCBS. The definition used as reference for the question was as follows: "Bullying is defined as the use of one's strength or popularity to injure, threaten, or embarrass another person on purpose. Bullying can be physical, verbal, social, sexual, or on the internet or cell phone. It is *not bullying* when two students who are about the same in strength or power have a fight or argument."[25] Participants were asked to rate how often these statements applied to them: 1) By this definition, I have been bullied at school in the past month; and 2) By this definition, I have bullied others at school in the past month. Response categories were as follows: never, once or twice, about once

per week or several times per week. Those who indicated any response other than "never" were coded as having the specific bullying experience.

Medical Record Review

To collect clinical and background data on participants, we reviewed the participant's medical record and extracted data on the current hospitalization. This review was done after the participant's discharge to make sure that the record was complete. Data were collected on clinical variables including diagnoses, suicidality, past psychiatric history, and abuse history (including physical, sexual, and emotional abuse).

Procedure

After obtaining written consent and assent, a member of the study team met with the participant to complete the study interview. The interview was conducted on the inpatient psychiatric unit during the time of hospitalization. Participants could stop the study interview at any time if they found the interview was causing them distress. During the interview, the study team member took notes, and the interview was also audio-recorded.

Results

Data Analysis

Based on self-report data from the SCBS, we first examined the frequency of bullying experiences. Youth were classified as a bully, victim or both (bully and victim). Next, to assess the relationships between background variables and types of childhood abuse with bullying experiences, we used Fisher's Exact Test. Any p-value < 0.05 was considered to be significant at the bivariate level. Using the approach suggested by Hosmer and Lemeshow,[29] any variables with a p-value of 0.25 or less were then entered into a multivariate model to see which factors might be jointly significantly associated with the outcome measures. In a stepwise fashion, non-significant factors, starting with the largest p-value, were removed from the multivariate model until the only remaining variables had p-values <0.05.

Rates of Bullying Experiences

Of the 91 participants, 52 youth (57.14%) reported that they had been bullied at school in the past month. About one-third of youth (n=30, 32.97%) reported that they had bullied others in the past month. Twenty-five youth (27.47%) reported that they had been bullied and had bullied others in the past month. For the purpose of the analyses, youth were not assigned to mutually exclusive groups; thus, some youth were included in multiple analyses.

Bivariate Analyses

We first examined relationships between the independent variables and each of the bullying experiences: being a victim, a bully, or both a victim and bully in the past month. There was a statistically significant relationship ($p<0.05$) between participants having been a victim of bullying and a history of any type of child hood abuse (OR=2.69) and school level (OR=2.71) (Table 2). For participants who reported bullying others at school, we found a relationship with this behavior and previous psychiatric admissions (OR=0.28, $p<0.05$). Having been both a bully and a victim of bullying at school was associated with a history of sexual abuse (OR=3.56, $p<0.05$) and school level (OR=2.88, $p<0.05$).

Multivariate Analyses

Multivariate analyses were constructed using our outcome measures (types of bullying experiences) and the independent variables with $p < 0.25$ at the bivariate level. Due to problems with multi-collinearity, the collective variable, "history of any abuse," was not included in the model concurrently with any of the other individual "history of abuse" measures. In our first model, as seen in Table 3, for "Bullying Victim," the best model did not have two significant predictors. When the two measures of school level and history of any abuse were jointly in the model, both had a p-value > 0.05. This outcome does not have a multivariable model form.

For our "Bully" measure, we used the collective variable, "history of any abuse" (OR=2.80) and previous psychiatric admissions (OR=4.60) as our final reduced model, with both measures having a p-value <0.05. School level was removed from the multivariate model after not being jointly significantly associated with the outcome when abuse and admissions were in the model. In a separately fit model (results not presented in Table 3), history of sexual abuse (OR= 6.1, p=0.011) and previous psychiatric admissions

Table 2. Bivariate Analyses: Bullying Experiences in Past Month

	Bullying Victim		Bully		Both	
Variable	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
School level	2.71*	[1.04, 7.06]	1.94	[0.76, 4.94]	2.88*	[1.09, 7.62]
History of any abuse	2.69*	[1.09, 6.61]	2.00	[0.82, 4.89]	1.73	[0.68, 4.39]
History of sexual abuse	3.22+	[0.97, 10.73]	2.43	[0.85, 6.97]	3.56*	[1.21, 10.46]
History of physical abuse	0.60	[0.18, 1.94]	0.87	[0.25, 3.10]	0.43	[0.09, 2.12]
History of emotional abuse	2.51	[0.63, 9.98]	1.00	[0.28, 3.63]	0.86	[0.21, 3.49]
Gender	1.14	[0.50, 2.61]	0.77	[0.32, 1.84]	1.08	[0.43, 2.72]
Previous psych admission	1.24	[0.49, 3.16]	0.28*	[0.09, 0.90]	0.37	[0.11, 1.22]
Note. OR = odds ratio; CI = confidence interval +p < 0.10. *p < 0.05.						

Table 3. Multivariate Analyses: Bullying Experiences in Past Month

	Bullying Victim		Bully		Both	
Variable	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
School level	2.40+	[0.89, 6.40]	n/a	n/a	n/a	n/a
History of any abuse	2.50+	[0.99, 6.30]	2.80*	[1.02, 7.50]	n/a	n/a
History of sexual abuse	n/a	n/a	n/a	n/a	7.90**	[2.00, 32.30]
Previous psych admission	n/a	n/a	4.60*	[1.30, 16.20]	6.00*	[1.30, 27.50]
Note. OR = odds ratio; CI = confidence interval +p < 0.10. *p < 0.05. **p < 0.01.						

(OR = 7.2, p=0.009) were significantly associated with the "Bullying" outcome measure. For the "Bully and Victim" measure, history of sexual abuse (OR=7.90, p<0.01) and previous psychiatric admissions (OR=6.00, p<0.05) were significantly associated with the outcome measure.

Discussion

This study is one of the first to describe the school bullying experiences of adolescents in an inpatient psychiatric facility in the United States. About half of participants reported being bullied in the past month, and about one-third indicated that they had bullied others at school. Just over a quarter reported both bully victimization and perpetration at school in the past month. Although direct comparisons with other reports should be made with caution, these rates are notably larger than other prevalence estimates from general school populations. For instance, results from the 2011 Youth Risk Behavior Survey found that approximately 20% of high school students had been bullied on school property in the 12 months before completing the survey.[30] Not surprisingly, school bullying appears to be a common experience for adolescents struggling with serious psychiatric difficulties. Although causal links between school bullying and the precipitating events before their psychiatric admission were not explored in this study, such links would be useful in better understanding the experiences of adolescents with acute psychiatric distress and thus better informing interventions in schools and inpatient psychiatric settings.

In our analyses, several background variables were associated with adolescents' school bullying experiences. A history of child abuse of any kind was related to bully victimization, with history of sexual abuse in particular significantly associated with bullying victimization and having experienced both victimization and perpetration. These findings are consistent with past research that discovered relationships between bully victimization and episodes of physical, emotional, and sexual maltreatment,[31] as well as links between chronic maltreatment and aggression towards peers.[32]

It is possible that traumatic events, such as sexual abuse, may be more common in youth involved in bullying. In our study, one-fifth of participants had a known history of sexual abuse. While the rate in our study may be related to the setting in which we recruited participants, others have documented comparable rates. Among bullied youth in a national British survey, 23.0% of bullied female youth and 10.10% of bullied male youth reported being touched as a child in a sexual way without their consent. By contrast, in a national U.S. survey of exposure to violence among children, Finkelhor and colleagues[33] documented that 2% of youth 17 years of age or younger reported sexual assault or abuse in the past year.

Researchers have proposed a number of possible explanations for the connection between history of abuse and bullying, such as emotional dysregulation[34] or a submissive interpersonal style.[18] In fact, others have suggested that youth who have experienced abuse may somehow appear more vulnerable to bullies at school,[20] even suggesting that a "victim personality" may contribute to this dynamic.[19] Thus, accessing appropriate psychiatric care appears to be important for youth with bullying experiences, especially those with histories of abuse. For example, existing research suggests that emotional dysregulation mediates the role between being maltreated and whether one bullies others or is victimized.[18] Difficulties with emotional regulation can be treated using existing methods of psychotherapy and may prevent bullying behaviors.

We also found that adolescents who bullied others, and those who were both bullied and who bullied others, were more likely to have had past psychiatric admissions, suggesting they had more chronic psychiatric distress. Again, whether school bullying was a cause of this chronic distress was beyond the scope of this study. However, this finding is certainly consistent with past research establishing a strong relationship between bullying and mental illness.[6-8]

Nearly all participants in this study were in middle or high school. We found a greater association with bully victimization and being both a bully and victim with attending middle school. Middle school is considered a particularly challenging developmental period that affects students' academic, social, and emotional functioning.[35,36] Our findings are consistent with research demonstrating that middle school students are at heightened risk of being bullied.[37,38]

Our findings also suggest that when youth are hospitalized, not only is it important to identify who has been a bully or a victim of bullying, but more intervention is needed during the hospitalization. At a minimum, a thorough evaluation that examines bullying experiences, as well as past victimization, must be conducted as part of the intake process. Asking about bullying acknowledges the existence of the problem and can be the first step in the process of preventing future bullying. The focus should be on letting victims know that they did not cause the bullying and should not have to resolve it on their own.[39] Intervention must also be provided to those who bully others. For example, the use of stress management skills can lower the incidence of bullying behaviors,[39] and such programs can easily be added to inpatient treatment protocols.

Once youth are discharged, schools must implement programming to address the problem of bullying. Many schools have programs to educate students about bullying others or being bullied themselves.[40] In 2011, the American Academy of Child and Adolescent Psychiatry advocated for schools to have bullying programs that promote mutual respect, sensitivity, tolerance to diversity, and disapproval of bullying. As noted by others, schools need to use evidence-based methods of prevention and intervention to stop bullying behaviors.[41] Otherwise, the long-term consequences of adolescent bullying can be a source of impairment, since being bullied in childhood can continue to cause mental health issues 40 years later.[42]

This study has several important limitations. First, we collected data used for our analyses from the participants' medical record, and did not verify its accuracy. In addition, we used self-reported data on bullying behaviors, and did not confirm these reports by parent interviews or other methods of verification. These interviews only assessed bullying in the past month, which may exclude youth with

less recent bullying experiences and may include youth who had only one bullying experience. Most importantly, this was a cross-sectional study; therefore, we cannot infer causality in interpreting the relationships between variables.

Although perspectives on bullying appear to have largely shifted from one of a "rite of passage" to a recognized public health challenge worthy of considerable attention, much work remains to be done. Scott and colleagues[43] stated that "bullying in school is arguably the most important aetiological factor for mental illness that could be systematically targeted at a population level." Our findings suggest that interventions geared towards adolescents who have experienced acute psychiatric distress should include an assessment of the role bullying played in the crisis itself and/or in the adolescent's history.

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Original Science

Hospital Utilization and Alcohol Use in Older Adults: A Post-hoc Analysis of GEMS Data

Hillary M. Fitzgerald, M.D.[1], Jeff D. Williamson, M.D., MHS[2], James F. Lovato, M.S.[3], Kathryn E. Callahan, M.D., M.S.[2]

Abstract

Background: Hospital utilization and readmission rates are under scrutiny nationally. Older adults, as high utilizers and more vulnerable patients, are important to include in studies evaluating inpatient care. Alcohol consumption in this high-risk group is an understudied social behavior that may provide insight into acute hospitalization rates.[1]

To explore the relationship between alcohol use and acute care utilization patterns in older adults, we used data from 2,977 enrollees in the Ginkgo Evaluation of Memory Study (GEMS). Participants were community-dwelling adults aged 75 or older, recruited from four academic medical centers.

Methods: We conducted a post-hoc analysis of hospitalization events to determine if self-reported alcohol consumption was associated with incident hospitalization or 30-day readmission.

Results: Moderate drinking (8–14 drinks per week), compared to abstention, had a lower risk of initial hospitalization (unadjusted hazard rate [HR] 0.79; 95% confidence interval [CI] 0.66 to 0.93; adjusted HR 0.80; 95% CI 0.67 to 0.96). Level of consumption was not significantly associated with 30-day hospital readmissions (adjusted odds ratios [ORs] for light drinking: 0.89; 95% CI 0.64 to 1.24; moderate drinking: OR 0.88; 95% CI 0.50 to 1.56; and heavy drinking: OR 0.71; 95% CI=0.40 to 1.27).

Conclusion: Moderate drinking was associated with reduced rate of initial hospitalization in older adults, but not with 30-day readmissions.

[1] Department of Family Medicine, Cone Health, Greensboro, NC

[2] Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC

[3] Department of Biostatistical Sciences, Wake Forest Health Sciences, Winston-Salem, NC

Address Correspondence To:
Hillary Fitzgerald, M.D.
Cone Health Family Medicine Residency
1125 N. Church St.
Greensboro, NC 27401
hillary.fitzgerald@conehealth.com
phone: 901-378-2408

Introduction

With high comorbidity and medical complexity, older adults are disproportionately the largest consumers of acute hospital care.[2] Hospital stays have serious health consequences for older adults, whose lower physiologic reserves put them at greater risk for adverse events compared to younger patients. One in five Medicare patients is readmitted within 30 days of discharge, so efforts to reduce preventable admissions have targeted older adults.[3] Although over 25 different models have sought to capture predictive measures that place individuals at higher risk for repeat hospitalizations[1] their utility in preventing admissions has proven limited.[4-6] Therefore, researchers have begun to explore broader factors that could be intervened upon, such as access to care and substance abuse.[1]

Alcohol use is understudied in older adults,[7,8] and its contribution to acute hospital utilization and 30-day hospital readmission in this age group is not well understood.[9] Predictive models for readmission events only include data on drinking if alcohol abuse was pre-identified as a comorbid condition within a patient's previous health record.[10,11] To our knowledge, self-reported alcohol use has not been studied in elderly patients in relation to hospital utilization and readmissions.

Both positive and negative clinical effects of alcohol consumption have been reported in research studies. The protective effects of moderate alcohol use against cardiovascular disease are well described in middle-aged adults.[12] Considering that cardiovascular diseases, (including congestive heart failure, myocardial infarction, and stroke) comprise the highest risk diagnoses for admission and readmission, moderate levels of drinking may protect against hospitalization.[3] In addition, low to moderate drinking may have neuroprotective effects against dementia and depression.[13] However, elderly Medicare recipients with substance use disorders experience higher rates of hospital readmission, suggesting that level of alcohol use could help identify at-risk older adults.[14] Rates of alcohol-related hospitalizations in the elderly are clinically significant — with admission rates similar to myocardial infarction — and financially significant: $233 million was spent on Medicare patients in 1989 for admissions where the primary diagnosis was alcohol-related.[15]

The goal of this study was to determine whether self-reported alcohol habits, an easily collectable measure of social history, could help identify a subset of elderly people vulnerable to high hospital utilization and readmissions. We used data from 2,977 enrollees in the Ginkgo Evaluation of Memory Study (GEMS). We predicted that GEMS participants would have a higher risk for index hospitalization (first hospitalization after enrollment) and higher odds of 30-day hospital readmissions in a "dose-response" fashion, according to weekly consumption of alcohol. Our analysis of the GEMS cohort is a starting point for considering how alcohol use in the lives of older adults could be a modifiable factor related to hospital utilization.

Methods

Setting

We performed a post-hoc analysis of prospectively-collected data from GEMS, a randomized, double-blind, placebo-controlled trial to study whether *Ginkgo biloba* might delay or prevent incident dementia.[16] The originating study enrolled 3069 community-dwelling adults 75 years and older across four academic medical centers (University of Pittsburgh, Wake Forest University, Johns Hopkins University, and University of California, Davis). It was completed in 2008 with a median follow-up of 6.1 years. Participants were evaluated for symptoms of dementia and cardiovascular disease at six-month follow-up intervals. GEMS reported no effects of *G. biloba* on the development of dementia. To assess adverse events, the protocol required documentation of all hospitalizations, meaning hospital admission data were available and complete for this study.

Participants

Participants were excluded if they had dementia or depression at baseline, or had been diagnosed with or treated for cancer within the past 5 years. Eligible participants spoke English as their primary language and could identify a proxy to report on their cognitive and functional performance.

For the index hospitalization analysis, we excluded GEMS participants without baseline alcohol consumption data and those with incomplete data on our selected covariates, which were age, sex, race, years of education, study site, income, smoking status, total number of prescription medications, and *G. biloba* treatment group. After applying these criteria, 2,977 participants were eligible for this study. For the readmission analysis, we included participants who experienced an initial hospitalization event (n=1,851) and survived 30 days post-discharge (n=1,793).

Alcohol Consumption

Level of self-reported weekly alcohol consumption was the independent variable. Each participant's consumption level was established at baseline from a health habits questionnaire that asked specifically whether the participant ever drinks alcohol (beer, wine, or liquor), how often (rarely/never, daily, weekly, monthly, or yearly), and how many drink equivalents

(12 ounces of beer, 6 ounces of wine, or 1 shot of liquor) are consumed per occasion. Alcohol use was later categorized as weekly drinking levels: none (0); light (1–7); moderate (8–14); or heavy (>14 drinks). Given the lack of consensus over the definition of moderate alcohol use, these ranges were chosen using a definition of moderate drinking (1–2 drinks/day) as the reference point.

Outcomes: Index Hospitalization and Readmission

We first explored hazard rates of index hospitalization by level of alcohol consumption, comparing drinkers of each level to those who abstained. Next, for those older adults who experienced an index hospitalization, we examined the relationship between baseline alcohol consumption and the subsequent odds of 30-day hospital readmission, defined as a hospital admission occurring within 30 days of discharge from the index hospitalization.

Covariates

Based on the literature, we considered the effects of various factors that may contribute to acute hospital utilization and readmission, including demographics (age, sex, race, education), baseline comorbidities (hypertension, diabetes, cancer, congestive heart failure, myocardial infarction, angina, kidney disease, liver disease, stroke, emphysema), number of prescription medications (a measure of multimorbidity), and clinic site (to address geographic variation in hospitalization).[1,17] Smoking status was included as a potential confounder with alcohol use. We tested for heterogeneity of the relationship between alcohol consumption and hospitalization/readmission (unreported analyses) among randomized groups, combined the data, and included randomization group status as a covariate.

Analysis

Baseline demographic data was compared between groups categorized by alcohol consumption level to characterize our study population and determine any obvious differences. We also separated out our covariates by drinking level for initial interpretation. Statistical tests were then performed.

Analyses were conducted using SAS version 9.2. Participants who died before an initial hospitalization event were included in the study population; analyses were conducted first censoring those who died prior to index hospitalization at the time of death. Secondly, we combined mortality with index hospitalization, yielding information regarding hospitalization-free survival. Results did not differ with the composite outcome and are thus presented with deaths censored. Participants who died within the period of initial hospitalization (n=49) or within 30 days of discharge (n=9) were excluded from the 30-day readmission analysis, for a population of 1,793 eligible for 30-day readmission. Of these participants, 210 were readmitted within 30 days. A log-rank test assessed the univariate association of level of alcohol consumption with initial hospitalization. Cox proportional hazards regression was used to determine the relationship between alcohol consumption and initial hospitalization, adjusted for the covariates.

A Chi-square test was used to evaluate univariate associations of alcohol consumption with 30-day readmission. Logistic regression was used to assess the relationship between alcohol consumption and 30-day readmission, again adjusted for the same covariates.

Results

Demographics

Table 1 shows baseline demographic information for our study population, stratified by alcohol consumption status. The average GEMS participant was about 78 years old and white with over 13 years of education and over $40,000 of annual income. In general, GEMS participants took more prescription medications than the average older adult, according to a recent survey by the CDC used for comparison.[18] Weekly alcohol consumption in this population was as follows: none (42.6%); light (38.2%); moderate (9.5%); and heavy (9.7%). Those who consumed more alcohol were more likely to be male, white, have more years of education, take fewer medications, and have a history of smoking.

Index hospitalization

Moderate drinkers had a lower rate of hospitalization than abstainers (p=0.03, Figure 1). The hazard rate of index hospitalization for moderate drinkers was 21% less than that for non-drinkers (hazard ratio [HR] 0.79; 95% confidence interval [CI] 0.66 to 0.93). When adjusted for covariates, this

Table 1: Demographics of GEMS* Participants by Level of Alcohol Consumption

	Abstainers	Light (1-7)	Moderate(8-14)	Heavy (>14)
	N=1264	N=1141	N=282	N=290
Age	78.9 ± 3.3	78.4 ± 3.3	78.7 ± 3.1	78.1 ± 3.0
Female	716 (55.7%)	527 (45.6%)	92 (32.2%)	60 (20.4%)
Race				
Caucasian	1199 (93.2%)	1112 (96.3%)	281 (98.3%)	292 (99.3%)
Black	55 (4.3%)	29 (2.5%)	3 (1.0%)	1 (0.3%)
Asian/Pacific Islander	21 (1.6%)	6 (0.5%)	0 (0.0%)	1 (0.3%)
Other	11 (0.9%)	8 (0.7%)	2 (0.7%)	0 (0.0%)
Education - Yrs	13.5 ± 3.0	14.7 ± 2.9	15.3 ± 2.6	15.3 ± 2.7
Income x1K	43.6 ± 11.8	45.5 ± 12.6	46.3 ± 12.9	47.9 ± 13.2
Study Site				
Wake Forest	334 (26.0%)	265 (22.9%)	67 (23.4%)	61 (20.7%)
UC-Davis	325 (25.3%)	315 (27.3%)	117 (40.9%)	131 (44.6%)
Johns Hopkins	238 (18.5%)	168 (14.5%)	19 (6.6%)	26 (8.8%)
Pittsburgh	389 (30.2%)	407 (35.2%)	83 (29.0%)	76 (25.9%)
Total Number of Medications				
0-2	120 (9.3%)	116 (10.0%)	26 (9.1%)	42 (14.3%)
3-6	471 (36.6%)	447 (38.7%)	127 (44.4%)	117 (39.8%)
7+	695 (54.0%)	592 (51.3%)	133 (46.5%)	135 (45.9%)
Treatment Assignment				
Placebo	632 (49.1%)	569 (49.3%)	150 (52.4%)	148 (50.3%)
Ginkgo	654 (50.9%)	586 (50.7%)	136 (47.6%)	146 (49.7%)
	Abstainers	Light (1-7)	Moderate(8-14)	Heavy (>14)
	N=1264	N=1141	N=282	N=290
Smoking Status				
Never	669 (52.6%)	405 (35.2%)	81 (28.4%)	53 (18.1%)
Former	551 (43.3%)	669 (58.2%)	191 (67.0%)	214 (73.0%)
Current	42 (3.3%)	59 (5.1%)	10 (3.5%)	24 (8.2%)
Unknown	10 (0.8%)	16 (1.4%)	3 (1.1%)	2 (0.7%)

*GEMS – Ginkgo Evaluation of Memory Study

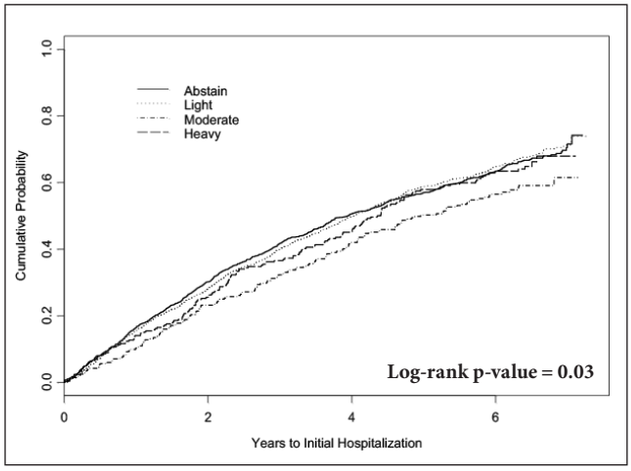

Figure 1. Probability of Index Hospitalization v. Time, Evaluated by Level of Drinking (Censoring at death)

association persisted (p=0.08, HR 0.80; 95% CI 0.67 to 0.96) (Table 2).

30-day Hospital Readmission

Level of drinking was not significantly associated with 30-day readmission (p-value= 0.45, Chi-square test). Results were not affected by adjusting for covariates (Wald test, p=0.69). Odds ratios for 30-day readmission compared to abstainers were as follows: light drinkers had an OR of 0.89 (95% CI= 0.64 to 1.24); moderate drinkers had an OR of 0.88 (95% CI= 0.50 to 1.56); and heavy drinkers had an OR of 0.71 (95% CI= 0.40 to 1.27). Abstainers and light drinkers made up the majority of participants who were readmitted, with 96 (of 751 eligible) and 81 (of 717 eligible) readmitted, respectively. Only 17 moderate drinkers (of 151 eligible) and 16 heavy drinkers (of 174 eligible) were readmitted within 30 days.

Discussion

Moderate alcohol consumption was associated with a lower rate of initial hospital admission in our study population of community-dwelling older adults. Moderate drinkers were less likely to be hospitalized initially compared to nondrinkers. Level of self-reported alcohol consumption was not associated with odds of 30-day readmission. This study may have been underpowered to demonstrate a difference between groups for 30-day readmissions; the readmission rate for our study population was only 11%, compared to 20% nationally.[3]

A lower incidence of the sequelae of cardiovascular disease in moderate drinkers may explain the lower rates of initial admissions observed here. In addition, alcohol use has been studied as a proxy for other measures that independently decrease acute health care utilization, namely health literacy and access to healthcare.[19,20] In a cross-sectional survey of

Table 2. Summary of Cox Regression for Time to Index hospitalization, Evaluated by Level of Drinking and Adjusted for Covariates, Total N=2977, n hospitalized= 1851

N	n hospitalized	Drinking Level	Hazard Ratio (95% CI)
1264	785	Abstain	Ref 1.0
1141	734	Light	1.00 (0.90 to 1.11)
282	155	Moderate*	0.80 (0.67 to 0.96)
290	177	Heavy	0.99 (0.83 to 1.18)
*p-value = 0.08			

older American adults, those who abstained from alcohol were more likely to have inadequate health literacy compared to their drinking counterparts.[21] Alcohol use might also indicate higher expendable income, which is associated with receipt of more preventive health services.[22] However, alcohol's value as a proxy measure for access to care and proactive utilization of health services is obscured by its potential for abuse, and may only be meaningful up to a certain level of consumption.

Alcohol worsens outcomes related to risks for hospitalization and readmission, such as recurrent falls and polypharmacy.[23] Older adults experience higher blood alcohol levels due to age-related changes in adiposity that decrease total body water volume.[24,25] Thus, older adults who consume alcohol face an increased risk of intoxication, interactions with prescription drugs, and increased fall risk.[9,26]

Strengths and Limitations

The strengths of this research are derived from GEMS' rich pool of data. Our analysis could address potential confounders, including measures of health status such as number of medications. The multi-year timespan of GEMS and its frequent follow-ups allowed us to capture hospitalization events. In addition, recall bias is of low concern because alcohol was not a focus of the original study, and consumption data were collected before any hospitalization events.

One limitation of the study is that exclusion of patients with depression, dementia, and substance abuse omits a large and highly vulnerable subset of older adults. Additionally, the presence of social support in the form of a proxy respondent and the relative affluence of GEMS participants (as is common in clinical trials), further limits the generalizability of these results to the older adult population in the U.S, whose median household income was $38,515 in 2015.[27] This income discrepancy pairs with a consumption discrepancy: all levels of alcohol consumption were higher in the GEMS population than in national surveys of alcohol use in the U.S. elderly population.[28]

A further limitation was that the health questionnaire did not distinguish between abstainers who never drank heavily and those who abstained due to problems with addiction.

Future Directions

Drivers of hospitalization and readmission are still being characterized.[29] Our results suggest that alcohol use is a worthwhile factor to explore, given the significantly reduced rate of initial hospitalization observed for moderate drinkers. Alcohol consumption in older adults remains to be studied prospectively in the context of hospitalization and high readmission rates in the United States, or with enrollment criteria that do not exclude patients with common medical conditions and those most at risk for alcohol abuse. Future exploration of alcohol is important in and of itself, both as a behavioral risk factor and potentially in the context of randomized trials.

Conclusion

Information regarding healthcare utilization patterns in older adults who drink alcohol is lacking. Despite recognized health benefits of moderate alcohol consumption, findings have not been replicated in older adults, who instead are routinely excluded from clinical trials leaving providers without definitive evidence on which to base recommendations on alcohol use.[30] Regardless of research biases, physicians will increasingly encounter alcohol-related problems in the elderly due to growth of this population. Further research is needed to explore the relationship between alcohol and healthcare utilization patterns, which is an important area to address due to the morbidity and cost associated with frequent hospitalizations in older adults.

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Conflict of Interest

None of the authors has any relevant conflicts of interest to disclose. None of the sponsors participated in the design, methods, recruitment, data collection, analysis or preparation of this manuscript.

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Original Science

Is Any Change a Prepulse? An Examination of White and Pink Noise Prepulses and Gaps

Hope Peterson, B.A.[1] and Terry D. Blumenthal, Ph.D.[2]

Abstract

The human startle eye blink response can be inhibited by a change in the stimulus environment briefly before the startling stimulus. The use of gaps in ongoing background has been proposed as a way to investigate tinnitus, the perception of ringing (or buzzing or whooshing) that many people experience, but first changes in stimulus environment must be assessed to determine how startle responding is affected. We measured startle eye blinks in 36 college students, where startle stimuli were preceded by (a) no prepulse, (b) a 75-dB(A) white or pink noise prepulse in silence or in 65-dB(A) background noise, or (c) a gap in that background. All prepulses inhibited startle, suggesting that a variety of types of change in ongoing stimulation can be used in studies investigating prepulse inhibition of startle. This suggests that prepulse inhibition of startle might eventually be sensitive enough to be used to evaluate the variety of manifestations of tinnitus in patients, although further study is necessary to make this determination.

[1]Wake Forest University Graduate School of Arts and Sciences, Department of Neuroscience, Winston-Salem, NC

[2]Wake Forest University, Department of Psychology, Winston-Salem, NC

Address Correspondence To:
Terry Blumenthal, Ph.D.
Department of Psychology
Wake Forest University
Winston-Salem, NC 27109
blumen@wfu.edu

Introduction

The startle response is a brainstem reflex that can be used as a tool to study a multitude of typical or abnormal behaviors or ailments. Many physiologic states and disorders affect startle responding: anxiety potentiates startle responses in humans and animal models, while patients with schizophrenia have shown deficits in prepulse inhibition and habituation of the startle response.[1-3] This study examines how changes in the environment preceding a startle stimulus, including frequency and intensity shifts, affect startle responding, in the hopes of using this information to create a diagnostic measure for chronic ear ringing, or tinnitus.

The startle reflex involves shifts in autonomic activity such as increase in heart rate and skin conductance, as well as muscular activity, meant to serve defensive purposes. The response interrupts ongoing neural activity and prepares the organism for action.[4] The startle reflex is observed across phylogenetic groups in mammals, birds, fish, and insects, as well as across ages in humans. The response can be elicited in awake or sleep states.[5] The sternocleidomastoid muscles of the neck and the flexors and extensors of the limbs are activated by the startle response, which is how the reflex is often measured in rodents (limb extensions). However, in humans, the eye blink

response is the most commonly examined element due to the ease with which it can be elicited by low intensity stimuli, its resistance to habituation, and its short latency as a component of the startle response.[4] Animal studies have been used to determine the underlying neuroanatomical systems of startle; the predominant centers lie below the mesencephalon, with moderate cortical control and plasticity arising from the forebrain.[6]

Startle responses can be elicited in many ways, including acoustic, visual, electrical, magnetic, or mechanical stimulation.[7] Although there are benefits and shortcomings with all of these techniques, this study focused only on acoustic stimulation of the eye blink component of the startle reflex. Many aspects of an acoustic stimulus can be manipulated to differentiate startle responses. Single or multiple eliciting stimuli can be used, and the bandwidth, intensity, rise time, and duration of the stimuli must be controlled. Broadband noise, often called white noise, is comprised of frequencies ranging from 20 Hz to 20 kHz, and is the most commonly used acoustic startle stimulus.[7] Although pure tones (with single frequencies) can be used to elicit the startle response, they are less effective than noise (which contains a wide band of frequencies).[8] A more intense stimulus will result in a greater blink magnitude, blink probability, and blink amplitude, and a decreased response onset latency.[8] The stimulus rise time describes how quickly the sound reaches its "full, steady-state amplitude".[7] Shorter rise time increases magnitude, amplitude, and probability of startle response, while decreasing onset latency. It is also important to use the most effective duration of stimuli; 50-milliseconds (ms) is ideal.[9] Increasing stimulus duration up to 50-ms will produce a larger magnitude startle response, meaning a larger response will be observed from a 50-ms stimulus than from a 40-ms stimulus. Increasing the stimulus duration over 50-ms, however, will not increase the observed response. The response latency for the startle reflex is approximately 50-ms; therefore, the neural centers will be fully activated after a 50-ms stimulus, and adding increased stimulation after that point will not increase the observed response. Also, multiple shorter stimuli can be more effective as startle stimuli when they occur in quick succession – a principle called temporal summation.[9]

Surface electromyography (EMG) is generally used to record human eye blink activity.[7] Small silver/silver chloride (Ag/AgCl) EMG electrodes are placed on the skin above the orbicularis oculi—the muscle that encircles the upper and lower portion of the orbital fissure and surrounds the eye, covering the ridge of the cheek bone and circling the eye up to the eyebrow. The EMG signal can then be differentially amplified, filtered, and integrated for data acquisition and quantification.

Changes in the environment preceding the startle stimulus can alter the observed startle response. Hoffman and Wible (1969) showed that embedding an acoustic startle stimulus in a background of steady random noise facilitates startle (increasing magnitude, probability, and amplitude) when compared to the same stimulus presented with no background noise.[10] Additionally, they found 1600-ms of background noise to be sufficient to cause the facilitation, but that the facilitation was lost if the continuous noise terminated more than 800-ms before the startle stimulus was presented. Blumenthal, Noto, Fox, and Franklin (2006) showed that background noise increased startle reactivity in humans when that background was increased from 30 to 50-dB.[11]

A separate stimulus can be presented shortly before the startle stimulus and cause either facilitation or inhibition of the startle response. This stimulus is called a prepulse. Filion, Dawson, and Schell (1993) found that the tones presented with lead intervals of 60, 120, and 240-ms before startle stimulus onset inhibited the startle response (prepulse inhibition, [PPI]), while the stimulus with a lead interval of 2000-ms facilitated the response.[12]

Marsh, Hoffman, and Stitt (1973) found that a gap in broadband noise background preceding a startle stimulus exhibited a similar effect as a prepulse.[13] This silent gap in background noise inhibited the startle response or facilitated it with the same temporal parameters as an acoustic prepulse.[14] This indicates that the underlying neurological components of startle inhibition are perhaps activated simply by a change in the stimulus environment. Based on this concept, Stitt *et al.* (1974) examined the hypothesis that a shift in the frequency of an otherwise steady band

of noise, with neither an increase nor decrease in energy, would display the same inhibition and facilitation results seen with an acoustic prepulse or gap in background noise in rats.[14] They found facilitation of the startle response with a steady background of broadband noise, and significant diminishment of startle responses when the frequency of the continuously presented noise changed. They established that the direction of the shift (low to high or high to low) was not significant, indicating that the "mechanisms responsible for modification of the acoustic startle response are largely insensitive to frequency."[14] These findings indicate that a change in environment preceding a startle stimulus is enough to activate the neural centers responsible for PPI in an animal model. Will a change be sufficient to decrease startle responding in humans? Will traditional white noise prepulses, changes in background noise, and gaps be equally effective at diminishing startle responding? This study was designed to answer these questions.

The startle reflex can be used in the study of many typical or abnormal behaviors; as such, it may be possible to use the response in the diagnosis of tinnitus, caused by unknown abnormalities in the auditory perception pathway. Tinnitus is colloquially known as chronic ear ringing, but not all who experience the disorder report a ringing sound: symptoms can present as a low hum, a high-pitched tone, a "whoosh" sound, or some variation thereof.[15] Additionally, perceived symptoms are not reported with consistency: sound variation can occur either over the short or long term. Although tinnitus can be triggered by exposure to loud sounds, the tinnitus sound experienced is without an external source.[15] The neurologic causes of tinnitus need further investigation, although current models suggest involvement of the perceptual auditory system, including the cochlea, the dorsal cochlear nucleus, and the nerve connections between.[16] Several studies have proposed that damage to the outer hair cells of the cochlea, but not yet the inner hair cells, or at the edge between the inner and outer hair cells may be responsible for the disorder.[16,17] This discordant damage would affect the coupling between the tectorial and basilar membranes, causing depolarization of the inner hair cells without activation. Alternately, the peripheral auditory system theory proposes that spontaneous otoacoustic emissions, or Kemp echoes, are generated by the outer hair cells of the cochlea and propagated into the external auditory canal, where they are "heard" and perceived as tinnitus symptoms.[16] The dorsal cochlear nucleus becomes hyperactive following the introduction of tinnitus-inducing agents such as intense sounds, and therefore may also play a role in tinnitus perception.[16] However, the variation of symptoms within and between patients may indicate multiple mechanisms of cause.[17]

It is estimated that tinnitus affects 3 million Americans.[15] 25% of people experience tinnitus at some point in their life, 13.8% experience tinnitus long term, and 4% experience symptoms severely.[18] Tinnitus is also the most common disability seen in veterans.[19] Tinnitus can be associated with sleep disturbances, disrupted concentration, anxiety, and depression, and sufferers report that the disorder can greatly affect their life and lifestyle, including occupation.[18,19] The only current clinical method of tinnitus diagnosis is self-report, and no effective treatments are currently available. To create useful treatments for the disorder, diagnostic tools are needed.

Previous theories have posited that a gap in background noise serving as a prepulse could be used to diagnose tinnitus. If the perceived internally generated sound filled the silent gap, the startle response would not be diminished compared to baseline responses, whereas inhibition would be observed in control patients without tinnitus. This proposal has been tested in several animal models thus far. Basura, Koehler, and Shore (2015) examined the somatosensory system's role in central auditory circuits and the subsequent role in tinnitus in mature female guinea pigs, all of which showed normal startle responding at baseline.[20] Tinnitus was induced using extreme noise exposure; guinea pigs exposed to the noise showed impaired gap detection, along with larger startle responses in gap conditions compared to controls, due to the facilitation of background noise and no inhibition from the filled gap.[20] Ralli and colleagues (2014) induced tinnitus in male adult Sprague-Dawley rats using an injection of salicylate, and then attempted to reverse the tinnitus with an injection of memantine, an NMDA channel

blocker.[21] Salicylate decreases the metabolism of arachidonic acid, and increased arachidonic acid potentiates NMDA receptor currents; cochlear NMDA activation causes tinnitus symptoms in rats.[22] Startle inhibition was significantly decreased in tinnitus group rats in gap conditions compared to controls, indicating that internally generated perception of sound from salicylate-induced metabolic disruption filled the silent gap in background noise and decreased inhibition seen in the controls.[21] Similar to Basura and colleagues, Turner, Larsen, Hughes and Shore (2012) induced tinnitus in mice using high-intensity, high-frequency noise; in control animals, gaps in background noise were effective prepulse inhibitors, whereas they were not in tinnitus animals.[23] Once again, this indicates that the sound caused by the tinnitus was filling the gap and removing inhibitory effects. Shore and colleagues have found consistent results across several studies.[24,25]

These studies suggest that a gap prepulse shows promise as a tinnitus diagnostic tool, but it must first be established how changes in stimulus environment affect startle responding. If the sound perception associated with tinnitus fills the silent gap but differs from the background noise in frequency or intensity, how will this change startle responses? This study examines how changes in the stimulus environment, both frequency and intensity shifts, affect startle responding.

Methods

Participants

Participants were recruited from Wake Forest University Introductory Psychology courses, and received one hour of class credit for their participation. A total of 41 individuals agreed to participate. Five subjects were removed from analysis due to use of medication (stimulants or sedatives), excessive electrical noise in the data, or experimenter error, leaving a sample of 36 participants (8 males, 28 females) ranging from 18-20 years of age. Among participants, 56% identified as Caucasian, 29% as Asian, 7% as Hispanic or Latino, and 7% as Black or African American. No participants reported experiencing tinnitus symptoms at the time of participation.

Materials and Apparatuses

Participants began by reading and signing an informed consent form, a health history questionnaire, and two tinnitus and hearing surveys.[26] They were seated in a sound-attenuated and electrically shielded room. All auditory stimuli were presented using Audacity software, and were controlled by SuperLab 5.0 (Cedrus) software. The startle stimuli were white noise bursts at 100-dB(A) with a duration of 50-ms and an instant rise time. All prepulses were presented 120-ms before the onset of the startle stimulus at 75-dB(A) with a 40-ms duration and a 5-ms rise time. Prepulses were either white or pink noise. Background noise was white noise presented for 6-sec at 65-dB(A). Gaps in the background noise were 40-ms of silence in the 6-sec of background noise, beginning 120-ms before the onset of the startle stimulus. Inter-trial intervals of 8, 9, 10, 11, and 12 seconds were randomly distributed across trials. The trials were divided into two blocks for analysis.

White noise, as previously described, is broadband noise at a passband of 20 Hz to 20 kHz with all frequencies at equal intensity. Pink noise also has a passband of 20 Hz to 20 kHz, but low-frequency wavelengths are relatively more intense and high frequencies are relatively less intense (see Figure 1).[27]

EMG activity was amplified using Biopac EMG amplifiers using filters passing 1-500 Hz, sampled (1000 Hz) by a Biopac MP150 workstation. The signal, filtered using a passband of 28-500 Hz, was then rectified and smoothed using a five-sample boxcar filter.[28]

Procedure

Participants had the skin below their left eye cleaned using 70% isopropyl alcohol on a cotton swab. The Ag/AgCl electrodes prepared with miniature double-sided adhesive collars and high-conductivity electrode gel were then adhered to the participant's skin. The temporal and nasal electrodes were placed below the ocular ridge (nasal directly below the pupil when looking forward, just below the lower eyelid; temporal just lateral and superior to the nasal), with a third ground electrode placed on the left temple. Participants were asked to place headphones comfortably over their ears, and then stimulus presentation began.

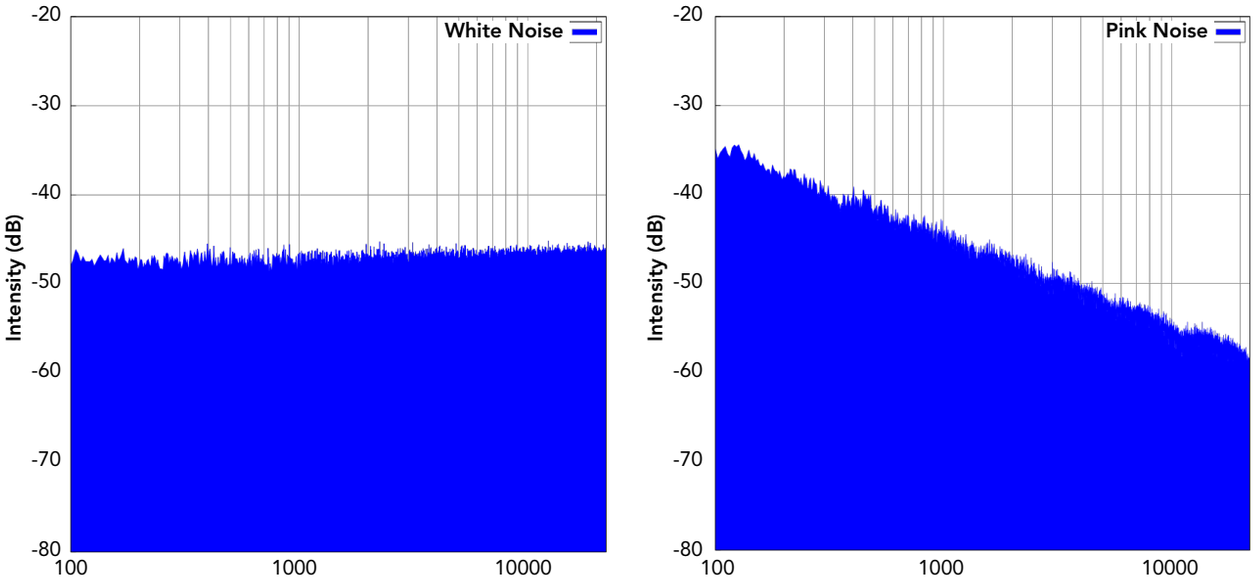

Figure 1: Spectrographs of white noise (left panel) and pink noise (right panel). Both white and pink noise contain frequencies ranging from 20 Hz to 20 kHz, but in pink noise the low frequencies are relatively more intense, and the higher frequencies are relatively less intense. Although they are both broadband noise, pink noise sounds lower in pitch.

All participants were presented with 62 startle stimulus trials, beginning with six control habituation trials (startle stimulus alone), followed by eight trials of each of seven stimulus conditions, presented in the same random order across participants. The stimulus conditions were startle stimulus alone in silence (1), startle stimulus with a white noise prepulse in silence (2), startle stimulus with a pink noise prepulse in silence (3), startle stimulus alone in background noise (4), startle stimulus with a white noise prepulse in background noise (5), startle stimulus with a pink noise prepulse in background noise (6), and startle stimulus with a silent gap in background noise (7).

Data Analysis

Startle responses were scored using a custom scoring program.[29] Responses beginning 20-120-ms after the onset of the startle stimulus were considered valid, with any trials involving movement artifacts, extraneous blinks, or excessive noise excluded from analysis. Trials with no observed response were assigned a magnitude of zero and included in analyses. Response magnitude, latency, and probability were examined on each trial. Control responses were averaged across blocks (first half of presentation versus second half of presentation) to calculate habituation. Responses were also averaged across trial by condition, such that an average magnitude, probability, and latency score remained for each stimulus condition. PPI of startle magnitude was calculated by subtracting the magnitude of the responses on control trials from that of the prepulse trials, then dividing by the control trial magnitude. This method controls for individual differences across participants and results in a ratio of inhibition for each prepulse condition. A negative ratio demonstrates inhibition; a 95% confidence interval was calculated for the mean of each group to determine whether this inhibition is significant—a confidence interval that does not contain zero demonstrates significant PPI. Repeated measures ANOVA were conducted to compare the inhibition of startle magnitude across conditions, with an alpha level of 0.05 in SPSS 24.

PPI of response probability and latency were calculated in a similar way: control trial probability and latency were subtracted from probability and latency of each prepulse condition respectively. Again, a difference below zero signifies inhibition for probability or a difference above zero indicating inhibition of startle latency, with a 95% confidence interval

that does not include zero demonstrating significance. Repeated measures ANOVA were conducted to compare the inhibition of startle magnitude across conditions, with an alpha level of 0.05 in SPSS 24.

Results

Startle inhibition was observed with all prepulse conditions. A repeated measures ANOVA showed that startle magnitude in control conditions habituated across blocks (the six habituation trials compared to the first half of stimuli and second half of stimuli) in both silent and white noise backgrounds, $F(2, 32) = 16.588$, $p < 0.001$. As expected, startle responses were facilitated by background noise, $F(1, 33) = 7.895$, $p = 0.008$ (see Figure 2). There was no significant interaction between background and blocks on startle stimuli alone.

When examining the white and pink noise prepulses in silence and in background noise, we found a significant main effect of prepulse type, a significant main effect of background, and an interaction effect. Thus, the pink noise prepulse was less effective at inhibiting startle when embedded in the background noise, $F(1, 35) = 5.410$, $p = 0.026$ (see Figure 3).

Pairwise comparisons were run comparing the PPI in the silent gap condition with that in each discrete prepulse condition. No significant differences were found between PPI in the silent gap and white noise prepulse conditions in silence or background noise, or pink noise prepulse in silence. There was a significant difference in PPI between the gap condition and the pink noise prepulse in the background noise condition, such that the pink noise prepulse was less effective at inhibiting the startle response, $F(1, 35) = 18.088$, $p < 0.001$ (see Figure 3).

All prepulse conditions caused startle inhibition to equivalent degrees, except for significantly less inhibition from the pink noise prepulse embedded in background noise.

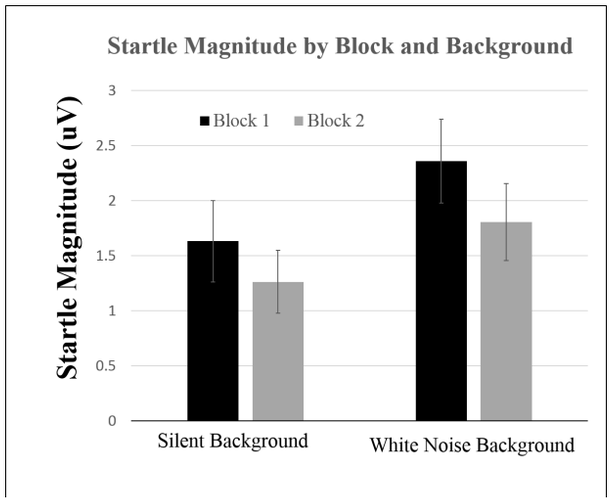

Figure 2. Startle magnitude decreased from the first half of testing to the second half in both backgrounds, and all responding was higher on background noise trials than on silent background trials.

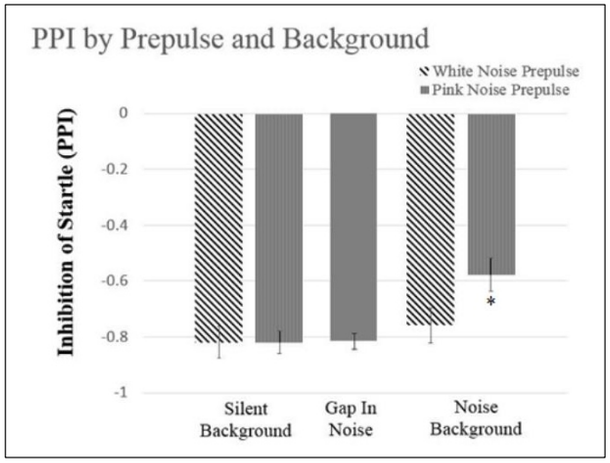

Figure 3. The white noise prepulse in silence, the pink noise prepulse in silence, and the gap in background noise were all equivalent inhibitors of startle magnitude. The white noise prepulse in the white noise background was minimally less effective as a prepulse inhibitor, although not to a significant degree. The pink noise prepulse in background noise was significantly less effective at inhibiting startle magnitude (most likely due to noise masking), although inhibition did occur.

** indicates significantly less PPI at p <0.05*

Discussion

All prepulse conditions effectively caused inhibition, observed as a decrease in startle magnitude across white and pink noise prepulses in silence or in a white noise background, and a silent gap in that background. In the silent background, the white and pink noise prepulses were equivalently effective inhibitors. The white noise prepulse in the background noise was slightly less effective at decreasing startle magnitude, but not to a significant degree; however, the pink noise prepulse in the background noise caused significantly less inhibition. We would expect a white noise background to most efficiently mask a white noise prepulse; however, we observed less inhibition from the pink noise prepulse embedded in the white noise background. This may suggest that masking of the prepulse by the surrounding white noise background is greater when the spectral composition of the prepulse differs from that of the background. The gap in the background noise was equivalent as a prepulse to the white noise prepulse in silence and background, and to the pink noise prepulse in silence (see Figure 3). These findings indicate that a gap is as effective as a discrete pulse in silence. This means that a break or a change is as effective as the commonly used discrete broadband prepulse, but that differential prepulse inhibition is based on prepulse bandwidth characteristics.

In upcoming phases of this study we hope to extend these findings by examining prepulses presented at lower decibels than the background noise, analogous to gaps that vary in depth, such as the stimuli used by Stitt *et al.* (1974).[14] We hope to elucidate what components of a prepulse cause effective inhibition, and possibly how the inhibition pathway involved in the startle reflex functions. Fournier and Hébert (2013) examined the efficacy of a gap compared to a white noise prepulse in control and tinnitus populations.[30] Equivalent inhibition of startle responding was found among all participants in prepulse conditions, while the silent gaps caused significantly less inhibition in the tinnitus group when embedded in both high frequency and low frequency backgrounds.[30] The question raised from these findings is why this result occurred. The results of this study, along with the upcoming partial gap study hope to answer this question. Moreno-Paublete, Canlon, and Cederroth (2017) have determined that gaps and prepulses trigger separate brain pathways to cause equivalent inhibition in mice.[31] Male mice had equivalent inhibition of startle responses compared to control responses on both prepulse and gap trials. D-amphetamine hemisulfate salt (which induces catecholamine release and blocks catecholamine reuptake, used in this study to enhance dopamine) and MK-801 (an uncompetitive NMDA receptor antagonist) both disrupt the inhibition caused by gaps and prepulses, while the increase in available dopamine more strongly affects gap inhibition.[31] Prepulses and gaps caused activation of the pontine reticular nucleus, while prepulses also activated the lateral globus pallidus and gaps activated the auditory cortex.[31] These findings suggest that both gaps and prepulses cause similar startle inhibition, although they activate separate neural pathways. This explains why we see equivalent inhibition from white noise prepulses and gaps, but does not determine which pathway is activated by a change, such as the pink noise prepulse in white noise background.

These results and those of future studies are steps toward creating an objective diagnostic criterion for tinnitus. Diagnosis is a critical first step towards treatment of this disorder. Once it is established how changes in sounds function as prepulses, it may be possible to examine how tinnitus fills a silent (or shallow) gap in a continuous background noise preceding a startle stimulus, and if these findings could be used to diagnose the condition. If this theory holds, the internally generated noise heard with tinnitus might fill the silent gap, presumably diminishing the inhibition observed from the prepulse, keeping the response closer to the magnitude of the control startle response. Csomor and colleagues (2006) examined a question regarding magnitude of environment change with their study of prepulses with less energy than startle stimuli.[32] Decreasing the intensity of a prepulse compared to the intensity of the startle stimulus results in diminished inhibition, or larger startle responses (closer to those observed on control trials); in their own words, "absolute reduction in startle reactivity resulting from a prepulse stimulus preceding the startle-eliciting pulse stimulus is fixed by the prepulse intensity regardless of the

pulse stimulus intensity."[32] That is to say, what determined the size of the startle response in the presence of a prepulse is not the size of the startle stimulus alone, but the prepulse. Findings such as these have also been observed in animal models, where noise-induced tinnitus has decreased the efficacy of gaps as prepulses,[33] but the mechanism is unclear and it is unknown if these results would hold true in humans.

This study and the future line of research will contribute substantially to the PPI knowledge base regarding how the neural network becomes activated and what can serve as a sufficient prepulse to cause inhibition, as well as creating new questions regarding how PPI functions. Knowledge regarding startle and PPI is far from complete, and these studies will add to our understanding of behavioral and neurological components of the startle reflex. It is possible that multiple inhibition pathways exist, activated by upward or downward shifts in energy, or that simply a change activates the startle inhibition pathway. Further exploration will be necessary to make this determination, but these studies will be a first step in uncovering this distinction. In addition to understanding startle, further knowledge regarding brainstem structures will contribute to our overall understanding of neural functioning, which will be useful in understanding typical and abnormal behaviors and disorders. It is hoped that these studies will provide a diagnostic tool for the detection of tinnitus, but if not they will provide useful knowledge to expand our understanding of the brain and psychological attributes.

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Original Science

A Randomized Controlled Trial of Ornamental Plants and Recovery from Cardiothoracic Surgery

Aaron Winkler, M.D.,[1] James M. Taylor, M.D., MPH[2], Tony Dang, M.D.,[3]
Alain G. Bertoni, M.D., MPH[4]

Abstract

Objectives: This pilot study investigated the effects of nature-assisted therapy (ornamental living plants) on pain control, vital signs, patient satisfaction, and length of stay for hospitalized patients recovering from surgery.

Design: A randomized controlled clinical trial. 292 patients who underwent cardiothoracic surgery requiring a sternotomy were randomized 1:1 to receive three living plants vs. no plants in their single occupancy post-intensive care "step-down" room.

Location: A large tertiary academic medical center in Winston-Salem, North Carolina.

Outcome Measures: Pain levels were evaluated using a subjective Likert pain scale and opiate intake in morphine equivalents per day. Patient satisfaction was assessed using standard Press Ganey post-hospitalization surveys. Length of stay and blood pressure after arrival onto the "step-down" unit were analyzed.

Results: Patients randomized to receive living plants required more opiate pain medication, reported higher levels of pain, and reported their pain was less well controlled. Patients receiving plants tended to have shorter hospital stays by almost a day and lower mean arterial pressures compared to those not receiving plants.

Conclusion: Ornamental plants reduced hospital length of stay and improved vital signs, but may also have negative effects on pain control. This study provides evidence that nature-assisted therapy can have a clinically meaningful impact, even in complex post-surgical hospitalized patients. Further research into this topic is warranted.

[1]Department of Psychiatry, University of Maryland Medical Center, Baltimore, MD

[2]Department of Internal Medicine, Cone Health, Greensboro, NC

[3]Department of Internal Medicine, Carolinas Medical Center, Charlotte, NC

[4]Department of Epidemiology and Prevention, Wake Forest School of Medicine, Winston-Salem, NC

Address Correspondence To:
Aaron Winkler, M.D.
Department of Psychiatry
University of Maryland Medical Center
Baltimore, MD 21201
awinkler@som.umaryland.edu

Introduction

A large and diverse body of literature supports the use of nature-based interventions to facilitate positive health and well-being.[1–2] Relevant research has consistently shown the physical environment can promote desirable patient outcomes in various healthcare settings.[3-4] Exposure to natural environments or replicas, whether through windows, murals, or other media, is associated with improved mental health and psychological well-being.[1-5] Research has demonstrated the effectiveness of designing an inpatient room with a greenspace view.[5] However, few clinical trials have assessed the impact of nature-assisted therapy within the inpatient setting on objectively measured health outcomes and patient-reported quality of care.

One retrospective study found that patients recovering from cholecystectomy assigned to a room with a window view, looking out on natural scenery, were associated with improved outcomes, including a shorter length of stay and reduced use of potent analgesics.[8] In a more recent study, Park and Mattson conducted a clinical trial of placing living, flowering plants in the rooms of patients recovering from hemorrhoidectomy and compared this group to a control group not receiving plants. They found a decrease in length of stay of approximately one day and a statistically significant but non-clinically meaningful variation in systolic blood pressure among patients who had plants in their rooms. They concluded that ornamental plants could be "a noninvasive, inexpensive, and effective complementary medicine for surgical patients.[7]" Additional studies have found benefits of incorporating natural scenery into healthcare environments.[6-7] However, many such studies rely on subjective, patient-reported questionnaires with metrics focused on comfort, stress, and anxiety levels. Few clinical trials have used objective metrics to evaluate the benefits of ornamental plants in the inpatient setting. Therefore, the present study was conducted to examine the health effects of living ornamental plants placed within the rooms of patients recovering from cardiothoracic surgery requiring sternotomy.

Methods

We conducted a pilot randomized trial to assess the effects of nature-assisted therapy on patients recovering from cardiothoracic surgery requiring sternotomy at Wake Forest Baptist Medical Center. Over 14 months, patients recovering from cardiothoracic surgery involving a sternotomy were randomized to receive three 12-inch Zamioculca plants or no study plants in their single-occupancy, post-intensive care "step-down" hospital room. Randomization was accomplished through shuffling and dealing out a deck of playing cards for each set of 52 enrollees. A set of numerically ordered and sealed envelopes containing group assignments were created using the order of black and red cards. When a patient was identified as ready for transfer from the cardiothoracic intensive care unit (ICU) to the "step-down" unit during morning rounds, the next sealed envelope in numerical order was opened and the patient was assigned to the group on the card inside. For patients assigned to the intervention group, three plants were placed around their "step-down" room during cleaning, prior to patient arrival. "Time from intervention" was defined as time from arrival in the "step-down" room. No attempts were made to alter the real world behavior of subjects or their visitors. Waiver of informed consent was obtained from the Institutional Review Board. Patients who inquired were told a local philanthropist had donated the plants. Medication intake, vital signs, subjective pain scores, admission, discharge, and transfer data were collected from the electronic medical record (EMR) for each participant. In addition, Press Ganey post-hospitalization survey information was collected from all patients who completed and returned the survey.

The following variables were abstracted from the EMR for all patients enrolled in the study: total hospital length of stay (LOS), opiate intake, pain scale rating, vital signs, age, gender, race, and smoking and alcohol status. LOS was defined as the time the patient arrived on the "step-down" unit, the time of intervention, until the date of discharge from the hospital. Opiate medications included all medications flagged as "opiates" in the EMR. Only opiates given while the patient was on the "step-down" unit were included in the analysis. Tapentadol and Tramadol were excluded from analysis as they are known to have multi-modal mechanisms of action, impacting the mu-opioid receptor and modifying neurotransmitter uptake.[8-9] All routes of administration were accounted for, including patient controlled analgesia (PCA) pumps. Opiate medication dosages were converted to morphine equivalents (MEQ).[10] The total number of MEQs were calculated for each patient during their entire length of stay on the "step-down" unit. Each patient's total MEQs were divided by their respective length of stay on the unit, yielding one value for each patient. This allowed a standardized value for comparison between groups with units of average MEQs per day. Furthermore, patient opiate usage was analyzed by day of hospitalization after arrival onto the "step-down" unit. One value per day was generated for each patient, representing average MEQ use per day after arrival onto the "step-down" unit.

Patients reported their pain severity to the nursing staff on a Likert scale ranging from 0 to 10 (no pain to worst possible

pain). Each patient's pain score was averaged so that every patient had one pain score for each day after admission to the "step-down" unit. Next, the pain scores were compared between groups. Patient satisfaction was obtained from the Press Ganey post-hospitalization survey. Values across all survey questions were compared between both groups. Vital signs examined included mean arterial pressure (MAP) and heart rate (HR). MAP was calculated from the systolic (SBP) and diastolic (DBP) blood pressure using the traditional formula — MAP= (2*DBP+SBP)/3.[11] Similar to the pain scale, MAP and HR were calculated then averaged so that each patient had one MAP and one HR value for each day after admission to the "step-down" unit. Then values were compared between study groups.

Statistical analyses were performed using STATA IC10 (STATA Corp, LLP, College Station, Texas). A power calculation was performed and a sample size of 284 was estimated to detect a 4 mm Hg difference in blood pressure, with an average systolic pressure of 135 mm Hg and 80% power to detect differences. Initially, baseline characteristics of the study population were examined using appropriate statistical analysis, using t-tests for continuous data and Chi-squared tests for categorical data. All tests were two-sided, with a significance level of alpha = 0.05. Results are reported as means (M) and standard deviation (SD). T-test results are shown with degrees of freedom within parentheses, T-statistics, and two-sided p-values.

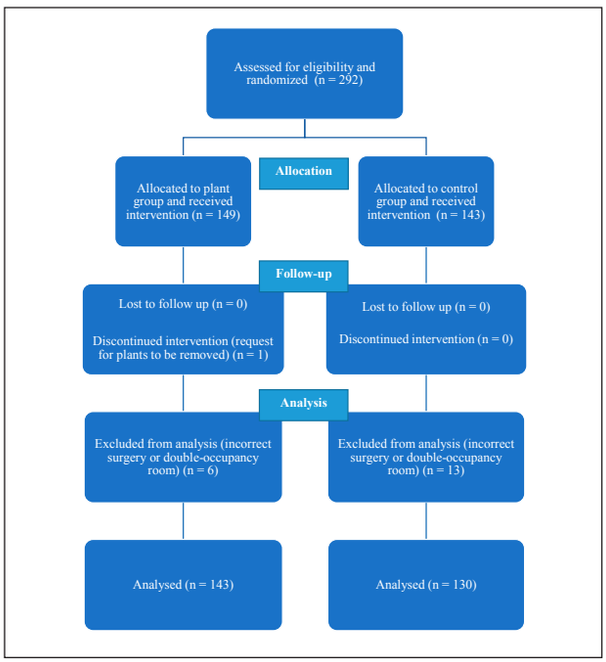

Figure 1: Patient Flow Diagram

Results

Initially, 292 patients were randomized to the intervention or control group. Of this group, 18 did not meet inclusion criteria and were excluded (Figure 1). In addition, one participant requested that plants be removed from their room. Thus, 273 subjects remained and were included in the final intention-to-treat analysis (143 subjects in the intervention group and 130 in the control). Baseline characteristics demonstrated successful randomization (Table 1). The majority of the sample was non-Hispanic white, and male. A high proportion of the study population was insured. Surgical interventions were evenly distributed between groups (Table 1). There were no intervention-related adverse events.

LOS: For patients in the intervention group, there was a trend towards shorter hospitalization (M = 5.33 days, SD = 5.30 days) compared to those in the control group (M = 6.10 days, SD = 5.49 days), t (271) = 1.1843, p = 0.24. Since the data were not symmetrically distributed, a log transformation was performed. The trend remained the same, but the differences did not reach statistical significance.

Table 1: Patient Characteristics

	Plants (n=143)	**No Plants** (n=130)
Average Age	62.68	63.34
White	129 (90.2%)	117 (90%)
Females	52 (36.4%)	40 (30.8%)
Insured	137 (95.8%)	119 (91.5%)
Living	139 (97.2%)	128 (98.5%)
Smoker	25 (17.5%)	19 (14.6%)
Former		
Smoker	68 (47.5%)	62 (47.7%)
Drinks Alcohol (yes or no)	28 (19.6%)	31 (23.8%)
Procedure Type		
CABG	75 (52.4%)	68 (52.3%)
Valve	37 (25.9%)	31 (23.8%)
Both	19 (13.3%)	20 (15.4%)
Other	12 (8.4%)	11 (8.5%)

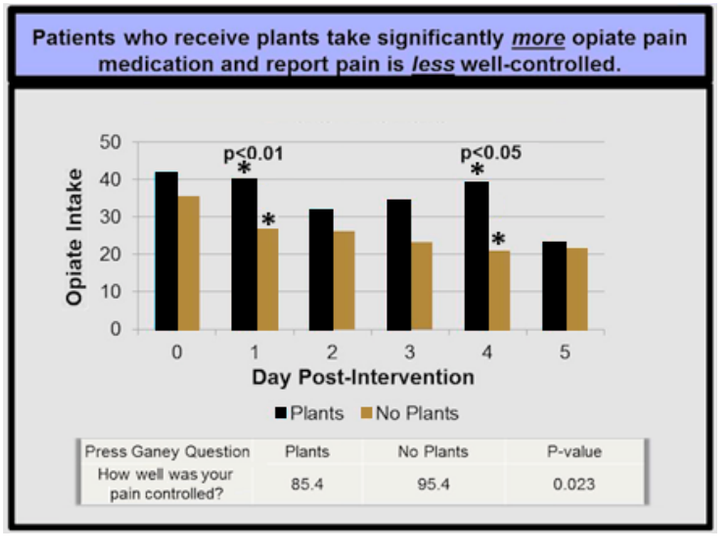

Figure 2: Opiate intake by days and Press Ganey post-hospitalization survey

Opiate usage: Subjects in the intervention group required more opiate pain medication (M = 33.5 mgMEQ/day, SD = 40.1 mgMEQ/day) compared to those in the control group (M = 24.9 mgMEQ/day, SD = 23.3 mgMEQ/day), t(271) = -2.1231, p = 0.035). To further characterize opiate usage, daily medication usage was determined and compared between the two study groups. There was a significant difference between the two study groups on the second and fifth days after arriving onto the "step-down" unit (Figure 2). On the second day after arriving at the unit, patients who received plants required more opiate medication (M = 39.3 mgMEQ/day, SD = 45.1 mgMEQ/day) than those who did not receive the intervention (M = 26.9 mgMEQ/day, SD = 25.8 mgMEQ/day), t(249) = -2.6416, p = 0.0088. On the fifth day after arriving in the unit, patients who received plants required more opiate medication (M = 39.3 mgMEQ/day, SD = 57.8 mgMEQ/day) than those who did not receive the intervention (M = 20.9 mgMEQ/day, SD = 22.8 mgMEQ/day), t(91) = -2.0502, p = 0.043).

Pain Scale: There was no significant difference between the study groups with respect to self-reported pain. However, on the days where opiate usage was significantly different between groups, the pain data trends were congruent. On the second day after arriving at the unit, there was a trend towards patients in the intervention group (which received more opiate medication) reporting more pain (M =2.79, SD = 2.16) than those in the control group (M = 2.34, SD = 1.82), t(265) = -1.8326, p = 0.068. On the fifth day after arriving at the unit, those who received plants continued to report more pain (M =2.64, SD = 2.42) than those not receiving plants (M = 1.95, SD = 1.94), t(115) = -1.7121, p = 0.090).

Patient satisfaction: Post-hospitalization survey data were obtained for all patients who completed and returned this survey. However, only a fraction of the patients (30% of the patients in the intervention group and 29% in the control group) completed and returned the survey by the time the study protocol had ended. On the survey, in response to "How well was your pain controlled?," subjects who received plants were less satisfied (M = 85.4, SD = 25.0) than those without plants (M = 95.4, SD = 9.8), t(77) = 2.3134, p = 0.023 (Figure 2).

Vital signs: On the fourth day after arriving at the unit, patients who received plants had lower MAPs (M = 82.7 mm Hg, SD = 9.45 mm Hg) than those not receiving plants (M = 85.4 mm Hg, SD = 9.16 mm Hg), t(187) = 2.0269, p = 0.044. On the fifth day after arriving at the unit, patients in the intervention group had lower MAPs (M = 80.9 mm Hg, SD = 8.86 mm Hg) compared with controls (M = 84.8 mm Hg, SD = 8.76 mm Hg), t(123) = 2.4983, p = 0.014). There was no significant difference in HR between study groups

Discussion

This pilot study was designed to measure the magnitude of possible clinical effects of ornamental plants on recovery from surgery. The purpose was to inform design of future studies, rather than elucidate a possible mechanism of action. Previous studies have shown benefit, but effect sizes and clinical applicability were unclear.

Patients who received plants in our study tended to have shorter hospital LOS and required statistically significantly more opiate medication compared with controls not receiving plants. In addition, patients in the intervention arm tended to report worse pain (Likert scale) on days when they took more opiates. Patient satisfaction (Press Ganey) with respect to pain control was significantly lower in the intervention arm. Lastly, among patients in the intervention arm, MAPs were lower on the fourth and fifth day compared with controls. There were no significant differences between groups with respect to other vital signs.

A previous retrospective study found that intake of potent analgesics decreases when patients could see a tree through a window.[5] The dependent variable reported in that study, 'doses of potent analgesics,' did not describe size of dose or potency of medication. The current study attempted to build on this previous work by more precisely investigating the intake of opiate medications as measured by milligrams given and normalized using morphine equivalency tables. As such, the fact that the results of the current study do not agree with this previous work may be due to methodologic differences in the way doses of opiate medications were reported and defined.

With regard to length of stay the current study and two previous studies all agree on direction and size of effect: a shorter hospital LOS in the intervention arm by approximately one day.[4] Though the current study did not obtain statistical power over the effect, the previous two studies did. This validates the current study and the use of nature-assisted therapy, making repetition to further clarify the opiate effect a necessity.

The significant effect on MAP we found mirrored a similar effect in previous work.[4] Although this may reflect opiate effects on blood pressure, the data showing opiate intake by day and MAP by day do not overlap, and in fact seem to contrast. This effect is of particular interest in the current study population, since blood pressure is carefully monitored and controlled in those recovering from cardiovascular surgery. Further work should attempt to clarify this effect as well.

The cardiothoracic surgery study population was chosen to match the post-operative length of stay, with the populations from two previous studies — cholecystectomy patients at a U.S. hospital in the 1970s (7–8 days) and hemorrhoidectomy patients from a Korean hospital in 2009 (7–8 days).[4,5] Currently, on average, neither population stays more than 2 days at our hospital. The length of stay effect might be too difficult to measure with an average stay of 2 or fewer days. Other medical populations deemed less suitable included neurologic patients (due to a bimodal average length of stay), oncologic or neutropenic patients who could not have plants or flowers in their hospital rooms, and the general medical population deemed too heterogenous to allow inclusion of a high volume of uniform patients.

The current study's strengths include a randomized controlled design, successful randomization, a relatively large number of subjects, and the potential to have immediate applicability to patient care. Additionally, the specific plant used offers benefit. The Zamioculca plant grows well in artificial light, requires infrequent watering and minimal maintenance, can be sourced in bulk year-round in any region of the United States, are common in hotels and thus likely to be generally benign, are inexpensive, and do not flower, thus decreasing the risk of allergic reactions to pollen.[12]

However, our study also has several limitations. The patient population was predominantly male, Caucasian, insured, and elderly, which could diminish the external validity of the study to a more diverse and younger population. Patients were quite heterogenous with respect to levels of care required following surgery. Thirty-nine of the 273 patients included in the final analysis were moved to another unit after first being transferred to the "step-down" unit. Some returned to the ICU transiently to receive a higher level of care, and others were transferred to other floors in the hospital that provided the same level of care. For those who returned to the ICU, randomization may have occurred anytime a

patient was transferred from the ICU to the "step-down" unit. An additional limitation is that the providers in the study were not masked to the assignment of the intervention. This could potentially bias the provider when recording pain metrics or prescribing medications. However, we believe the pragmatic nature of the trial was strengthened by not masking providers, since in normal clinical operations providers would see plants in a particular patient's room.

Only one patient was randomized into the study twice. For this patient the second randomization was discarded. Importantly, plants could not be transferred with patients who were moved to other floors. Thus, any transfer away from the "step-down" unit for those in the plant group meant they were no longer exposed to the intervention. For calculating opiate use, then, only time spent on the intervention "step-down" unit was included in the analysis. For LOS, the time was calculated between arrival onto the "step-down" unit until discharge from the hospital (to either home or a rehabilitation center) regardless of any transfers within the hospital between those two points in time. This LOS calculation is conservative and may bias the results toward the null hypothesis; thus, any effect size found might actually be larger than calculated.

Finally, as a potential limitation is the lack of pre-surgical BMI data or narcotic use. Patients with higher BMI may require higher opioid quantities to achieve equal pain control. Similarly, if patients required or used narcotic medication prior to surgery for various reasons, this could also affect the quantity of pain medication required to achieve pain control. Although the study would be strengthened by these variables, we believe that the study design and randomization should lead to balance of these potential covariates across strata. However, this limitation should be considered when interpreting the results of this study and incorporated in the design of future similar studies.

Conclusion

This study is novel in that it used both subjective survey data and objective measures to assess the health effects of nature assisted therapy on post-operative patients in the inpatient setting. The results obtained are compelling yet confusing. Three different measures of pain (medication intake, subjective report and post-hospitalization survey) all indicate that those who received plants experienced greater pain compared to patients not receiving plants. Despite the fact that this is the opposite of what was expected and what has been reported in similar studies, the effective randomization, large study size, increased precision of characterizing medication intake, and correlation with the expected improvement in blood pressure and length-of-stay all reinforce the validity of the findings of the current study. Though the results were not as originally hypothesized, this study provides high quality evidence that nature-assisted therapy can have a clinically meaningful impact on patient care. Comprehensive understanding of these effects cannot be obtained from this study alone. Further research into the role of nature-assisted therapy and the value of ornamental plants in particular for hospitalized patients is required for clarification.

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Original Science

Maternal Benefits of Early Skin-to-Skin Contact Following Cesarean Delivery

Melissa G. Potisek, M.D.[1], Laura S. Dean, M.D.[1], Lynnette C. Harris, BSN, RN[1], Scott Tonidandel, Ph.D.[2], Ashley M. Tonidandel, M.D.[1]

Abstract

Early postpartum skin-to-skin (STS) contact between mother and infant is routinely practiced in many hospitals immediately following vaginal delivery. STS after Cesarean delivery is more variable due to practical limitations and the lack of well-established protocols and available personnel to assist with the process. Neonatal health benefits have been identified, labeling early STS as a "Healthy Birth Practice," but little is known about the maternal benefits of early STS contact. This study evaluates the impact of early STS contact after Cesarean delivery on maternal satisfaction, pain reporting, and opioid usage in the 24-hr postpartum period. Fifty-five women who received early STS contact following elective Cesarean delivery were compared to a group of 55 women who received standard care. Primary outcomes included intraoperative supplementation of spinal anesthesia as well as pain scores, maternal satisfaction, and opioid requirements. We found a significant improvement in maternal satisfaction with operating room atmosphere ($p<0.001$, Cohen's $d= 0.97$) and resting pain at 24 hours (17.64 and 23.69, $p=0.0398$). This study supports implementation of early STS contact after Cesarean delivery. However, the operating room setting does pose some physical barriers to STS contact following Cesarean delivery, requiring the need for safe and efficient protocols.

[1] Department of Anesthesiology, Wake Forest School of Medicine, Winston-Salem, NC

[2] Department of Psychology, Davidson College, Davidson, NC

Address Correspondence To:
Ashley Tonidandel, M.D.
Department of Anesthesiology
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157
atonidan@wakehealth.edu
Phone: 336-718-8278
Fax: 336-718-9271

Introduction

Early STS contact after delivery has known neonatal benefits, including improved temperature regulation, maintenance of blood glucose, improved cardiorespiratory stability, and improved breastfeeding.[1,2] As a result, early STS contact is labeled as a "Healthy Birth Practice"[3] and a component of the "Baby Friendly Hospital Initiative" and has been made routine following vaginal delivery in birthing suites across the country. While it has been postulated that this intervention may reduce postpartum hemorrhage[4], the evidence identifying and characterizing maternal benefits of early STS contact is limited.

The national Cesarean delivery (CD) rate was reported to be 32.2% in 2014 by the Centers for Disease Control, and in our institution is consistently just under 30%.[5] Operating room birth remains a barrier to early STS contact due to delay between delivery and physical contact between the mother and baby.[6] Protocols for STS contact in the OR have been described[7] and their implementation has been associated with minimal risk and significantly decreased maternal time spent in the recovery room.[8] There has been little research, however, to establish maternal benefits beyond the post-anesthesia care unit (PACU).

Pain perception, and the surrogate of pain scores as reported by patients, is a common target for OR interventions in the anesthesia literature. Compared to vaginal delivery, women with CD experience more pain 24 hours after delivery.[9] Additionally, poorly managed acute pain during and after surgery is associated with persistent pain at 8 weeks and postpartum depression.[9] Skin-to-skin contact could theoretically decrease anxiety and improve pain scores by promoting the release of oxytocin, a maternal hormone with analgesic benefits that also affects uterine muscle tone.[10] The purpose of this study was to evaluate the impact of early STS contact after CD on maternal satisfaction, pain scores, and narcotic usage over the first 24 hours post-delivery compared to routine care. We hypothesized that new mothers exposed to STS contact in the OR would have less pain and more satisfaction compared to women who received standard care at our institution.

Methods

This research had IRB approval, and subjects were recruited between July and December 2015. All participants were patients at a tertiary care referral center with a Level 1 nursery and approximately 6,000 births per year. Patients were at term gestation, ASA class I or II, with singleton pregnancies, and scheduled for CD under spinal anesthesia with neuraxial morphine. Spinal morphine is the standard of care at our institution and many others across the country, with doses ranging from 100-200 μg depending on the anesthesiologist's preference. Spinal morphine in that dose range results in similar quality and duration of postoperative analgesia over the first 24 hours after surgery compared to controls, with no significant benefit at higher doses.[11] Therefore, all patients received our standard spinal morphine regimen for postoperative pain control, allowing for comparison of groups. Exclusions included anticipated neonatal or surgical complications, non-English speaking mothers, and age <18 years. General and epidural anesthetics were excluded to allow comparisons of opiate usage and pain scores.

After delivery, patients had their neonate placed across their chest when initial neonatal interventions were complete, including 1- and 5-min Apgar scores, diapering, and administration of antibiotic eye ointment and vitamin K. The infant was evaluated by the neonatal intensive care unit (NICU) team during this time and stimulation and resuscitation was initiated, if indicated. The presence of the NICU team at all CDs is standard protocol at our institution. The mother's arms were free to move, and her gown was unsnapped to allow the infant to be placed directly on her skin, typically in a transverse position so as not to interfere with surgery. A warm blanket was tucked over the infant's body. Similar protocols for STS have been described and utilized elsewhere.[6] Initial latching was neither encouraged nor discouraged. Practically, latching is challenging given the supine positioning necessary for surgical exposure, and none of our mothers attempted to breastfeed in the OR. The neonate remained STS throughout the CD unless removed by request or medical necessity. Further STS contact was encouraged but left to the discretion of the mother. We intentionally did not mandate length of STS contact, because our goal was simply the initiation of STS in the OR.

Participants were visited 24 hours after delivery to rate their pain and satisfaction. This methodology is commonly used in other trials evaluating the impact of specific interventions on maternal pain scores.[1,2] Charts were reviewed for medication usage in the OR and recovery areas. The STS intervention group was compared to a control group with the same inclusion and exclusion criteria who were participants in a different study evaluating pain outcomes. The controls received "routine care," including the same neonatal interventions followed by a partner holding the infant within 2 feet of the mother's head. Since multiple private practice groups and a teaching service perform deliveries at

our facility, participants were matched by surgical group to account for differences in length of surgery. Surgery length at our institution generally varies from approximately 30 to 90 minutes, depending on surgeon and maternal surgical history.

Measures

Primary outcomes included intraoperative supplementation of spinal anesthesia as well as pain scores, maternal satisfaction, and opiate usage in the first 24 hours after surgery. Participants rated their pain at rest, while moving from lying to sitting, average pain over the prior 24 hours, and worst pain experienced since surgery using a sliding visual analog scale (VAS) with anchors of "no pain at all" and "worst pain imaginable," recorded as 0-100 mm, respectively.[13]

Maternal satisfaction has been evaluated multiple ways in the literature, including a 0–100 scale.[14] For consistency in pain ratings, we asked participants to also rate satisfaction using a VAS with anchors of "not at all satisfied" to "completely satisfied," recorded as 0–100 mm by the evaluator. Questions assessed maternal satisfaction with pain control during surgery, over the first 24 hours following surgery, and overall satisfaction with anesthesia care. We added a series of questions targeting satisfaction with the OR atmosphere that were modified from a previously reported satisfaction scale designed for use in CDs.[15]

Records were reviewed for intraoperative supplementation of spinal anesthesia with inhaled nitrous oxide, intravenous opiates, midazolam, or ketamine. Anesthesia personnel were not blinded to STS contact by necessity, and no instructions were given to providers other than to treat pain and anxiety as they would normally. Postpartum opiate usage, recorded via chart review, was converted to morphine equivalents for comparison.

Statistical Analyses

Sample size calculations suggested a need for 55 evaluable subjects in each group to detect a medium effect size at a power of 0.9. All tests were conducted using R (R Core Team, 2016) using an α-level of 0.05.[16] Welch's independent samples t-tests were used to detect differences in primary outcomes of pain scores, morphine equivalent consumption, and maternal satisfaction, and to ensure no differences in demographics, including gravida and para status, Apgar scores, and neonatal weight. Outcome data that were not normally distributed were compared with the Wilcoxon rank test. Pearson's χ^2 test was used to evaluate differences in intraoperative analgesic supplementation.

Results

Seventy women were enrolled in the STS intervention group. Fifty-five received STS and were included in further analyses. Fifteen women did not receive STS: 1 because of neonatal grunting, 4 because of maternal dysrhythmias or discomfort, and 10 for study failures such as lack of personnel, surgery cancellation, exclusion of spinal morphine, or missing 24-hour follow-up data. The average time to initiation of STS following delivery was 10.45 min (range 3 – 15 min, SD = 3.12). Comparisons of demographic data between groups are shown in Table 1. Per study inclusion criteria, all patients received spinal morphine, ranging from 100–200 μg per our institution's normal procedure. The specific dose given was left to the discretion of the anesthesiologist, and there were no significant differences between groups (see Table 1).

Table 1. Demographic Data for Standard Care and Skin-to-Skin Groups

Demographic	Standard Care Group	Skin-to-Skin Group	p-Value
Maternal age (yr)*	31.26 (5.54)	30.83 (5.00)	0.67
Height (in)*	65.76 (4.76)	64.66 (2.75)	0.15
Weight (lb)*	202.00 (42.69)	213.55 (47.68)	0.18
Gravida†	3 (1-7)	3 (1-8)	0.43
Para†	1 (0-5)	2 (0-4)	0.62
Spinal morphine dose (mcg)*	149.09 (9.62)	150.00 (9.62)	0.71
Apgar at 1 min†	8 (7-9)	8 (7-9)	0.53
Apgar at 5 min†	9 (8-9)	9 (8-10)	0.25
Baby weight (gm)*	3632.60 (542.08)	3513.80 (424.41)	0.20
*Mean (SD)			
†Median (range)			

Table 2 displays results on the VAS questionnaires. The item total correlation, which correlates each item to the total score of the remaining items, was ≥ 0.59, and the internal consistency reliability of the OR atmosphere scale, as assessed via Cronbach's alpha, was 0.75. Taken together, these metrics indicate satisfactory reliability of the composite measure. There were no significant differences in evoked, average, and worst pain over 24 hours between groups. Resting pain at 24 hours was significantly lower in the STS group (17.64 and 23.69, $p = 0.0398$). Effect size was 0.62, expressed as a probability that a random person in the treatment group would report lower pain scores than a person in the control group.[17] Both groups were similarly satisfied with pain control and anesthesia care. Mothers who had STS reported significantly higher satisfaction with the OR atmosphere compared to controls ($p < 0.001$, Cohen's $d = 0.97$). There were no significant differences between groups in need for intraoperative supplementation of spinal anesthesia ($\chi 2 = 0.72$, $p = 0.40$) or 24-hour morphine equivalents ($t = 0.66$, $p = 0.51$).

Discussion

This prospective trial comparing STS to standard care after elective CD found lower resting pain scores at 24-hr and higher maternal satisfaction scores with the OR atmosphere in the STS group at 24-hr after delivery. This improvement in experience is valuable, since anxiety and depression risk have been shown to increase following CD, particularly in low-risk patients who perceive having had a "negative" birth experience.[18,19] This study supports early STS contact as a low-risk, non-pharmacologic intervention that may improve postoperative pain and intraoperative experience.

The physiologic mechanisms by which early STS contact after CD may improve postoperative pain are not known. It is possible that elevated levels of oxytocin or a reduction in total oxidative stress that accompany early STS contact and breastfeeding could contribute to improved postoperative analgesia.[20]

We did not find a significant difference between groups in need for intraoperative medication supplementation, 24-hour opiate requirements, or satisfaction with anesthetic care. Overall, satisfaction with care was high regardless of intervention, perhaps impacting our ability to identify differences. The routine use of intrathecal morphine in our patient population may have contributed to the lack of difference between groups in opiate requirements at 24 hours as well as other pain parameters such as evoked pain, average pain and worst pain over 24 hours. Institutions that do not use long-acting intrathecal opioids for postoperative pain may see different outcomes. Our study excluded non-elective CD, though these mothers may be more likely to benefit from early STS contact if their expectation was for a "more natural" experience.

Table 2. Comparison of Visual Analog Scores of Skin-to-Skin versus Standard Care Groups

Measure	Skin-to-Skin*	Standard Care*	Test Statistic	p-Value	Effect Size
Resting pain†	17.64 (19.88)	23.69 (18.58)	1854.5	0.0398	0.62
Evoked pain†	43.55 (25.34)	46.06 (23.52)	1610.5	0.5599	0.53
Average pain over 24 hr†	37.97 (23.88)	37.96 (20.93)	1579	0.6931	0.52
Worst pain over 24 hr†	62.31 (25.32)	63.67 (26.22)	1585	0.6666	0.52
Satisfaction: Anesthesia care	95.91 (8.19)	93.56 (12.38)	-1.17	0.24	0.22
Satisfaction: Pain control in OR	94.93 (15.52)	93.51 (15.03)	-0.49	0.63	0.09
Satisfaction: Pain control over 24 hr	81.52 (23.68)	85.86 (12.91)	1.20	0.24	0.23
Satisfaction: OR atmosphere	95.98 (8.94)	83.18 (14.76)	-5.04	<0.001	0.97
Baby weight (gm)*	3632.60 (542.08)	3513.80 (424.41)	0.20		
*Mean (SD)					
†Median (range)					

We did not randomize patients in this study because we felt it inappropriate to withhold a previously desired STS experience given known benefits to the neonate. However, women may be more likely to report "satisfaction" with an experience of their choosing, which could have affected our results. We also elected to have a brief delay in initiation of STS to ensure adequate fetal resuscitation, which led to varied and sometimes substantial delays in STS contact. On average, this process took about 10.45 min, though the range of 3 to 18 min indicates high variability in provider practice. The reason for this variability is unclear. Apgar scores ranged from 7 to 9 at 1 minute, and 8 to 10 at 5 minutes, suggesting fetal distress was not a likely cause for this delay. Other investigators have avoided such delays in their protocols. Smith et al.[7] describe a "natural cesarean" with immediate transfer of the infant over the drape that shows promise in terms of safety for the mother and baby. Posthuma et al.[8] found significantly less neonatal admissions in their STS group with immediate transfer to the mother after operative delivery, suggesting a delay for fetal assessment may be unnecessary.

The duration of STS contact in this study was determined by the patient and was variable. We did not record the total time spent STS in the OR, and this variation in the duration of our "intervention" has unknown significance. An optimal "minimum" time spent STS immediately after birth to obtain neonatal benefit is also unknown to these authors. Since initiation of breastfeeding and STS contact in the recovery room is already routine at our institution, we did not include this time spent STS in our study. It is possible that this variable is significant and should be considered in future studies.

Following the conclusion of study enrollment, it has been challenging at our institution to consistently offer a STS experience for parturients having CD. Staffing limitations, culture, and lack of a dedicated staff member for neonatal monitoring remain barriers. Variable maternal body habitus and an inability to elevate the patients' position from supine have been voiced as concerns about STS in the OR at our hospital. Other institutions likely have similar limitations to routinely offering this valuable experience during CD. Given the high CD rate in this country, optimizing the safety, outcomes, and experience of women undergoing CD is of utmost importance. Our study focused on pain and satisfaction scores; however, reported effects of STS on other outcomes, such as postpartum hemorrhage and time to discharge from the PACU and hospital, should be considered for study. Further research is needed to define the benefits and risks of STS after CD and to outline an optimal protocol, including an appropriate staffing model.

Conclusion

This study found a significant improvement in maternal resting pain at 24 hours and satisfaction with OR experience when STS contact was initiated early after CD. These results support the development of STS protocols to be offered to mothers having CD. Implementation of new practices in the OR can be difficult, and there are barriers to STS contact after CD that do not exist following vaginal delivery. An optimal STS protocol that maximizes benefits and minimizes risk to mother and baby remains undetermined, and may depend on institutional staffing models.

Appendix 1. 24-Hour Assessment Tool

Pain:

Using the sliding visual analog scale provided: (0 = no pain at all to 100 = worst pain imaginable)

1. What is your pain at rest?
2. What is your pain while moving from a lying to sitting position?
3. What is your average pain over the past 24 hours?
4. What is the worst pain you have experienced since your surgery?

Satisfaction:

Using the sliding scale provided: (0 = not at all satisfied to 100 = totally satisfied)

1. What is your satisfaction with your pain control during surgery?
2. What is your satisfaction with pain control over the past 24 hours?
3. What is your overall satisfaction with your anesthetic care?

4. During surgery, what was your satisfaction with your ability to:
    a. Interact with your partner?
    b. Bond with the baby?
    c. Have a sense of control?
    d. Communicate with the staff?
    e. See the baby after delivery?
    f. Hold the baby after delivery?

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Original Science

Patient and Patient-Partner Perspectives of the Shared Medical Appointment for Matters Related to Sexual Health

Charles C. Peyton, M.D., Robert C. Kovell, M.D., Jung H. Kim, M.D., Ryan P. Terlecki, M.D.

Department of Urology, Wake Forest School of Medicine, Winston Salem, NC

Address Correspondence To:
Charles C. Peyton, M.D.
Department of Urology
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157
cpeyton@wakehealth.edu

Abstract

Background: Shared medical appointments (SMAs) — also known as group visits — are gaining appeal in outpatient, clinical medicine. To this point, SMAs have not been widely reported in the setting of patients with urologic disease, especially those related to sexual health. We performed a pilot evaluation of the perceptions of patients and their partners towards the use of SMAs in relation to erectile dysfunction (ED) and Peyronie's disease (PD).

Methods: Separate SMAs were conducted for patients with a history of ED or PD, including several unique components not typically offered at standard clinic visits. Patient and patient-partner satisfaction questionnaires were compiled and evaluated.

Results: A total of 11 patients and 5 patient-partners completed the ED questionnaire. Seven patients and 3 patient-partners completed the PD questionnaire. Patients and patient-partners unanimously expressed high levels of satisfaction with the SMA. Patient-partners unanimously expressed feeling more comfortable being involved in the ED treatment decision-making process following the SMA.

Conclusions: SMAs represent a promising instrument in the management of patients with ED and PD. Both patients and their partners felt comfortable discussing sexual health in this setting and expressed high levels of satisfaction with this approach. Further investigation is warranted.

Introduction

As advocates for men's health, urologists have the opportunity to address sensitive topics, such as sexual health, with their patients. These issues can be difficult for patients to discuss, and men may be reluctant to seek treatment.[1] Patients presenting for evaluation and management may lack a sophisticated understanding of conditions such as erectile dysfunction (ED) and Peyronie's disease (PD), leading to relatively lengthy visits to cover the information necessary to make informed treatment decisions. Unfortunately, busy clinic schedules can limit the time available for office visits. Additionally, limited physician access within the traditional one-on-one model of clinic-based healthcare is associated with patient dissatisfaction.[1,2] Shared medical appointments (SMAs) allow

practitioners to simultaneously evaluate multiple patients affected by the same condition. While this model has been reportedly successful in patients being treated for bariatric surgery, diabetes, and nephrolithiasis, it is not clear how this would translate to the field of sexual health.[1-5]

SMAs differ from traditional clinic visits in several respects that may be particularly useful in the evaluation and management of sexual health. The group environment promotes patient-to-patient interaction and fosters a sense of community offering support and acceptance.[6] The provider alone cannot offer a patient's perspective, but the SMA format encourages this interaction between those with similar conditions.[7] The care team may also include advanced practice providers, therapists, and patient advocates, adding further perspectives.

Multiple specialties have demonstrated that SMAs alleviate provider time-anxiety and represent a cost-effective method of delivering patient education and management.[1,2,5,8] SMAs increase provider productivity without increasing work hours, and decrease overall costs associated with care.[5,8] Furthermore, SMAs are well suited for routine evaluation and management of chronic disease, suggesting that this approach may be useful for patients with ED and PD.[7] However, this approach may not be palatable for some patients and/or couples, given the intimate nature of these conditions. The current literature demonstrates only one instance of a pharmacy-coordinated visit for patients with ED, but no other reports exist regarding physician-led SMAs for ED or PD.[9] To investigate these issues, we designed a pilot study of SMAs for patients with ED and PD. We invited both patients and their partners to participate, with a goal of evaluating satisfaction among both groups.

Methods

We invited a random, consecutive series of established patients with ED and PD to participate in an SMA relevant to their particular condition. The visit was limited to the first 11 men to accept the invitation for each group; they were encouraged to bring their spouse/partner, if applicable. Two separate SMAs were evaluated — one specifically pertaining to ED and one to PD. A total of 18 patients were evaluated (11 for ED session and 7 for PD session).

Shared Medical Appointment Process

On the day of the visit, patients were greeted, registered by the medical staff at the urology clinic, and directed to a conference room with an open seating layout. Patients received a packet including a printout of slides for the physician's presentation, a copy of the current AUA Men's Health Checklist, SHIM questionnaire, and confidentiality agreement. All patients and patient-partners were required to sign a confidentiality agreement prior to the SMA. A physician gave a 15-minute multimedia presentation to educate patients on the epidemiology, etiology, pathophysiology, available treatment options, and expected post-treatment outcomes for ED or PD. A 10-minute question-and answer session followed. The last component of the visit included a 5- to 10-minute visit by the physician for a physical exam (if required) or further discussion with the patient and partner regarding diagnosis and possible treatment options. The next follow-up appointment and/or intervention was decided based on an individual patient needs and treatment plans.

SMA Assessment

Upon completion of the SMA, each patient and their respective partner were given a satisfaction questionnaire. The questionnaires included six Likert-scale questions scored in the following manner: 1 = strongly disagree, 2 = somewhat agree, 3 = neither agree nor disagree, 4 = somewhat agree, 5 = strongly agree. Questions were designed to assess the level of satisfaction of the SMA experience, and to identify the strengths and weaknesses of the program. Patients and partners anonymously completed the SMA satisfaction questionnaire before leaving the clinic, and these were submitted privately. All questionnaires were de-identified for analysis. Frequency distribution charts were established to provide visual representation of survey results. Statistical analysis was not performed.

Results

ED SMA

The first 11 patients invited to participate in the ED SMA accepted the invitation. Six of their partners attended as well. We received completed questionnaires from all patients and 5 patient-partners (100% and 83.3% response rate, respectively).

The survey questions and corresponding results are shown in Figures 1 and 2. For the ED SMA, patients unanimously expressed the highest possible level of agreement with the statement that, "overall I was satisfied with the SMA." Responses to each statement were close to total agreement among the group, with few patients per statement expressing a lower level of agreement. Patient-partners of the ED SMA unanimously expressed the highest level of agreement with the statement "I feel more comfortable being involved in his decision-making in regard to his/our sexual health." The patient-partners appeared to be quite satisfied with the overall experience of the SMA. All of the collective responses received a rating of 4 or better, except for the statement, "I felt the SMA allowed me to better understand my partner's condition," which received one response of "neither agree or disagree."

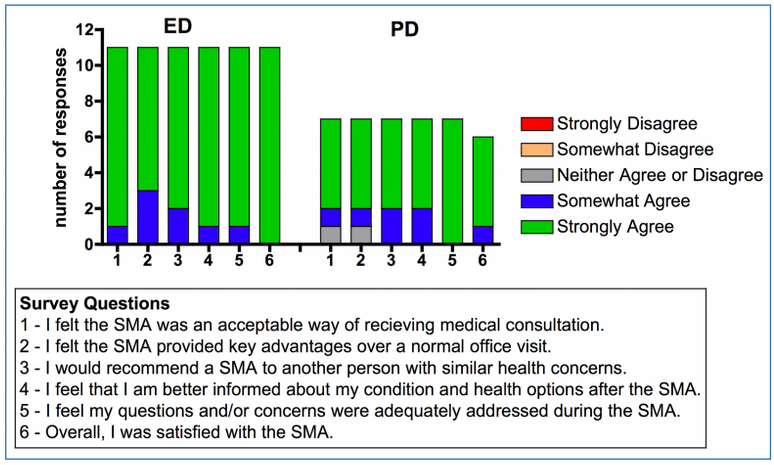

Figure 1: Patient satisfaction questionnaire results for ED and PD SMAs.

PD SMA

Seven patients and 3 partners attended the PD SMA. All questions were completed, except for one question on a single patient survey. The results of the surveys are collected in Figure 2. Fewer patients and patient-partners attended the PD SMA; however, the overall results seemed favorable and similar to those seen in the ED SMA group. The patient-partners in the PD group universally responded with either a 5 — "strongly agree" or 4 — "agree" for every survey question.

Discussion

Despite the relatively personal nature of ED and PD, our pilot study suggests that SMAs are well received by patients and their partners. All except one patient expressed strong satisfaction with the SMA format.

Similar SMA evaluations have been performed for patients with diabetes, heart disease, or undergoing bariatric surgery, yielding positive results similar to ours.[1,2,4,7,10] Fletcher et al. previously examined the implementation of a drop-in medical appointment in urological practice.[10] However, we found no publications examining feasibility or patient satisfaction regarding a physician-led SMA for any sexual health issue, including ED or PD.

Oehlke et al. described the success of a pharmacy-coordinated follow-up SMA for patients on sildenafil therapy focusing on education, counseling, and dose adjustments.[9] They reported increased physician access and decreased wait times, obvious advantages to SMAs. However, the applicability of this report to a large urologic practice interested in developing SMAs for ED or PD is limited, given the variety of treatment options that can be offered.

Jhagroo et al. recently extended the concept of the SMA to patients being managed medically for nephrolithiasis, examining 112 patients via 27 SMAs. They demonstrated decreased wait times (180 to 84 days) and a 43% increase in patients seen per month. Additionally, 87% of patients rated their SMAs as excellent or very good, and 90% would recommend this type of visit to others. Overall, patients who participated in their SMA format demonstrated better understanding of their condition relative to controls.[3]

Our study found that patients strongly agreed that the SMA as an educational experience. It is likely that patients who better understand how to manage their disease are more likely to confidently select a therapy that suits their needs and expectations. Likewise, patient-partners felt more comfortable with involvement in the patient's decision-making process, and felt increasingly encouraged with the patient's pursuit of treatment. We find this to be a major achievement of the SMA model. Furthermore, patients felt

that the SMA provided key advantages over a normal office visit. The fact that patients were strongly willing to recommend SMAs to others suggests that this may be attractive for providers trying to build their practice, and, compared to the traditional model, may be better suited to reach potential patients that could benefit from therapy. While certainly not all patients will be open to a group setting for sexual health topics, this study suggests that for those willing to try it, satisfaction is quite high.

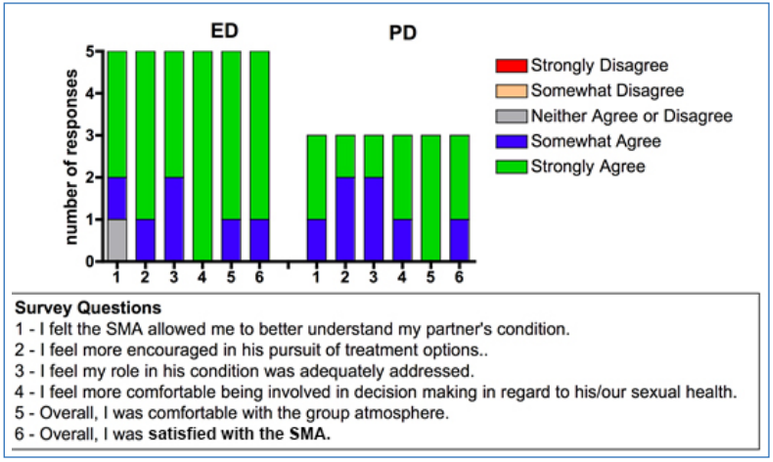

Figure 2: Patient-partner satisfaction questionnaire results for ED and PD SMAs.

Limitations of this report include the small number of participants and the limitations inherent to questionnaire-based survey data. In addition, the individual personalities of the physician, treatment team, patients, and patient-partners could all certainly affect success and perceptions of any given SMA.

In the future, we hope to identify trends in treatment choices and quality of life ratings for patients who have attended SMAs and compare them to men who have been evaluated in the traditional one-on-one model. Additionally, we plan to evaluate application of SMAs to other urologic conditions that may well be suited to this approach, such as bladder pain syndrome, benign prostatic hyperplasia, and survivors of prostate cancer.

Conclusions

The structure of the SMA may be well suited for patients with ED or PD, despite the sensitive nature of these conditions. An SMA model including both patients and their partners resulted in high levels of patient satisfaction. Our preliminary study suggests the SMA may facilitate patient decision-making and at least provides an acceptable alternative to the traditional model of care. Further study of this model with application to other urologic conditions seems warranted.

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Original Science

A Single-Center Experience with Allograft Pancreatectomy

Robert J. Stratta, M.D., Alan C. Farney, M.D., Ph.D., Giuseppe Orlando, M.D., Ph.D., Muhammad A. Khan, M.D., Baha Alradawna, M.D., Jeffrey Rogers, M.D.

Abstract

The purpose of this study was to analyze our single-center experience with allograft pancreatectomy (AP), which is both an index of technical morbidity and pancreas transplant (PT) failure.

Methods: We retrospectively reviewed outcomes in 202 consecutive PTs in 192 patients; all received either rabbit anti-thymocyte globulin or alemtuzumab induction with tacrolimus/mycophenolate ± steroids.

Results: From November 2001 to March 2013, we performed 162 simultaneous pancreas-kidney transplants (SPKT) and 40 solitary PTs. With a mean follow-up of 5.5 years, the death-censored pancreas graft failure rate was 29%, of which 22 (41.5%) resulted in AP. AP was performed in 11.5% of patients overall. Of the 53 death-censored pancreas grafts lost, 19 occurred early (within 3 months of PT) and 34 occurred late. Indications for AP were early thrombosis (within 3 months of PT, n=15), late thrombosis (n=2), rejection (n=1), infection (n=1), duodenal fistula (n=1), ruptured pseudoaneurysm (1), and at retransplantation (n=1). Rates of AP were 95% for early (<3 months) and 11.8% for late graft loss (p<0.001). Rates of AP were 10.5% in SPKT and 12.5% in solitary PTs, 12.5% in pancreas retransplants compared to 10% in primary PTs, and 13% with systemic-enteric compared to 10% with portal-enteric drainage (all p=NS). With a mean follow-up of 5.5 years in patients with and without AP, rates of patient survival (81% versus 87%) and kidney graft survival (67% versus 76%) were comparable. There were no early deaths or kidney graft losses following AP. When comparing outcomes before and after 2009, the incidence of early AP has decreased from 10.8% to 4.8% (p=NS). Eleven patients underwent successful pancreas retransplantation following AP.

Conclusion: At our center, AP is performed in 41.5% of death-censored pancreas graft losses, is most commonly performed for early graft loss due to thrombosis, and does not appear to adversely influence medium-term patient or kidney graft survival rates.

From the Department of General Surgery, Wake Forest School of Medicine, Winston-Salem, NC

Address correspondence to:
Robert J Stratta, M.D.
Wake Forest School of Medicine
Department of General Surgery
Medical Center Blvd.
Winston Salem, NC 27157
rstratta@wakehealth.edu
Phone: 001-336-716-0548
Fax: 001-336-713-5055

Introduction

With improvements in organ retrieval and preservation technology, refinements in diagnostic and therapeutic technologies, advances in clinical immunosuppression and antimicrobial prophylaxis, and increased experience in donor and recipient selection, success rates for PT have steadily improved.[1] As of December 2014, >48,000

PTs were reported to the International Pancreas Transplant Registry and the Scientific Registry of Transplant Recipients, including >29,000 in the United States (US).[1,2] PT is divided into 3 major categories; those performed simultaneously with a kidney transplant (SPKT), those performed after a successful kidney (PAK) transplant, and pancreas alone (PA) transplant. The latter 2 (PAK and PA) categories are usually combined and analyzed together as solitary PTs (SPT) because of similar outcomes. The majority (75%) of PTs in the US are performed as SPKTs whereas 16% are performed as PAK and 9% as PA transplants.[1,2] For recipients of primary deceased donor PTs, one-year patient survival rates exceed 95% in all 3 categories, and more than 70% of patients are alive at ten years post-transplant.[1,2] One-year pancreas graft survival (insulin-free) rates are 85.5% in SPKT (93% kidney graft survival), 80% in PAK, and 78% in PA transplant recipients, which translates to pancreas graft half-lives approaching 14 years in SPKT and 10 years in SPT recipients.[1,2] In the last decade, era analyses have demonstrated improving outcomes over time primarily due to reductions in early technical failures and early immunologic graft losses, particularly in SPTs. The need for allograft pancreatectomy (AP) may be considered as an index both of technical morbidity and graft failure following PT. However, few studies have addressed issues pertaining to AP.[3-5] Because most early pancreas graft losses result in AP, the purpose of this study was to retrospectively review our single-center experience with AP.

Methods

Indications for PT were insulin-requiring diabetes with complications and the predicted ability to tolerate the operative procedure and manage the requisite immunosuppression and close follow-up, irrespective of C-peptide production.[6,7] Selection criteria for SPT were similar to SPKT except for renal function, in which the calculated glomerular filtration rate was >70 ml/min in PA (native renal function) and >40 ml/min in PAK (renal allograft function) transplant recipients. Donor selection criteria have been previously reviewed.[8] All patients were T- and B-cell negative by flow cytometry crossmatch. All PTs were initially approached as intent-to-treat with portal-enteric drainage (n=179) using an anterior approach to the superior mesenteric vein (SMV) and enteric exocrine drainage to the proximal ileum in the recipient.[9] In the absence of favorable SMV anatomy, PT with systemic venous (iliac vein) and enteric exocrine drainage (n=23) was performed. In SPT and selected SPKT recipients, 2,000–3,000 units of intravenous heparin (30-50 units/kg) were administered as a single dose during surgery prior to implantation of the pancreas, and a heparin infusion was continued posttransplant (continuous infusion of 300 units/hour for 24 hours, then 400 units/hour for 24 hours, and then 500 units/hour until post-operative day 5) in the absence of bleeding. Indications for intravenous heparin included all SPT or preemptive SPKTs, history of thrombophilia or clotting disorder in the recipient, small or diseased donor or recipient vessels, prolonged pancreas cold ischemia (>15 hours), extended donor criteria, or history of prior pancreas graft thrombosis.[7-10] Patients received depleting antibody induction with either alemtuzumab (n=122) or alternate-day rabbit anti-thymocyte globulin (rATG) (n=80, 1.5 mg/kg/dose, total 3–5 doses) in combination with tacrolimus, mycophenolate mofetil, and tapered corticosteroids or early steroid withdrawal.[11] All patients received anti-infective prophylaxis with cefazolin for surgical site prophylaxis, fluconazole, valganciclovir, and trimethoprim-sulfamethoxazole. All also received oral aspirin (81 mg/day) as anti-platelet therapy. Treatment of hypertension, hyperlipidemia, anemia, and other medical conditions was initiated as indicated, aiming to maintain blood pressure <140/90 mm Hg, fasting serum cholesterol <200 mg/dl, and hematocrit >27%.

Results

From November 2001 through March 2013, 202 consecutive PTs were performed in 192 patients, including 162 SPKT, 35 sequential PAK, and 5 PA (40 SPTs). A total of 186 PTs (92%) were primary and 16 retransplants. Donor and recipient characteristics are described in Table 1. With a mean follow-up of 5.5 years (range 0.5-11.8 years, 130 patients had a minimum follow-up of 5+ years), overall patient, kidney, and pancreas graft survival rates were 86.5%, 75%, and 65%, respectively. A total of 71 pancreas graft losses occurred, of which 22 (31%) resulted in AP (Figure 1). AP was performed

in 11.5% of patients. Causes of pancreas graft loss included acute/chronic rejection (n=30), thrombosis (n=18), death with a functioning graft (n=18), and infection/other (n=5). Rates of early thrombosis were 9.9% in SPKT and 5% in SPT patients; respective rates of AP were 10.5% and 12.5% (Table 1, both p=NS). The death-censored pancreas graft failure rate was 28.8%; of the 53 pancreas grafts lost, 19 occurred early (within 3 months of transplant) and 34 occurred late (Figure 1). The death-censored rate of AP following pancreas graft loss was 41.5%. Indications for AP were early thrombosis (within 3 months of PT, n=15), late thrombosis (n=2), rejection (n=1), infection (n=1), duodenal fistula (n=1), ruptured pseudoaneurysm (n=1), and to create space at the time of retransplantation (n=1). Rates of AP were 95% for early (<3 months) and 11.8% for late graft loss (p<0.001, Figure 1). The only case of early graft loss that did not result in AP was primary nonfunction in a type 2 diabetic patient with high insulin resistance. The incidence of AP was 12.5% in pancreas retransplants compared to 10% in primary PTs. In addition, the incidence of AP was 13% with systemic-enteric compared to 10% with portal-enteric drainage (both p=NS). With a mean follow-up of 70 months in patients with AP compared to 65 months in PT recipients without AP, respective patient survival (81% versus 87%) and kidney graft survival (67% versus 76%) rates were comparable. There were no early deaths or kidney graft losses associated with AP and no major complications or re-operations occurred. When comparing outcomes from 2002–2009 to 2009–2013, the incidence of early AP has decreased from 10.8% to 4.8% (p=NS). Eleven patients have undergone successful pancreas retransplantation subsequent to AP.

Discussion

According to registry data, the incidences of early technical graft failure (usually secondary to thrombosis) and early immunologic graft failure (in the first year post-transplant) have declined over time, and are currently each below 10% in all three PT categories.[1,2] Similar to the role of allograft nephrectomy in kidney transplantation, the majority of cases of AP occur in the setting of early graft failure.[3-5] Although the judicious use of anti-coagulation, duplex ultrasonographic monitoring, and either open surgical or percutaneous

Table 1: Donor and Recipient Characteristics and Results According to PT category

Mean ± SD	SPKT N = 162 in 161 patients*	SPT N = 40 in 38 patients*	p-value
Donor age (years)	27.3 ± 10.6	22 ± 7.6	0.004
Donor BMI (kg/m2)	23.9 ± 1.4	23.5 ± 6.8	NS
Cold ischemia time (hours)	16.2 ± 7.4	14.8 ± 3.8	NS
HLA-mismatch	4.5 ± 1.2	2.7 ± 1.5	<0.001
PRA >10%	27 (16.7%)	8 (20%)	NS
CMV Donor+/ Recipient-	45 (27.8%)	11 (27.5%)	NS
Retransplant	2 (1.2%)	14 (35%)	<0.001
Portal-enteric technique	147 (90.7%)	32 (80%)	0.09
Recipient age (years)	42.7 ± 11.3	42.2 ± 8.7	NS
Patients aged 50 or older	42 (26.1%)	8 (21.1%)	NS
Recipient gender: Male	94 (58.0%)	19 (50%)	NS
Recipient: African American	36 (22.2%)	3 (7.9%)	0.03
Recipient weight (kg)	71.1 ± 13.5	70.7 ± 12.8	NS
Duration of pre-transplant diabetes (years)	25.3 ± 9.8	26.7 ± 7.7	NS
Waiting Time (months)	10.1 ± 6.3	5.8 ± 7.2	0.002
Patient survival	133/154 (86.4%)	33/38 (86.8%)	NS
Kidney graft survival	120 (74.1%)	28/35 (80%)	NS
Pancreas graft survival	105 (64.8%)	26 (65%)	NS
Follow-up (months)	68.7 ± 96	92.1 ± 37	NS
Early thrombosis	16 (9.9%)	2 (5%)	NS
Pancreas graft loss	57 (35.2%)	14 (35%)	NS
Death-censored pancreas loss	16 (9.9%)	2 (5%)	NS
Allograft pancre-atectomy	17 (10.5%)	5 (12.5%)	NS
Death-censored pancreas loss	16 (9.9%)	2 (5%)	NS
Allograft pancre-atectomy	17 (10.5%)	5 (12.5%)	NS

*One patient(s) had 2 SPKTs, two had 2 SPTs, and seven had SPKT followed by SPT at our center.

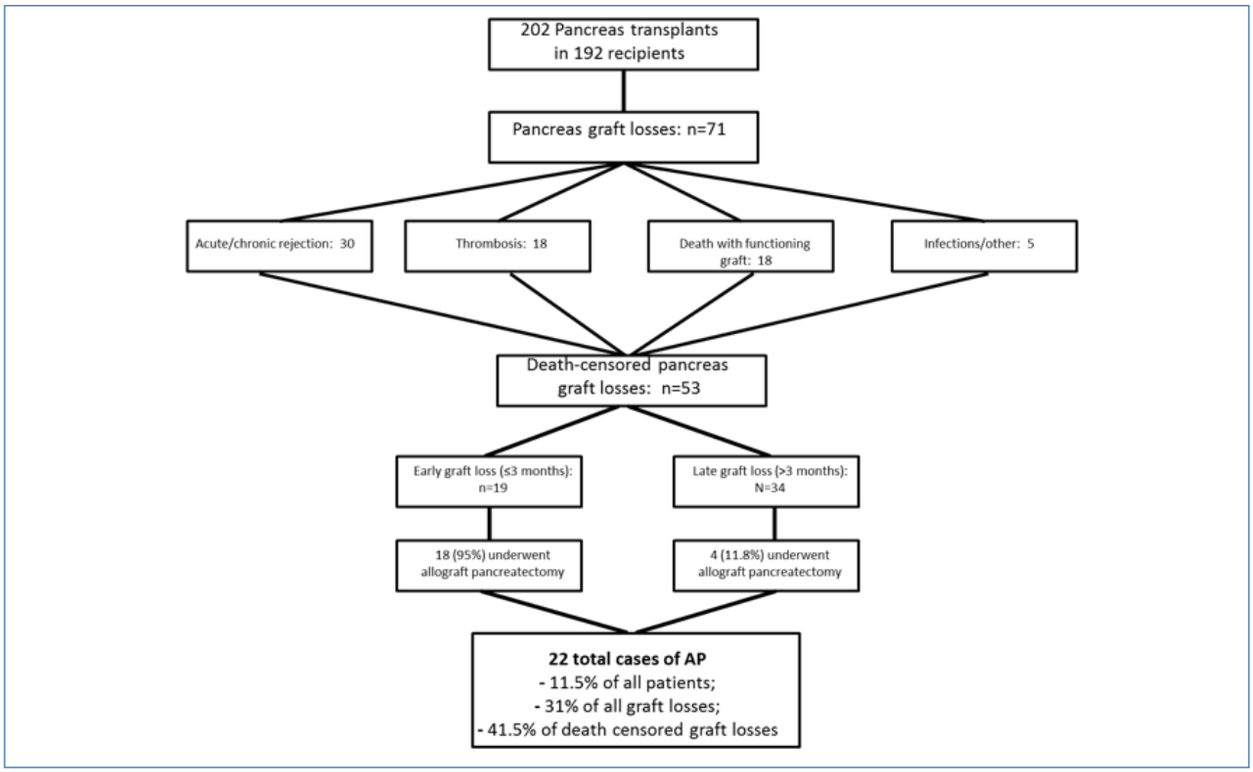

Figure 1: Flow diagram of pancreas graft loss leading to allograft pancreatectomy (see text for details).

thrombectomy or thrombolysis have contributed to early graft salvage following thrombosis, a finite (albeit low) risk of irreversible vascular thrombosis exists following PT and necessitates early AP.[4,5,10] Alternatively, late AP is uncommon and may be related to late thrombosis secondary to rejection or hypotension, withdrawal of immunosuppression because of severe infection or malignancy, a vascular or intra-abdominal catastrophe such as an enteric fistula, ruptured/infected pseudoaneurysm, or bowel obstruction/volvulus, an uncontrolled duodenal or pancreatic fistula, or to create space for another transplant.[3-5]

Limited recent data are available on AP. A study published in 1999 reported a 23% incidence of AP following PT and an AP rate of 53% following graft loss.[3] The incidences of AP were similar according to type and technique of transplant; 77% of grafts lost within 3 months of PT underwent AP, and 25% of pancreas grafts lost after 3 months resulted in AP. There were 5 early deaths and kidney graft losses related to AP. In our study, the overall incidence of AP (11.5%) and proportion of graft losses resulting in AP (31%) are lower than previously reported. The death-censored rates of AP following pancreas graft loss in the two studies are 67% and 41.5%, respectively. Additionally, our rate of AP for early graft loss (95%) is higher, but the rate of AP for late graft loss (11.8%) is lower than previously reported. Importantly, however, in the past 4 years, our incidence of AP is <5%, which may be related in part to more stringent donor and recipient selection and shorter cold ischemia times, resulting in less early pancreas graft loss secondary to thrombosis. Moreover, patient and kidney graft survival do not appear to be adversely affected by AP, since no early deaths or kidney graft losses occurred following AP. In contrast, previous studies have reported that early kidney graft loss following SPKT is associated with mortality and pancreas graft loss.[1,2,4]

In the past decade, the annual number of PTs performed in the US has steadily declined.[12] From 2004–2011, the overall number of SPKTs in the US declined by 10%; by contrast, PAK and PA transplants decreased by 55% and 34%, respectively.

Paradoxically, numbers of procedures have decreased at the same time that improvements in graft and patient survival outcomes allowed transplanting higher-risk patients. This national trend in decreasing numbers of PTs is related to a number of factors, including lack of a primary referral source, better diabetes care and management, changing donor and recipient demographics (particularly older age and more obesity), inadequate training opportunities, and increasing risk aversion because of regulatory scrutiny.[12] A national initiative is needed to "re-invigorate" SPKT and PAK transplants as preferred options for appropriately selected uremic patients taking insulin, irrespective of C-peptide levels or "type" of diabetes. Moreover, many patients may benefit from PA transplants because all categories of PT are not only life-enhancing but life-extending procedures.

Conclusion

Based on these results, we conclude that AP is most commonly performed for early pancreas graft loss from thrombosis. The incidence of AP is decreasing, and AP does not appear to adversely influence medium-term patient or kidney graft survival rates or preclude successful pancreas retransplantation.

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Case Files
of Wake Forest Baptist Medical Center

A Nagging Cough

Christin Lawler, M.D., Pediatrics
Leslie Ellis, M.D., Hematology and Oncology
Cara Haberman, M.D., Pediatrics – Hospital Medicine
Thomas Russell, M.D., Pediatric Hematology/Oncology
Tricia Lucin, M.D., Pediatrics – Hospital Medicine
Daniel Krowchuk, M.D., General Pediatrics and Adolescent Medicine

In **Case Files of Wake Forest Baptist Medical Center,** the clinical presentation of a real patient is described in stages to a panel of experts. The panel discusses the differential diagnosis, asks relevant questions, and explains their clinical thought process.

Case Presentation

Christin Lawler, M.D. **The patient is a five-year-old white girl who presented to Wake Forest Baptist Medical Center with cough, respiratory distress, and hypoxia.**

Dr. Haberman Given this child's age and presenting symptoms, we start thinking about infectious etiologies. Pneumonia and viral infections are at the top of the list. Fever is not mentioned, however, and a lack of fever would be unusual in these infections, so this makes you broaden your differential.

Dr. Lucin This is also a prime age for asthma exacerbations.

Dr. Russell That is a good starting place. We would certainly want to know whether this is a recurrent versus a first-time problem and whether the process is acute or chronic. If this is an otherwise healthy five-year-old girl with new-onset symptoms, an infectious cause would be first, second, and third on the differential.

The patient has had a month-long history of cough, which is sometimes productive with sputum. The cough happens mostly at night and it does wake her in the middle of the night. She was hospitalized three weeks ago with an atypical pneumonia, and her mother thinks she has not returned to her baseline state of health since that time. She was referred to the Emergency Department (ED) today by her allergist/immunologist, who measured her oxygen saturation in the low 90s and heard crackles on her pulmonary exam.

Dr. Russell Receiving subspecialty care by age five suggests that there is an underlying issue. We often have to be careful when considering the patient's history and defining the significance of what it meant for her to have pneumonia. By convention, pneumonia is a clinical diagnosis and requires auscultation and examination of the patient, and that can be validated with blood tests or x-rays to confirm the diagnosis. Many children are reported to have had recurrent pneumonia or recurrent infections but who are otherwise not concerning. Alternatively, a patient who has an immunologist at age five might suggest an underlying immunologic process or significant predisposition.

Dr. Haberman This is edging on the differential between acute and chronic cough. Some say it can be even six to eight weeks before it can truly be called chronic. Even some viral illnesses can persist with a cough for two or three weeks, but once it passes the four-week mark, most of us start thinking about a more chronic cause. As Dr. Russell said, how was she diagnosed with an atypical pneumonia? Was that from someone just listening to her? Did they hear crackles? Without knowing exactly what that was, it is difficult to say whether she had that illness and now has sequelae from that, or whether it was originally a misdiagnosis. The way she presents now, with oxygen saturation in the low 90s, is not overly concerning; certainly even healthy adults probably drop down there occasionally. Hearing crackles on an exam is definitely unusual. Even if she had atypical pneumonia three weeks ago, we would not expect her to continue having crackles for this long. Is there any mention of fever?

No mention of fever.

Dr. Haberman It is unusual to have a month of what is being called pneumonia and yet to have no fever. I would expect persistent fevers if she had such a severe pneumonia that it still has physical manifestations. The lack of fever makes me worry about atypical pneumonias, fungal infections, or underlying chronic lung pathology that we have yet to uncover.

Dr. Lucin When I am thinking about chronic cough in a child who may have pneumonia but who also has crackles, I want to know the location of those crackles. Are they diffuse or are they in a specific spot? Certainly, latent atrial septal defects can present later in life outside the infancy period, so she could be having pulmonary overload or circulatory overload causing those crackles.

Dr. Krowchuk I will add that, in this community, many of our patients are immigrants. We would want to know about her travel history or exposure to others who may have been incarcerated. You might think about tuberculosis, for example.

Question from audience **Does the fact that it is worse at night give you any ideas?**

Dr. Krowchuk I think that's a symptom that we often see in children who have asthma, and this is one symptom that we monitor to determine how well-controlled the asthma is. Coughing at night does not exclude other entities, but it certainly makes you wonder about the possibility of asthma.

To continue with her past medical history, she was a term infant born via spontaneous vaginal delivery. She had a normal newborn course with no NICU stay, and she was diagnosed with asthma two years ago. She currently takes Advair 115/21 and takes two puffs of that twice a day. She sees her allergy/immunologist for immunotherapy for her allergies to dust mites, she is on Singulair and Nasonex, and she takes albuterol PRN. She also has a history of acid reflux. When she was two years old, she was hospitalized for burns (on her chest, from a hot pot; the burns did not affect her airway at all), but otherwise she has had no hospitalizations and no surgical history.

To elaborate on her recent hospitalization, she was admitted on scheduled albuterol. She had an oxygen requirement of two liters during that stay. Her blood culture was negative and it was ultimately decided that she had an atypical pneumonia, so after one dose of ceftriaxone that she received in the ED, she was changed to a course of azithromycin that had been started by her pediatrician prior to her presentation. She had no other recent history of antibiotic use.

To clarify, she was put on asthma treatment for her recent hospitalization when she had the atypical pneumonia that was treated with azithromycin. Again, at that time, she had a two-liter oxygen requirement, and then she was weaned from the oxygen and discharged home. She has not been treated with any antibiotics or additional asthma medication at this point in time; she just walked in the door.

She lives with her mother, her mother's boyfriend, her younger brother, and her older sister. Her mother does smoke but says she smokes outside. The patient attends elementary school. The family history is positive for asthma, lung cancer, and prostate cancer in her maternal grandfather and asthma and emphysema in her maternal grandmother. Her mother, brother, and sister are all healthy.

Review of systems for this patient was significant for cough that worsens with activity and is worst at night. She has strabismus and hypermetropia, so she wears glasses. Otherwise, review of systems is negative.

On physical exam, the patient was at the tenth percentile for her height and her weight; her BMI was at the 28th percentile. Her blood pressure was 84/53, heart rate was 132, temperature was 97°F, and respiratory rate was 48. Her oxygen saturation on two liters of oxygen was 92%.

On her pulmonary exam, she had rhonchi and crackles bilaterally but on the right more so than on the left, and she had suprasternal retractions. It was noted that she had equal air exchange bilaterally. On her cardiovascular exam, it was noted that she was tachycardic for her age. Her exam was otherwise unremarkable.

Dr. Haberman There is a danger of taking this patient as she has been labelled. We could easily think that this is a patient who has asthma and is wheezing and simply treat her asthma. This is not the exam that we would expect in a child with asthma only. The crackles and rhonchi, especially with the asymmetry, the lack of wheezing, and the lack of a prolonged expiratory phase steer us away from treating asthma in this patient. It is easy to do that, though, when a child comes in and you hear the history and then make decisions based on the child's history. It is important to make sure that it actually fits with what you see in front of you. Here, the history does not fit with the patient's present condition; the asymmetry, the fact that rhonchi and crackles are the most prominent finding, and the degree of hypoxia are concerning. This is all unusual for asthma.

Dr. Russell Do you know what that medical term is when you make a decision and then stick with that decision? It is called anchoring, and it is common. It is easy to remember—you drop your anchor, you are stuck with that diagnosis, and you cannot move away from or broaden your differential. I wholly agree that the exam does not fit with what we would otherwise expect from an asthma exacerbation.

Dr. Ellis Keep in mind that the reason that Dr. Haberman and Dr. Russell can say that is because they understand the illness script of asthma and other pulmonary disorders. It is important to remember as you go through medical school not to learn just the facts, but to study the natural history of the disease. They are using their knowledge of the illness scripts of all these different disorders that we have on our differential diagnosis list and determining whether those match.

Dr. Russell We can consider the pathophysiology of asthma a bit more to understand this better. The way I usually counsel families is by explaining that asthma is a lung allergy. If you have inflammation in your lungs, the most common feature that we see is that patients inhale sufficiently, but they exhale insufficiently, and that causes the wheezing sound you hear clinically. Taking more time to exhale the air prolongs the second, expiratory phase of breathing. That combination—wheezing and prolonged expiration—is concerning. Additionally, a lung allergy is a parenchymal issue involving the entire lung, so the asymmetry does not fit that script. The constellation of symptoms that our patient has is more concerning for something either instead of or in addition to the asthma. Lastly, we absolutely know that children with asthma have inflammation at baseline, even if they are appropriately treated, and so if you have another underlying diagnosis that can explain the present symptoms, asthma certainly cannot be taken away. Asthma is something that this child has on a chronic basis and certainly might even contribute to toxicities or side effects that are co-occurring.

Dr. Lucin Another notable element is her small size. Perhaps that is simply her familial stature, but that, in combination with how much asthma therapy she requires at baseline, makes me wonder about something more chronic.

She is not known to have a history of chronic lung infections. Her only hospitalizations in the past were for asthma. The most recent one, which we discussed, was just a few months ago, and she had one other hospitalization for asthma prior to that.

Dr. Krowchuk Has she had interictal examinations that are normal?

There are none documented in the system, because her pediatrician is in the community, but her family reports that she has had normal exams and there have been times when she has been well, and she has had plenty of well child check-ups.

Dr. Krowchuk I want to make sure that this is not someone who has slipped through the cracks, who could have something like cystic fibrosis, for example, which would be responsible for chronic pulmonary infections.

Dr. Lucin Is there an exposure history? Is anything new or different? Did the family just move?

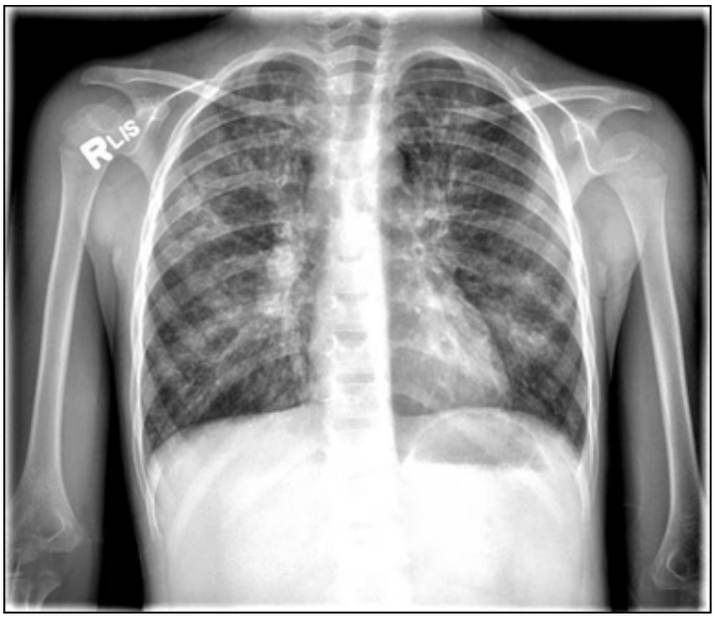
There have been no changes in their house, and they do have a pet, but it has been there for a while. She did start daycare recently, but nothing is really different, and there has been no international travel and no ill family members.

Dr. Haberman How about the grandmother with emphysema? Was that someone who smoked?

The relative with emphysema did smoke, and it was later in life, but the family could not remember the details.

Dr. Haberman I was just asking, because if it was someone who did *not* smoke, and it was early in life, we would start thinking about more intrinsic, genetic pathology, like an anti-trypsin deficiency or something similar.

This is the first chest x-ray that could be found in our system.



Dr. Haberman Although pneumonia is a clinical diagnosis, certainly for someone who has been in and out of the hospital many times, there should be more than one x-ray, so that you could compare and determine whether one is significantly worse and whether there are changes. Was it perfectly normal a year ago and now looks terrible?

Dr. Russell Also, children diagnosed with asthma deserve a chest x-ray, because there are a many anatomic abnormalities that can mimic asthma. Heart disease, anterior-mediastinal masses, or some other kind of process that explains what from a structural or parenchymal standpoint can mimic wheezing. Asthma is certainly the most common and prevalent rationale for wheezing in our population, so a chest x-ray is a high-priority test that we do, and then certainly any time when a patient is having an exacerbation like this or symptoms that persist, it is worthwhile to repeat tests and establish the patient's current status. These results are absolutely abnormal.

Dr. Lucin We prefer for our students to have a systematic way of looking at any sort of imaging study, and we look at a lot of chest x-rays, so we have some systematic ways to do this. Choose one and stick with it so you can be good at it. I prefer the ABCDEF method.

A stands for airway. You can pick out the trachea and follow it down to the bifurcation. It is relatively midline, perhaps a bit of rotation there, but no ill-defined borders.

B is for bones. We look at the clavicles and the ribs, and we check for any fractures or misalignment. We also want to make sure that the lucency of the bones is appropriate, and that comes with practice.

C is for cardiac silhouette. You can see that it is appropriately sized, about a third to half of the chest diameter. There is some blurring of the right heart border; it is ill-defined there.

D is for diaphragm. We want to make sure it is smooth, and there should be a bit of curvature to it, but not too much. Hers is fairly smooth, but also a bit hazy, as is everything else in this picture.

E is for everything else. Does she have a line, a tube, leads, or anything else?—she does not.

F is for lung fields. Her lung fields look awful. There is diffuse haziness throughout; there is no focal opacity, but there are numerous interstitial markings and cloudiness everywhere.

We will continue with a CBC.

WBC	19.6 x 10^9/L
Hemoglobin	1.8 g/dL
Hematocrit	34.9%
Platelets	365 x 10^9/L

Dr. Russell This looks reassuring. First, you want to see that all three cell lines have normal numbers. Starting with the white count, it is elevated, which draws us into the differential. Of note, in a normal patient without any inflammation or chronic issue, 20-25% of their marrow will have

a neutrophil reservoir, and this is important to have, because when you have an infection, your body needs to be able to react to it. In a patient with an infection, you will see an increased percentage of neutrophils, which is the marrow response to the stress of whatever provocation is occurring. The fact that the segments are not elevated is not that meaningful, because it is a broad number, but on average it should usually be about 50%. Beyond that, this patient does not have anemia—patients should never be less than about 11 to 11.5 g/dL with rare exceptions. Platelets are in the normal to upper normal range; it is not uncommon, especially in pediatric patients, to see reactive thrombocytosis. Again, an elevated platelet count tells us that the bone marrow is responding to some stress, whether the source is inflammation, trauma, or infection. Overall, this looks reassuring.

Dr. Haberman At this point, I would try to track down another x-ray for comparison, because obviously something is there, and whether it is acute or chronic changes the differential. She does not have a fever right now, although she does have a slightly elevated white count, and you can see something like that chest x-ray with atypical pneumonia, which she has obviously been diagnosed with, but if it is so chronic, then the x-ray doesn't really fit that picture. If we have another chest x-ray that shows it was better a while ago or that it has always been there, it does help to give a sense of disease progression. In the meantime, you sort through your differential and think of what other labs you want to obtain.

Dr. Krowchuk I would add that the interstitial pattern you see is so bad as to suggest chronic lung disease, so suddenly something like cystic fibrosis or chronic aspiration move higher in your differential.

Dr. Russell To return to a point from before, she is quite small, at about the tenth percentile. Is that consistent with the rest of her family?

Her mother does not appear to be in the tenth percentile, and her siblings were not present but are definitely above the tenth percentile, as well.

Dr. Krowchuk One thing we consider is whether the child's height and weight are justified based on her genetic potential. Calculating midparental height is one way to determine whether her short stature is consistent with her genetic capability. In this case, it appears that her size is not justified by her genetics, which also makes us consider a chronic disease.

At this point, her aunt has come to the hospital and is telling you that the patient has actually had a cough, nasal and chest congestion, and rhinorrhea more in the past two years. The time course is therefore more prolonged than was initially presented to you, although we've already reached that point through our reasoning. She was diagnosed with allergy to dust mites based on skin testing a year and a half ago. She started asthma and allergy therapy and improved for a while, and then her symptoms worsened when she started kindergarten.

Dr. Haberman When she got worse upon starting kindergarten, was she was catching more colds, or was she consistently worse on a daily basis?

It was difficult to tell, but it seemed more of a chronic problem, along with more frequent infections.

Dr. Haberman Was she getting infections that she needed antibiotics for?

She did not have any antibiotics; her asthma therapy was increased.

Dr. Haberman Just thinking about recurrent infections, certainly we see other immunodeficiencies, but it sounds like these are more viral-sounding, or maybe a chronic bacterial infection.

Dr. Krowchuk To develop this list further, a ciliary defect would explain pulmonary disease and sinus infections.

Would you request any further labs or tests?

Dr. Haberman We request a sweat test.

She did have a sweat test. The normal range is 1-40 mmol/L. We tested from both arms, and her results were 114 mmol/L on the left and 121 mmol/L on the right, which were consistent with a diagnosis of cystic fibrosis.

Dr. Haberman To explain the sweat test, when you consider the pathophysiology of cystic fibrosis, it centers on a chloride transporter. Everything that happens downstream of that is because of one protein that normally makes chloride go from one side of the cell to the other. A defective chloride transporter causes problems in the lungs and in the gastrointestinal tract. In the skin, what it means is that the chloride cannot enter the cells, so more sodium and chloride stay in the sweat. It is one of the best tests. For cystic fibrosis, there are so many genetic defects that can produce the disease, so even if you run a large panel with hundreds of them, you're still going to miss some, so this is a good test, because it is testing the actual mechanism that is wrong in the disease.

Dr. Ellis How does that affect the lung?

Dr. Haberman In the lungs, the opposite problem is occurring. The cells are unable to pump the chloride into the alveoli. Water always follows salt, so if salt is pumped out, water follows and thins everything. When salt and water are not pumped out, the mucus in the alveoli, which is made up of cell debris, neutrophils, and macrophages, grows thick and sticky, resulting in obstruction, because of the difficulty in clearing such thick mucus. The mucus then sits in the lungs and creates an environment that favors infection.

Dr. Krowchuk I am a generalist, so this would be the point at which I would go back to my references to refresh my memory, because I don't see children with cystic fibrosis every day.

A sputum culture from this hospitalization did grow *Pseudomonas*, α-hemolytic and non-hemolytic *Streptococci*, and *Staphylococcus*.

Dr. Russell Where was she born?

She was born in North Carolina.

Dr. Russell Was there a reason why she didn't get her newborn screening?

She did undergo newborn screening, and everything was normal. She was born in 2007, before cystic fibrosis was added to the newborn screening.

Dr. Ellis We do still miss cases, even with the newborn screening. Can you also comment on whether you would expect to see this many bacteria in cystic fibrosis? Is that typical?

Dr. Russell Yes, very much so.

Dr. Haberman The type of bacteria is also a clue. Most average, healthy people do not have *Pseudomonas* in their lungs, so that is one type of bacteria indicating chronic disease. Also, the vast amount of bacteria is common in cystic fibrosis.

To explain a bit about newborn screenings, it is good to know what your state does and does not test. North Carolina did not screen for cystic fibrosis until April 13, 2009, so that is why this patient was missed. Everyone picked up on the family history of asthma and emphysema, and it is significant for one family to have so much pulmonary disease. We were actually one of the last states to add cystic fibrosis to the newborn screening. What it measures is immunoreactive trypsinogen (IRT), a pancreatic enzyme that is elevated in patients with cystic fibrosis. Elevated IRT suggests that exocrine function of the pancreas may be compromised. Patients within the top 5% of elevated IRT have DNA testing to check the CFTR gene, which is the affected gene in cystic fibrosis. The most common defect is in CTFR-ΔF508, and that is defect that this patient has, so we did DNA testing to confirm.

Abnormal results from the newborn screening are sent to the pediatrician, and then the patients undergo confirmatory testing. Everyone still undergoes a sweat test, because it is the biggest catchment group for cystic fibrosis and it is a quick test.

Dr. Ellis Would someone on the faculty panel like to comment about the genetics of cystic fibrosis and how that relates to the family history that this patient has?

Dr. Lucin The most common mutation is ΔF508. Often there will be a family history of pulmonary disease, yet sometimes this can occur de novo. There are many other mutations that can cause cystic fibrosis.

Question from audience **Why did it take so long for states to adopt cystic fibrosis in newborn screenings?**

Dr. Russell It is very much legislatively based, and certain states are more proactive and see the benefits. There are criteria for inclusion, and we try to include diseases in newborn screening that have some element of potential treatment or possible intervention soon in life, and we try to avoid diseases for which we lack good treatment options for families. It is built on a state-by-state basis, which is a bit of a challenge. Some of us have strong opinions; I think it should be federally mandated, but we have reached the point now where most states are aligning their resources.

Case Reports

Adult Tethered Cord Syndrome Presenting as Piriformis Syndrome: A Case Report

Brian T. Muffly, M.D.[1], Bennett R. Gardner, M.D.[2], Christopher T. Whitlow, M.D., Ph.D.[3], Christopher M. Miles, M.D.[4]

Abstract

A 36-year-old male physician experienced sudden-onset back and buttock pain. After several weeks he was diagnosed with adult-onset tethered cord syndrome (TCS). The tethered cord was surgically reduced, and the patient experienced near-complete symptomatic relief postoperatively. This case illustrates the variable presentation of adult-onset TCS and the incompletely understood role of surgical management for this condition.

Introduction

Tethered cord syndrome is a disorder in which the spinal cord is abnormally anchored, leading to increased tension on the caudal portion of the cord. It presents with a constellation of symptoms — most commonly pain, motor weakness, and bladder dysfunction — along with radiologic findings demonstrating either a normally or abnormally positioned conus medullaris.[1-3]

Case Report

A 36-year-old man with a two-year history of infrequent urge urinary incontinence initially presented to an urgent care center with sudden-onset, right-sided low back pain and radicular symptoms upon waking. The sharp, shooting pain radiated to the right buttock and posterior thigh. Prior to this event, the patient regularly engaged in vigorous physical activity without discomfort or impairment. There was no history of trauma. Pain was aggravated by sitting, bending, and ambulating, and was relieved in the supine position. An injection of intramuscular ketorolac and corticosteroid administered at the urgent care center provided temporary relief.

At subsequent evaluation by physiatry, the patient was diagnosed with sacroiliitis and was given a targeted injection of corticosteroids. The injection, along with physical therapy, nonsteroidal anti-inflammatory drugs, and acetaminophen-hydrocodone, provided temporary, moderate symptomatic relief. Over several weeks, his symptoms progressed to include periodic right foot numbness, right testicle pain, and right lower extremity weakness. The patient reported a single episode of urinary incontinence without an urge component. Given these symptoms, magnetic resonance imaging (MRI) was obtained and demonstrated a small disc bulge at L5-S1 without evidence of stenosis.

[1] Department of Orthopaedic Surgery and Sports Medicine, University of Kentucky College of Medicine, Lexington, KY

[2] Department of Obstetrics and Gynecology, Wake Forest School of Medicine, Winston-Salem, NC

[3] Department of Radiology, Wake Forest School of Medicine, Winston-Salem, NC

[4] Department of Family and Community Medicine, Wake Forest School of Medicine, Winston-Salem, NC

Address Correspondence To:
Christoper M. Miles, M.D.
Department of Family and Community Medicine
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, NC, 27157

Despite benign findings on MRI, the patient could not perform any of his work duties. Walking was difficult and required a cane. He sought further evaluation from primary care sports medicine. Examination of the back showed impaired mobility with flexion of 20 degrees and extension of 15 degrees. A positive Trendelenburg sign, positive piriformis testing, and re-creation of symptoms with the figure four maneuver were all observed. Both straight leg raise as well as flexion, abduction, and external rotation (FABER) tests were negative. Right quadriceps, hamstrings, and tibialis anterior demonstrated 4/5 strength. Sensation was intact. Based on these results, piriformis syndrome was diagnosed. The patient was prescribed cyclobenzaprine and additional physical therapy exercises, along with his prior treatment regimen.

A follow-up visit with physiatry showed further deterioration. The patient was given a third injection of corticosteroids, this time at the site of the L5-S1 disc bulge. After two weeks without improvement, the patient was seen by an orthopedic spine specialist. On exam, lumbar extension elicited severe pain. Hip range of motion was normal. Patellar and Achilles reflexes were 2+ bilaterally with normal Babinski responses. Sensation was intact throughout lower extremities, although the patient reported slightly decreased sensation on his right foot. Both FABER and straight leg tests were positive bilaterally. Given the concern for progressive disc herniation, a repeat MRI was ordered which revealed unchanged severity of disc extrusion. In addition, a low-lying conus medullaris terminating at L2-L3 and fatty infiltrate in the filum terminale were seen (Figure 1). Although similar findings were mentioned in the body of the initial MRI report, the concern for disc pathology overshadowed the potential for adult tethered cord syndrome. A literature search conducted by the patient revealed these findings to be consistent with a tethered spinal cord. He sent a review article on adult-onset tethered cord syndrome to primary care sports medicine and orthopedics, who arranged a consultation with neurosurgery.

Neurosurgery concluded that presentation and imaging were consistent with adult TCS. The patient then underwent an L5-S1 laminectomy with resection of a fatty filum lipoma and reduction of tethered spinal cord. Intraoperative

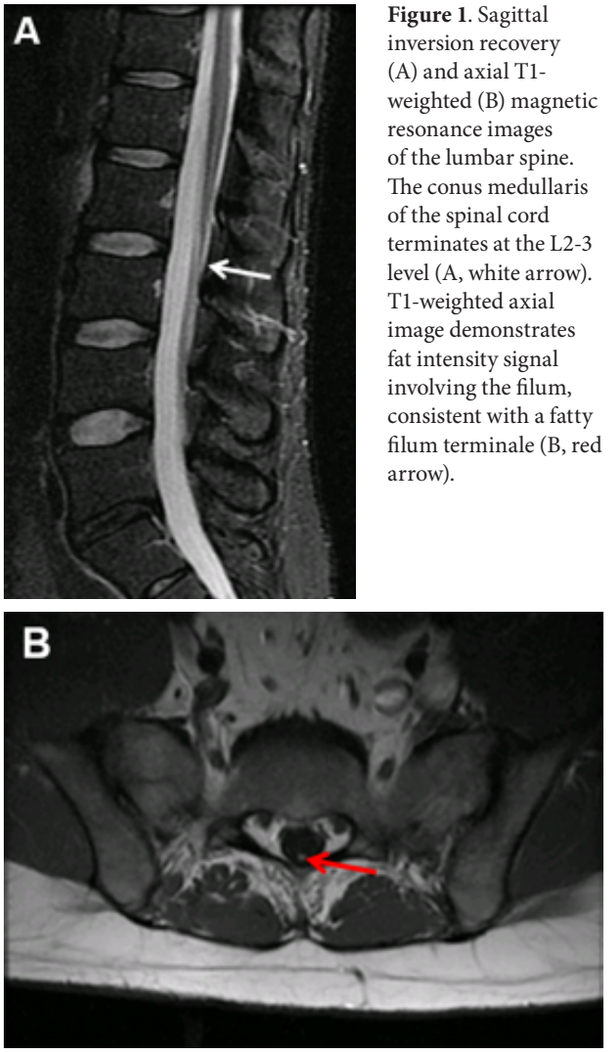


Figure 1. Sagittal inversion recovery (A) and axial T1-weighted (B) magnetic resonance images of the lumbar spine. The conus medullaris of the spinal cord terminates at the L2-3 level (A, white arrow). T1-weighted axial image demonstrates fat intensity signal involving the filum, consistent with a fatty filum terminale (B, red arrow).

evaluation and surgical pathology of the fatty filum terminale confirmed findings consistent with tethered cord. At a 90-day postoperative appointment, the patient showed marked improvement. He could walk normally without an assistive device and had returned to work duties. Although he reported mild residual right back and buttock pain, he denied numbness, weakness, or urinary incontinence. He reported continued progress with physical therapy.

Discussion

The constellation of signs and symptoms potentially associated with adult TCS can be dermatologic, urologic,

gastrointestinal, neurologic, and orthopaedic in nature. Some have concluded that the degree of cord traction is the predominant factor related to the onset of symptoms.[4] Patients with less severe traction remain asymptomatic in childhood, and present with dysfunction later in life. Symptomatology may also mimic lumbar degenerative disease.[1] Because the diffuse weakness experienced by our patient did not fit any particular radicular pattern, the presentation was considered pain-mediated rather than a true myelopathy.

Though our patient initially presented with what appeared to be piriformis syndrome, several case reports detail other presentations of adult TCS, including refractory diarrhea, unilateral calf atrophy, and severe chest and back pain.[5-7] Components of the history may be equally vague and varied. Trauma, pregnancy and childbirth, straight leg exercises, sexual intercourse, and prolonged sitting have all been noted as factors precipitating the onset of symptoms.[1,8] Although variably defined in the literature, piriformis syndrome is a non-discogenic cause of sciatica resulting from sciatic nerve impingement through or around the piriformis muscle. Neurodiagnostic studies are usually normal and are used to rule out other etiologies for sciatica. As was true for this patient, reports exist describing pain and/or paresthesias in the back, groin, buttocks, posterior thigh, calf, and foot.[9] Individual physical exam maneuvers differ greatly in their sensitivities and specificities for detecting piriformis syndrome. There are currently no gold standard tests to diagnose the pathology.[10]

The role of surgical management in adults with TCS remains incompletely understood.[11] Our patient experienced immediate symptomatic relief postoperatively. Several authors report pain as the most responsive symptom to surgical untethering, while urinary dysfunction is less responsive.[12,13] Differences in surgical success are believed to correlate with the severity and chronicity of the condition. Thus, prompt diagnosis and operative treatment of adult TCS may decrease symptomatic progression and maximize satisfactory surgical outcome.[13]

This case highlights the variable presentation of adult-onset TCS and the incompletely understood role of operative management. Aside from infrequent urinary incontinence, our patient had no prior symptoms of TCS, despite maintaining a high level of physical activity. His presentation stands in contrast to numerous reports describing a subtle, insidious course. Given the lack of specific clinical or structural features, the diagnosis of adult-onset TCS requires a high index of suspicion. Adult-onset TCS should be considered in patients unresponsive to treatment for more common pathologies, especially in those patients with findings that do not follow myotomal and dermatomal patterns. Moreover, clinicians should be aware that a normally-positioned conus medullaris on imaging does not preclude the diagnosis of TCS. We encourage physicians to diagnose and treat patients based on clinical presentation, physical exam findings, treatment response, and, where appropriate, imaging. Large prospective studies are needed to clarify diagnostic criteria for adult-onset TCS, as well as to identify patients most likely to experience surgical benefit.

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Case Reports

Cardiac Arrest and *Mycoplasma Pneumoniae* Infection: An Atypical Presentation

Tiffany R. Earle, M.D., Jason A. Bonomo, M.D., Ph.D., Olivia Gilbert, M.D., Ashleigh Owen, M.D., Barbara Pisani, DO

From the Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC

Address Correspondence To:
Tiffany Earle, M.D.
Department of Internal Medicine
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, N.C. 27157
tearle@wakehealth.edu

Introduction

Mycoplasma pneumoniae has been associated with numerous extrapulmonary manifestations, including myocarditis, pericarditis, and thrombosis.[1] Many of these complications may occur in the absence of pneumonia, the usual clinical manifestation of infection with *M. pneumoniae*.[1] Although venous and arterial thromboses have been previously reported, intracoronary thrombosis has not been described in previous published reports.[2-8] We report the case of an adolescent who presented with cardiac arrest, possibly due to intracoronary thrombosis associated with acute *M. pneumoniae* infection.

Case Report

A 17-year-old female high school softball player presented to the ED with 30 minutes of sudden-onset left-sided chest pain, dyspnea, nausea, and palpitations. She additionally reported one day of left arm swelling. Past medical history was notable for asthma. Family history and sociodemographic characteristics were unremarkable. While undergoing evaluation in the ED, the patient experienced ventricular fibrillation and cardiac arrest, which responded to a single defibrillation.

On admission, the physical exam revealed fever (38.3°C), tachycardia (136 bpm), tachypnea (38 breaths/min), diffuse wheezes on lung auscultation, and bilateral upper extremity edema, which was worse on the left. The initial electrocardiogram revealed a normal sinus rhythm without ST segment abnormalities. Cardiac biomarkers were initially negative (troponin <0.006 ng/mL), but later peaked at 34.8 ng/mL. Creatinine kinase-MB (166.5 ng/mL) and myoglobin (2809 ng/mL) levels were also elevated. Other notable laboratory values on admission included white blood cell count (22,000 cells/mm^3) with absolute neutrophilia (20,500 cells/mm^3). Hemoglobin, platelets, and international normalized ratio were within normal limits. A urine drug screen was negative and a respiratory virus panel was also unremarkable. Computed tomography of the chest with contrast ruled out pulmonary embolism or aortic pathology. However, it did reveal diffuse bilateral airspace opacities, slightly worse in the right upper lobe, which were suspicious for pneumonia. A post-resuscitation electrocardiogram revealed inferior lead ST segment elevation (Figure 1) that quickly resolved. An echocardiogram revealed severe global hypokinesis of the left ventricle

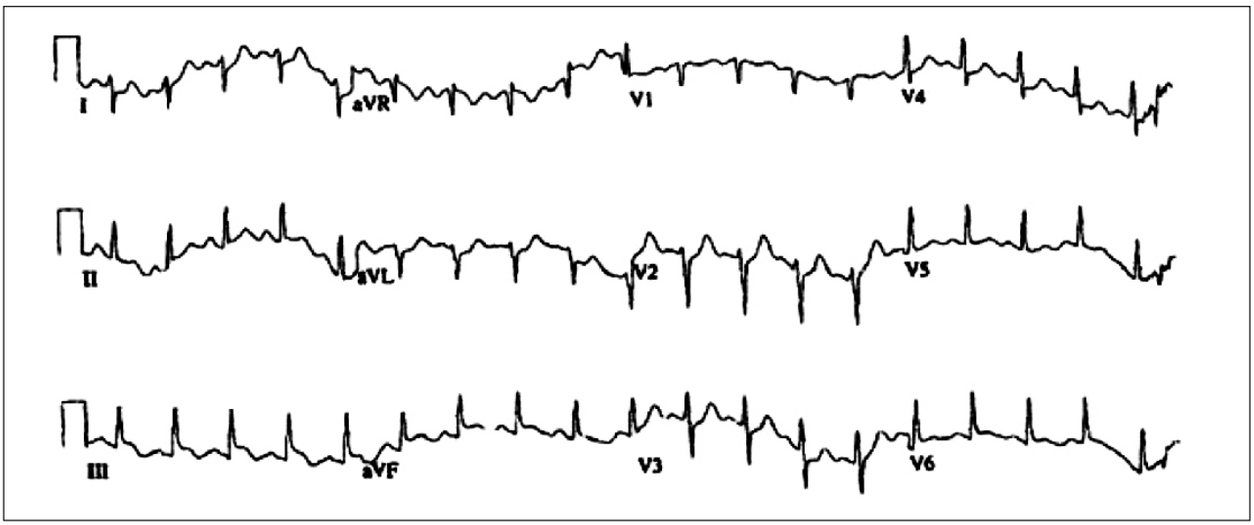


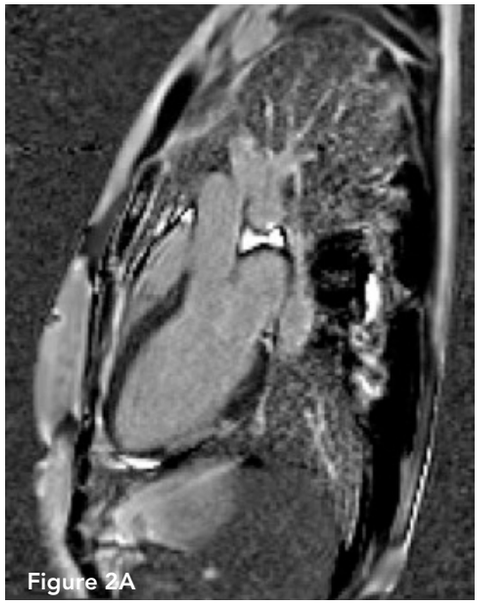
Figure 1. Post-resuscitation electrocardiogram, revealing inferior ST-segment elevations.

with left ventricular ejection fraction (LVEF) of 15% and no evidence of intraventricular thrombus.

Due to acute respiratory failure and cardiogenic shock, the patient required intubation, vasopressor and inotropic support, and veno-arterial extracorporeal membrane oxygenation (ECMO). Empiric doses of vancomycin and piperacillin/tazobactam were initiated, given the patient's fever and leukocytosis. Myocardial infarction was thought unlikely due to the resolution of ST-segment changes without the usual evolutionary changes, lack of focal wall motion abnormalities, and suspicion of myocarditis with a pseudoinfarction pattern on the ECG.

Because myocarditis was the favored diagnosis based on the initial echocardiographic findings, an urgent endomyocardial biopsy was performed at the time ECMO was begun. Hematoxylin and eosin staining of biopsied tissue revealed interstitial edema, but no evidence of lymphocytic infiltrates or multinucleated giant cells. After 4 days on ECMO support, the patient was decannulated and extubated. After a second echocardiogram, the patient's LVEF improved to 50%. A cardiac magnetic imaging (CMR) study was then obtained, which revealed nearly transmural late gadolinium enhancement in the mid-posterior wall of the left ventricle, raising further suspicion for focal myocarditis (Figure 2). Doppler ultrasound of all 4 extremities on hospital day 1 revealed superficial thrombophlebitis of her bilateral cephalic veins. Exhaustive serologic testing for viral and bacterial causes of infection were remarkable only for positive *M. pneumoniae* IgG (2.67) and IgM (1013 U/mL) antibodies (obtained by enzyme immunoassay) prompting de-escalation of antibiotics to doxycycline. Soon after, she was discharged home to complete a two-week course of doxycycline.

Because the patient wished to resume playing competitive softball, she returned three months later, and an adenosine perfusion CMR was performed for risk stratification. The study revealed a fixed perfusion defect and ongoing nearly transmural late gadolinium enhancement in the mid-posterior wall consistent with a completed infarction, which ruled out myocarditis (Figure 2B). The coronary angiogram clarified that atherosclerotic coronary artery disease had not been the underlying cause of cardiogenic shock. In light of the bilateral cephalic vein thrombophlebitis, we concluded that the patient had likely experienced a transient *Mycoplasma*-induced coronary artery thrombosis, with subsequent infarction of the left ventricular wall.



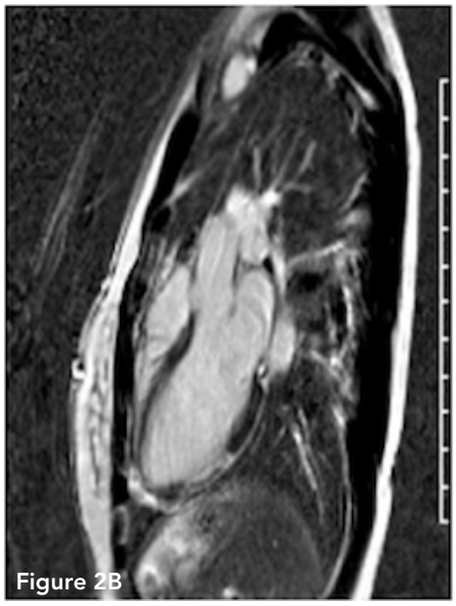


Figure 2. A) Cardiac magnetic resonance imaging (CMR) with segmented phase sensitive inversion recovery. The three-chamber view revealed a left ventricular ejection fraction of 51%, left ventricular mid-posterior wall akinesis, and late gadolinium enhancement. **B)** Repeat CMR 3 months later. LVEF was 53% and persistent left ventricular mid-posterior wall akinesis were observed.

Discussion

Venous and arterial thromboses associated with *M. pneumoniae* infection have been reported in the literature and include deep vein thromboses, pulmonary emboli, paradoxical brain embolism, cerebral artery thrombus, and aortic thrombus.[1-9] Intracardiac thromboses of the right and left ventricles have also been reported, but are rare.[10-12] Involvement of the coronary arteries is not well documented. Coronary plaque rupture related to *M. pneumoniae* has been documented in the setting of co-infection with *Chlamydia pneumoniae*,[14] but myocardial infarction in the setting of normal coronary arteries associated with *M. pneumoniae* alone has not been described.

Although the pathophysiology is poorly understood, several mechanisms behind *M. pneumoniae*-associated thrombosis have been proposed. These include 1) inflammatory cytokines induced by lipoproteins in the bacterial cell membrane, causing local vasculitis or thrombosis in the absence of systemic hypercoagulability, 2) immune modulation via cross-reactivity between bacterial and human cells, and 3) bacteria-mediated vasculitis and thrombosis.[1] Others also have described transient elevations of antiphospholipid antibodies [aPL]; (e.g., anticardiolipin and lupus anticoagulant) leading to activated protein C resistance as a possible mechanism.[3,4,10,12,13] In our case, intracoronary thrombosis could have been the result of a temporary hypercoagulable state secondary to an increase in aPL antibodies or direct invasion of the coronary vasculature as a result of focal vasculitis, with the latter being the favored mechanism for a *M. pneumoniae*-associated cerebral artery thrombus.[9]

This case is a rare presentation of possible intracoronary thrombosis associated with *M. pneumoniae* infection leading to myocardial infarction, cardiac arrest, and cardiogenic shock. Genetic pro-thrombotic susceptibility may have been contributory; however, the patient's age and lack of personal or familial cardiac risk factors, hematologic disease, or illicit drug abuse render other causes of cardiac arrest unlikely. Although initially thought to be clinically insignificant, the short-lived inferior ST-segment elevations on the post-cardiac arrest ECG represented a true myocardial infarction based on the CMR results, possibly due to a transient intracoronary

thrombus. Moreover, the concomitant superficial bilateral upper extremity thrombophlebitis correlates to the patient's initial complaint of left upper extremity edema and is consistent with previously documented cases of *Mycoplasma*-induced thromboses. Finally, the negative endomyocardial biopsy and the persistence of late gadolinium enhancement on the CMR scan three months post-cardiac arrest is consistent with a completed infarction rather than focal myocarditis.

The relationship between *M. pneumoniae* infection and myocardial infarction deserves further study. While this association is rare, infection with *M. pneumoniae* should be considered in patients under 40 years old who present with myocardial infarction and signs of infection without typical risk factors for coronary artery disease.

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Case Reports

Congenital Pulmonary Airway Malformation in an Adolescent Boy: The Timing of Medical Versus Surgical Management

Laura Tran, M.D. and Sean Ervin, M.D., Ph.D.

From the Department of Pediatrics, Wake Forest School of Medicine, Winston-Salem, NC

Address Correspondence To:
Sean Ervin, M.D., Ph.D.
Department of Pediatrics
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157
servin@wakehealth.edu
Phone: 336-713-8733

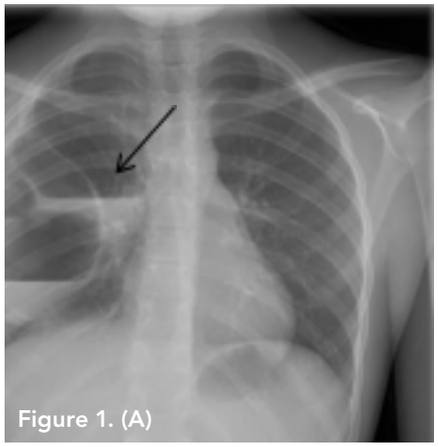
Introduction

Bronchopulmonary malformations (BPM), also known as congenital lung abnormalities, have an estimated incidence of 1 in 2,000 to 1 in 2,500 live births. The most common type of BPM is congenital pulmonary airway malformation (CPAM), accounting for nearly 40% of cases of BPM with an estimated incidence of 1 in 10,000 live births.[1] The majority of CPAM (90%) are found via prenatal ultrasounds or post-natal imaging in a symptomatic newborn.[2] However, some instances of CPAM remain asymptomatic at birth and are not discovered until the patient becomes symptomatic, typically manifesting with repeated lung infections, bronchiectasis, lung abscess, pneumothorax, and/or malignant transformation.[3] These symptoms usually occur in early childhood, but rarely the initial presentation can be found in adolescents or adults. In this situation, the most effective management strategy is not well established.[4] We report our experience with a 12-year-old boy who presented with fever and cough and was ultimately diagnosed with an infected multi-cystic CPAM. We were confronted with the dilemma of medical management versus a surgical approach and the optimal timing of each.

Case Report:

A previously healthy 12-year-old boy with no significant past medical history and described by his mother as "athletic," presented with six days of fever, fatigue, and a mild, non-productive cough. Physical exam revealed diminished right-sided breath sounds. Chest x-ray and subsequent chest CT revealed several, non-communicating, large lucent thin-walled lesions in the right lung with air-fluid levels and no surrounding airspace disease (Figure 1).

The patient was hospitalized and treated with intravenous (IV) vancomycin and ceftriaxone. Additional work-up was signficant for elevated C-reactive protein (172 mg/L) and white blood cell count (13,900/microliter). Urinalysis, blood uric acid, and LDH (as screening modality for carcinoma) were normal. Based on imaging, clinical presentation, and physical exam, the leading diagnosis was infection of a previously undiagnosed congenital pulmonary airway malformation (CPAM). Based on recommendation from the pediatric Infectious Disease team, the antibiotic regimen was switched to IV vancomycin and ampicillin/sulbactam to include anaerobic coverage. Pediatric surgery consultants recommended no immediate surgical intervention, but



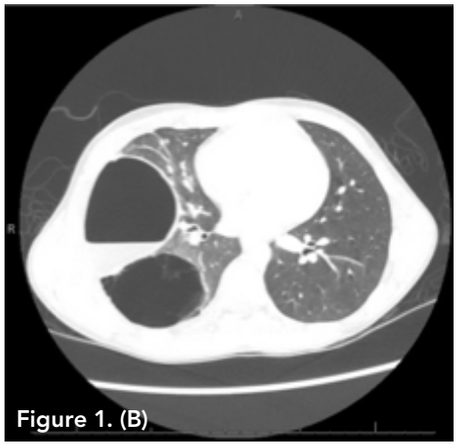


Figure 1. (A) Initial chest x-ray. Black arrow indicates multi-cystic lesions and air-fluid level. **(B)** Chest CT image. Note lack of parenchymal disease surrounding the cystic lesions and prominent cystic fluid.

indicated that lobectomy would likely be necessary once the present febrile illness had resolved.

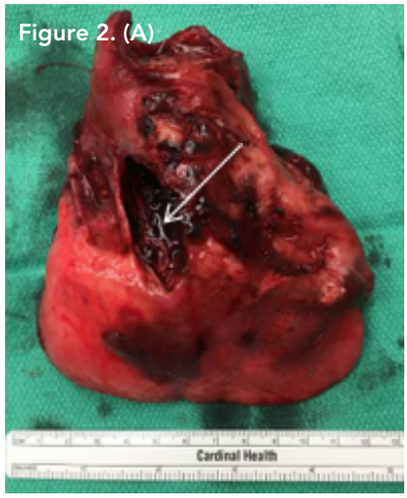
Despite broad-spectrum antibiotic coverage, the patient continued to have multiple spikes of fever daily (up to 103˚F), cough, and a persistently elevated C-reactive protein and white blood cell count. Frequent testing for other sources of fever, including recurrent blood and urine cultures, abdominal ultrasound, echocardiogram for possible endocarditis, urinary system/renal ultrasound, PPD, Histoplasma, Bartonella, Blastomyces, and Cryptococcal testing were all negative. Repeat chest x-ray after 14 days of IV antibiotics revealed an apparent increase in fluid in the pulmonary cystic lesions, with posterior airspace opacification and a small right pleural effusion. Given the lack of clinical improvement and worsening of the chest x-ray findings, on day 16 of hospitalization the patient underwent surgery for a right lower lobectomy via thoracotomy (Figure 2).

Figure 2 demonstrates the gross pathology of the right lung (Panel A) after the lobectomy and post-operative chest x-ray (Panel B). The pathologist reported the gross specimen as demonstrating "two distinct cavities. One cavity is lined by *benign respiratory epithelium;* the second cavity is lined by fibrous tissue with prominent acute and *chronic inflammation*". The postoperative chest x-ray (Panel B) demonstrated expected post-surgical volume loss with elevation of the right hemi-diaphragm, haziness of the right mediastinal border, right basilar consolidation, and the presence of a thoracostomy tube. While this is not a normal chest x-ray, it is much improved over the pre-operative x-ray (Figure 1, Panel A). The final pathologic diagnosis was cavitary bronchiolitis obliterans organizing pneumonia, a pathologic finding associated with numerous primary conditions including idiopathic, post-infectious, and drug-related conditions.[5] Based primarily on the benign nature of the epithelium, the size of the cysts, and the absence of other congenital anomalies in this patient, these lesions likely represent Type I cysts in the classification scheme of Stocker.[6]

The patient did well postoperatively and was transitioned to oral amoxicillin/clavulanate and oral sulfamethoxazole/trimethoprim. Tissue samples from the lobectomy did not grow any organisms, and he completed a total of 21 days of antibiotic therapy. He continued to have intermittent low-grade fevers postoperatively, but 6 days after surgery was determined to be stable enough to be discharged. The patient was seen in the Pediatric Surgery outpatient clinic 3 weeks after discharge. He had been afebrile and doing well. The follow-up chest x-ray revealed a small right pleural effusion, which was improved from the chest x-ray 3 weeks earlier.

Discussion

Since CPAM is typically discovered prenatally or soon after birth, this case was rare as the patient was 12 years old when he initially presented, and he had no prior illness. Although this was this child's first pulmonary infection, recurrent chest infections are often the presenting complaint in adolescent



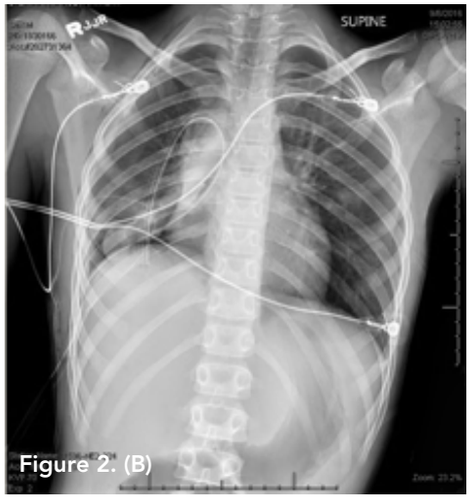


Figure 2. (A) Lobectomy specimen. White arrow indicates cavitary lesion of CPAM. **(B)** Post-operative chest x-ray.

and adult patients with CPAM. There are reports in the literature of late presentations of CPAM, either discovered in the context of recurrent infections or as an incidental finding on a chest x-ray obtained for other reasons.[7] A 2006 report[8] estimated a total of 36 adult cases reported, ranging from 17–64 years of age. By 2016, that number had increased to 60 reported cases in the literature.[6] Despite this relative increase in the numbers of reported adult cases, the appropriate management of a pediatric patient remains patient-specific. In our case, surgery and bronchoscopy were initially deferred due to the intraoperative infectious risks. In the post-natal patients, a surgical approach may be optimal when they are asymptomatic. In the meta-analysis by Kapralik et al[9] the risk of postoperative morbidity in symptomatic patients at the time of surgical intervention compared to asymptomatic patients was significantly higher (odds ratio 4.6). Similarly, the complication rate in symptomatic patients was 32% compared to 10% in asymptomatic patients.

Our initial approach was treatment with broad-spectrum IV antibiotics and a planned later lobectomy based on the increased risk of postoperative morbidity and complications.[9] While there is no clear consensus on the optimal timing of surgery, a minimum of 4 weeks after resolution of the acute infection was suggested by pediatric surgery consultants. Although lobectomy is recommended for all patients with CPAM due to a tendency towards malignant transformation in these lesions[10], the appropriate management of the asymptomatic patient with a known CPAM remains controversial. One line of thought is that early resection of CPAM is indicated for diagnostic certainty, as CPAM mimics may be a carcinoma. A second reason for early resection is to prevent complications such as malignant transformation or complicated infection, and a third is to obviate the problem of long-term follow-up for asymptomatic lesions.[11] On the other hand, the actual risk of malignant transformation is unknown and there is an intrinsic risk associated with surgical resection. The risk for future potential symptoms (such as infection) is undefined, and to obviate unnecessary exposure of children to surgical risk, asymptomatic patients with CPAM should be medically observed. Furthermore, there may be an increased surgical risk during an infective episode, such that the optimal timing for surgery is when the patient is asymptomatic. The natural history of CPAM is not known, and it is reasonable to opt for medical observation.[12] Our patient survived 12 years without complications and did not have significant complications from surgical resection during an infective episode, supporting the concept of a period of medical observation for the asymptomatic patients with CPAM.

Bronchoscopy and percutaneous fluid sampling were both considered as ways to test for the causative organism and tailor antiobiotic therapy accordingly. However, the consulting pulmonologist did not support these procedures, due to the risk of pneumothorax and the possibility of seeding the lung with infected fluid. Ultimately, in a multi-disciplinary meeting involving the Pediatric Hospitalist and Infectious Disease teams and surgical consultants, it was agreed that given the lack of improvement after 2 weeks

of IV antibiotics, recurrent venipuncture, placement of a percutaneous intravenous central catheter, and non-diagnostic laboratory testing, lobectomy was the best course of management. Our patient underwent surgical resection via thoracotomy, but there has been a recent move towards the use of minimally invasive surgeries via thoracoscopy to avoid some potential complications of an open surgical approach, including shoulder girdle weakness, chest wall deformity, loss of breast volume, and scoliosis. Compared to thoracotomy, a minimally invasive surgical approach provided comparable 30-day outcomes and safety in the surgical management of CPAM, and it could be considered in future cases.[13]

No clear data exist on the optimal duration of antibiotic therapy before surgical management in adolescent or adult patients presenting with CPAM. However, the experience of Jhun et al[8] is informative. They report on 19 adult patients with CPAM who were initially treated with a median duration of 22 days of broad-spectrum antibiotic before lobectomy. All acute symptoms of pneumonia had resolved at a median time of 10 days, and 94% of their cohort showed improvement or normalization in inflammatory markers by 8 days. Their lone patient (a 20-year-old) who showed no improvement despite 13 days of antibiotic proceeded directly to surgery, which accords with our experience.

Omar et al[3] further highlight some of the considerations in our case. They report a 25- year-old man who presented with right-sided chest pain, fever, and cough; a CPAM was found on imaging. He was initially managed medically with IV broad-spectrum antibiotics. Bronchoscopy was performed on day 3 of hospitalization, which yielded large amounts of pus with methicillin-resistant *Staphylococcus aureus*. The patient improved clinically on antibiotic therapy and was discharged. This case study demonstrates that early procedural intervention with bronchoscopy and antibiotic therapy can be therapeutic.

The differences in management strategies between our case and those discussed above[3,8] illustrate the lack of concrete evidence for the optimal timing of treatment of patients presenting with infected CPAM later in life, and may represent different strategies for adults versus adolescents. The 25-year-old patient[3] received an intervention (bronchoscopy) on day 3 of hospitalization, while our patient (age 12) received an intervention (lobectomy) on day 16 of hospitalization. The 20-year-old patient[8] proceeded to surgery after 13 days of broad-spectrum antibiotic and failure to demonstrate clinical, radiologic, or laboratory response to therapy; as in our case.

Based on this single case reported here and the few cases in the literature, procedural intervention, such as bronchoscopy or lobectomy, appears to be a crucial element in the management of with CPAM.[14] Early procedural intervention correlated with a shorter hospital stay for the patient reported by Omar et al[3] compared to our patient (13 days versus 22 days). If after 8 to 14 days of broad-spectrum antibiotics there is no improvement in clinical symptoms, radiologic results, or laboratory values, this would be a further consideration to proceed to lobectomy.[8] One may infer from these cases that earlier procedural intervention may result in a more rapid recovery and shorter hospital stay. A randomized trial comparing early procedural intervention with antibiotic therapy followed by an intervention might clarify this point, but given the small numbers of cases is unlikely to prove feasible. The need for a multidisciplinary team for appropriate management is essential.

Conclusion

Limited literature is available regarding the management of CPAM discovered in adolescence or adulthood. In this case report of a 12-year-old boy with a febrile illness resulting from a previously unknown infected CPAM, clinical improvement did not occur until after lobectomy. Lobectomy should be considered when there is no apparent improvement in clinical, laboratory, or radiologic findings within 10 to 14 days of initiation of broad-spectrum antibiotic therapy. The importance of procedural interventions (bronchoscopy, lobectomy) in the management of patients presenting with CPAM in adolescence or adulthood is emphasized. Controversy remains over the optimal timing of intervention.[15]

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Case Reports

Left Ventricular Assist Device Implantation in a Patient with Deep Brain Stimulator

Jodie Franzil, M.D.[1], Sahil Prasada, B.S.E.[1], Olivia Gilbert, M.D.[1], Mustafa Siddiqui, M.D.[2], Barbara Pisani, D.O.[1]

Background:

As life expectancy is increasing, the number of people with heart failure is expanding. It is projected that the prevalence of heart failure will increase nearly 50% in the next 15 years, resulting in over 8 million American adults affected by the year 2030.[1] With a limited number of donor hearts available each year for transplantation, options for advanced heart failure such as left ventricular assist devices (LVADs) have become increasingly relevant. With improvements in these devices over time, more people are being considered for this therapy, even those with significant non-cardiac medical history, as shown by the increasing numbers of LVADs placed for both destination therapy and as a bridge to cardiac transplantation.[2] Between June 2006 and December 2014, more than 15,000 mechanical circulatory support devices were implanted in the United States.[3]

With scientific advances, non-cardiac implantable devices, such as deep brain stimulators (DBS), are also being used more often. Over 100,000 people worldwide have been treated with a DBS for various indications, including depression, movement disorders, and Parkinson's disease.[4] As such, patients with indications for both cardiac and non-cardiac implantable devices will increasingly be encountered more frequently.

Objective:

To report the first case of a patient with bilateral DBS who underwent LVAD implantation.

Case Report:

A 71-year-old African American woman with a medically-refractory essential tremor underwent bilateral DBS electrode implantation in the ventral intermedius nucleus of the thalamus. She developed chemotherapy-induced end-stage dilated cardiomyopathy decades after treatment for breast cancer. Within 6 months of the diagnosis of cardiomyopathy, a subcutaneous cardioverter-defibrillator was implanted for primary prevention of sudden cardiac death. She presented with congestive heart failure exacerbation (New York Heart Association Class IV), despite more than 6 months of guideline-directed optimal medical therapy and home inotrope infusions. She was evaluated for mechanical circulatory support, specifically LVAD therapy.

[1] Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC

[2] Department of Neurology, Wake Forest School of Medicine, Winston-Salem, NC

Address Correspondence To:
Jodie Franzil, M.D.
Department of Internal Medicine
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157
jfranzil@wakehealth.edu

While LVAD implantation was being considered, a discussion started between the departments of Cardiology and Neurology, Medtronic Incorporation (Minneapolis, MN), manufacturer of the DBS, and Thoratec Corporation (Pleasanton, CA), manufacturer of the LVAD, regarding the potential for electrical crosstalk between the two devices. Neither manufacturer could provide literature regarding interference between the LVAD and the DBS. Thus, the team proceeded with the implantation of Heartmate II LVAD (Figure 1). The perioperative course was uncomplicated and the patient recovered well from her surgery from a cardiac perspective. She has not been hospitalized again for years post-LVAD.

Unfortunately, her tremors progressively worsened, despite maximal output from the generators. She underwent successful bilateral DBS pulse generator replacements (Medtronic; Activa SC Generator 37602-SNLA725595H and 37602-SNLA721027H) within a year of the LVAD placement. Systemic anticoagulation was not interrupted, as is recommended in patients with LVADs to reduce the risk of pump thrombosis.

Discussion

This is the first case report describing LVAD implantation in a patient with bilateral DBS. There was much discussion regarding the safety of LVAD implantation, particularly with the need for cardiopulmonary bypass and the concern regarding the potential for electrical interference between the LVAD and DBS. Although simultaneous use of brain stimulators and cardiac pacemakers and/or defibrillators is well-reported,[5,6] there were no previously reported cases of LVAD implantation in a patient with DBS.

As LVAD implantation has become standard of care in patients with advanced heart failure, it is essential to broaden eligibility requirements for patients who may benefit from these devices. This case illustrates the potential for advanced options to treat heart failure in patients with multiple co-morbidities and other implantable devices, such as DBS, to undergo successful LVAD placement. The safety and efficacy of LVAD implantation in such patients has not yet been fully evaluated. Thus, adding cases such as this one to the literature is essential to ensure that advanced therapeutic options are considered in patients with non-cardiac co-morbidities.

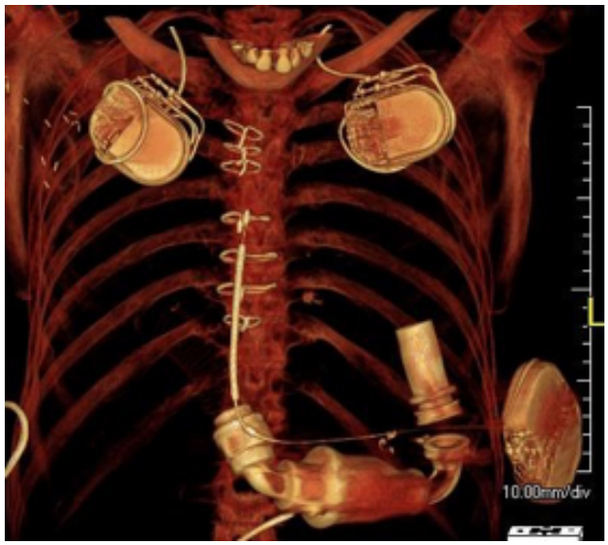

Figure 1. Helical computed tomographic image (anterior-posterior projection), of the patient's chest depicting bilateral DBS, LVAD, and a subcutaneous ICD.

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