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AveraUrogyn.org
President's Comments
435 Reflecting on Health Care Challenges Inspired Association Involvement – Benjamin Meyer, MD

Editorial
437 South Dakota Medicaid Implements Coverage for Immediate Postpartum Long-Acting Reversible Contraception – Kelly Landeen, MS III; Ashley Briggs, MD

The Journal
439 Regional Infant and Child Mortality Review Committee – 2015 Final Report – Ann L. Wilson, PhD; Jim Sideras, MSN; Brad Randall, MD
447 Blastomycosis and Histoplasmosis in a Patient with Glioblastoma Receiving Temozolomide – Aiham H. Jbeli, MD; John Yu, MD

Primers in Medicine
451 A Primer on Bleeding Risk and Management Strategies of Newer Oral Anti Platelet Agents in Cardiovascular Disease – Jimmy Yee, MD; Vishesh Kumar, MD; Amornpol Anuwatworn, MD; Marian Petrasco, MD; Adam Stys, MD
459 New Age Treatment for Fecal Incontinence: Sacral Nerve Modulation – Elizabeth E. Blears, MD; Kevin Benson, MD, MS
465 Vaccines and Autism: A Misconception that Persists – Maya Gogoi, NREMT; Archana Chatterjee, MD, PhD

Pharmacology Focus
468 Getting Ahead of Head Lice: Treatment in the Setting of Resistance – Hannah Packer; Amy Heiberger, PharmD, BCPS

Special Features
471 Board News – Margaret B. Hansen, PA-C, MPAS
473 DAKOTACARE Update: Dear Participating Provider – E. Paul Amundson, MD
474 Quality Focus: Improving Adult Immunization Rates – Stephan D. Schroeder, MD
475 Patient Education: Frankenstein Meets a Greek God – Richard P. Holm, MD

Member News
476 For Your Benefit: Get Involved in the SDSMA
  SDSMA President Visits Medical Districts
  Support Medical Student Scholarships
477 Sign up to be Doctor of the Day at the Stare Capitol!
  2017 SDSMA Membership Dues Renewal Now Available
  Legal Brief Highlight: Physician Employment Agreements
478 The Issue Is…CMS Tool Would Allow Physicians to Determine Possible Impact of MACRA on Their Retirement

For the Record
479 CME Events

Advertisers In This Issue
480 Physician Directory
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Perhaps the single most influential moment in my journey that ultimately led to my involvement in organized medicine occurred while I was employed as an emergency department scribe in Minnesota, a part-time job I took to gain some health care experience during my senior year of college. A fellow scribe made the suggestion that I read the book Better by Atul Gawande, the noted oncologic surgeon and writer. In his book, Gawande describes the somewhat complicated nature of what it means to be successful in medicine, and how we can do it, well, better. Contemplating the political and economic nature of this endeavor, I then discovered The Healing of America by T.R. Reid, a journalist with a bum shoulder who traveled to various health care systems of the world, both as a patient and a reporter. He shares anecdotes about the care he received in each country and describes how these experiences illuminate strengths and weaknesses of American health care.

Reflecting on these books in the summer prior to beginning medical school led me to realize that a responsibility of an aspiring physician should be to not only learn how to treat the sick patient with whom he or she interacts but also to do his or her part to improve the health care system in the U.S. The U.S. is one of the richest nations in the world which, in international comparisons, spends the highest percentage of its gross domestic product on health care only to result in an overly complex albatross of a system that leaves millions of individuals without access to high-quality, affordable care. Thus is the paradox that presents itself to those of us engaged in reform – how do we simultaneously reduce costs and improve quality, all the while preserving the physician-patient relationship that inspired many of us to go into medicine in the first place? I find this challenge to be among the most worthwhile intellectual, political, and communal pursuits I have encountered in my young life. This is what inspired me to become involved with the SDSMA and the AMA just several weeks after I matriculated at my medical school.

I could not have imagined the extent to which such involvement would ultimately shape my medical education and develop my skills as a leader, knowledge as a policy wonk, and passion for being an advocate for our patients. My experiences ranged from the simple “Policy and Pint” discussion sessions we conducted informally with classmates at a local Vermillion bar to lobbying a sitting U.S. Senator in his Capitol Hill office for preservation and expansion of graduate medical education. I could write a novel going into the details of the many enriching experiences I have been privileged to have in organized medicine, but allow me to briefly reflect on a few of my favorites.

At the local level, attending the legislative dinners hosted by the Seventh District Medical Society in Sioux Falls was a definite highlight. I relished the opportunity to not only network with physicians in my community but also to directly advocate to the state senators and representatives who attended. For certain issues, other students and I would encourage classmates to make their voices heard by organizing letter writing campaigns. In line with these efforts, I felt, and continue to feel, especially passionate about advocating for Medicaid expansion in South Dakota.
Dakota. I encourage South Dakota medical students and physicians to share with their representatives about how Medicaid expansion would help their patients and practices so that this legislative priority of our SDSMA is finally achieved.

Within the AMA, I became involved within the MSS in a variety of capacities. Perhaps the endeavor I enjoyed the most was collaborating with other medical students and physicians across the country to research for and write resolutions related to policy ideas and then work in the appropriate bodies to achieve the consensus necessary to pass these ideas as official MSS or AMA policy. Resolutions I have co-authored or helped in some extent to ultimately pass spanned a broad range of topics, including lead contamination in water, drug pricing and shortages, prior authorization reform, radon testing in rentals, improving vaccination rates, ethical physician conduct in the media, access to preventive and reproductive health services, and reducing gun violence. I feel that such work is empowering in that it allows us to amplify our voices, on behalf of our profession and our patients, in directing a powerful lobbying arm of organized medicine to advocate for policy that is evidence-based and socially just.

As I look back on these enriching medical school experiences, I realize they would have been impossible if not for the generous support the SDSMA provided to interested students. Thus, I would like to express my deep gratitude to the SDSMA, district medical societies, and individual physicians who contributed their resources and time to assist us in building our student section. I have cherished the mentorship of so many of you. I hope my experiences inspire other medical students to engage deeply with policy and advocacy and encourage the SDSMA to continue supporting students in these endeavors. This “hands-on” format of learning and leadership development will no doubt pay valuable dividends in the future when these students develop into physicians committed to involvement in organized medicine in order to better our profession and improve our health care system. Looking forward to the rest of my residency and onward, on behalf of our patients, I certainly feel called to continue my involvement and envision it as an integral component of my career.

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South Dakota Medicaid Implements Coverage for Immediate Postpartum Long-Acting Reversible Contraception

By Kelly Landeen, MS III; and Ashley Briggs, MD

In July of this year, an article was published in South Dakota Medicine entitled “Spacing Pregnancies Appropriately: Long-Acting Reversible Contraception in the Immediate Postpartum Period.” This came directly after the American Medical Association (AMA) passed policy on immediate postpartum LARC placement, recognizing the practice as “a safe and cost effective way of reducing future unintended pregnancies,” and supporting insurance coverage for both LARC devices and the procedural fee at the time of delivery. At that time, only 12 state Medicaid agencies offered this kind of coverage. Since then, the American College of Obstetricians and Gynecologists (ACOG) has taken a stance on the matter, stating that immediate postpartum LARC placement “has the potential to reduce unintended and short-interval pregnancy” and leads to healthier babies and mothers. Going beyond simple support, ACOG even recommended strategies for patient counseling, procedures, reimbursement, and advocacy. Now, with the full support of ACOG and the AMA, the push for Medicaid coverage of immediate postpartum LARC has come to the forefront of obstetrics and gynecology.

In August, South Dakota joined the ranks of those states whose Medicaid agencies cover immediate postpartum LARC. One of the first women who benefitted from this coverage had an IUD placed at the time of cesarean delivery in August. She was a high-risk patient; this was her sixth cesarean, and she had been incarcerated and was participating in New Start, a program geared toward pregnant women and mothers with chemical drug dependence. Unfortunately, high-risk patients like this are likely to miss postpartum appointments and be lost to follow-up. By electing for an immediate postpartum LARC, this patient was able to take control of her contraception and space her pregnancies appropriately.

All of this would not be possible without the newly implemented coverage by South Dakota Medicaid, and we applaud the efforts of the South Dakota Department of Social Services for their hard work in making this possible. As more women choose this method of contraception, it will ultimately lead to healthier babies and families. It goes without saying that this is a huge win for maternal and child health in South Dakota.

REFERENCES
4. South Dakota Department of Social Services, Division of Medical Services. Aug 2016. <dss.sd.gov>

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The Regional Infant and Child Mortality Review Committee (RICMRC) was established in 1997 with the aim of examining deaths of infants and children to identify preventive strategies that may decrease the risk of loss of young life in Minnehaha County. The committee’s mission is “to review infant and child deaths so that information can be transformed into action to protect young life.” The committee continues to serve Minnehaha, Lincoln, Turner, McCook, Lake, Moody, Union, Hanson, Miner and Brookings counties.

The committee is chaired by the chief of Sioux Falls Fire Rescue and is composed of professionals representing expertise in pediatrics, medico-legal death investigations, nursing, law enforcement, child protective services, emergency medical services, and mental health. Sherriff and police departments from the participating counties are invited to be present for the reviews of deaths of children occurring in their counties. Representatives of the South Dakota Department of Health (SDDOH) also attend the meetings to help coordinate infant death investigation throughout the state. To operationalize its goal of prevention, these criteria are used for reviewing deaths of infants and children (under the age of 18):

- Residents of the RICMRC region whose death occurred subsequent to hospital discharge following delivery (or did not occur in a hospital) from causes sustained in the region; and
- Non-residents of RICMRC region whose deaths occurred in the region from causes sustained in the region.

Eighty deaths occurred in the 10-county review area in 2015 (77 in Minnehaha and one each in Moody, Lincoln, and Brookings counties). For illustrative purposes, the age distribution of all childhood deaths of Minnehaha County residents (who represent 61 percent of the total resident deaths in the 10-county RICMRC review area in 2015) is presented in Table 1. Important to recognize in these 2015 data is that 42 percent of the Minnehaha County resident...
deaths of children under the age of 18 occurred in the first 28 days of life (neonatal) and some of these occurred within hours of birth. Noted in Table 1 is how the population of Minnehaha County has grown by almost 33 percent between 1990 and 2015. Apparent over this span of time is year to year variation in the number of infant and child deaths in the county. However, a comparison of the mean number of infant and child deaths for the intervals of 1991 to 2002 and 2003 to 2015 shows a slight decrease. The mean number of annual infant and child deaths was 26.6 for the first 12 years of this time interval and 25.4 for the more recent 13 years. In light of the growth of the county’s population, this is an encouraging finding. For children (ages 1 to 17), the approximate 2010 through 2014 regional rate of death (22 per 100,000 population) is lower than the state rate of 29, but higher than the national rate of 20 for these years. 1-2

Though caution must be exercised when calculating rates with the small population base of the RICMRC area, the 2010 through 2014 rate of infant death (birth to age 1) in the RICMRC counties of southeast South Dakota is approximately 5.1 per 1,000 live births and is lower than the state rate of 6.9 during the same period. The national rate of infant mortality for these years was 6.0.1-2

In 2015, 24 deaths met the committee’s criteria and all were reviewed (compared to 32 cases in 2013 and 25 cases in 2014). Of the 24 reviewed cases, 18 were residents of Minnehaha County, four were from Lincoln County, and one each from Turner and Lake counties.

The reviewed deaths listed below are separated by their manner (natural, accidental, suicide, homicide and undetermined) with an additional section that addresses those attributed to sudden unexpected infant deaths (SUID). The number of deaths for 2015 in each manner category is indicated in bold adjacent to its heading. Numbers listed in parentheses represent the comparable number of deaths from 1997 through 2014. Care must be taken in comparing yearly data due to the addition of Lincoln County (1998), Turner County (1999), McCook County (2000), Lake and Moody counties (2001), Union County (2002), Hanson and Miner counties (2003), and Brookings County (2004) in years subsequent to the establishment of the review committee’s work in Minnehaha County in 1997. However, as approximately two-thirds of the reviewed cases since 2005 have been residents of Minnehaha County, some meaningful comparison of data between years is justified.

### Table 1. Minnehaha County Resident Deaths and Population

<table>
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<th>Year</th>
<th>Infant 1-14 Years</th>
<th>15-17 Years</th>
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Population data from U.S. Census Bureau.


Ten children died in 2015 from natural causes. Four of these children died of neuro-developmental conditions that they experienced from birth or early childhood. Three children died of malignancies, two from rapidly
progressing infections, and one from a chronic severe respiratory condition.

As noted in Figure 1, in 2015, similar to the four previous years, there were no deaths attributable to sudden infant death syndrome (SIDS). There were seven deaths of infants that occurred during sleep whose manner was coded as “accidental” or “undetermined” (see the SUID section below).


The number of childhood deaths (n=7) caused by accidents in 2015 is comparable to the mean for this manner of death observed in previous years. Two children died in a single motor vehicle crash that involved an adult driver who also died. Neither child was in a seat belt at the time of the crash. Unlike previous years, there were no auto crashes involving teen drivers.

Two deaths in 2015 involved choking. A preschooler choked on a household item and a young infant succumbed after being given a piece of candy.

In 2015, three infants who died unexpectedly in sleep were attributed to accidents. In each of these cases the baby was put to sleep in an unsafe location. These deaths will be further discussed in the SUID section below.


There was one death due to suicide in 2015. As noted in the above annual data, typically, with the exception of 2013, there have been one or two such tragedies in the region. The one death in 2015 again confirms that the spike of five deaths observed in 2013 was indeed an unusual spike. In 2014, the national rate of suicide for ages 1 to 17 was 1.9 per 100,000. This rate would equate to one death per year for our region which was observed in 2015. The death that occurred in the RICMR region was of a child known to the mental health community and reflects the complexity and challenges of serving this population of youth at risk for self-harm.


While in 2014 there were no homicidal deaths in the region, unfortunately, the typical trend for the region was resumed with one such death in 2015. Strained family relationships and stressed economic circumstances contribute to dynamics that tragically become manifest in this tragic loss of life.


There were four deaths of infants that occurred during sleep whose manner was certified as undetermined. These cases will be further described in the SUID section below. Two of these cases involved co-sleeping with an adult and two involved other unsafe sleep positions or environments. There was an additional death that involved issues related to care and sequelea from birth.


(Note: These deaths are included by their manner in the above sections of this report.)

As nearly 30 percent of the cases reviewed by the committee in 2015 were attributed to SUID, they will be discussed in this separate section of this report. The term SUID, which began to be used on a Center for Disease Control and Prevention investigation form issued in 1996, now describes deaths attributed to three different coded causes classified as also having three different “manners.” These are sudden infant death syndrome
(SIDS) (a “natural” manner); strangulation and suffocation – to include overlaying – in bed (an “accidental” manner); and other causes (an “undetermined” manner). The most recent 2014 data show that the rate of death for SUID observed nationally is 0.9 per 1,000 live births. For the RICMRC region, the 2015 SUID rate is approximately 1.5. Over time, nationally and locally there has been a decline in the rate of SIDS, which may only be coded as a cause for an infant death when it cannot be explained by a complete autopsy, examination of the death scene, and review of the clinical history. With increasing use of death scene investigations, hazards identified in the sleep environment lead to the manner of unexpected infant deaths during sleep more frequently being coded as accidental or unknown. It is quite likely that in earlier RICMRC annual reports the deaths listed in this report as SUID would have been listed as SIDS. As noted in Figure 1, in the RICMRC region, there has not been a SIDS death since 2010 while there have been between two and seven SUID deaths in subsequent years.

Among the seven 2015 SUID deaths in the RICMRC region, four of these deaths were coded as “undetermined” and three as “accidents.” Six of these deaths occurred during the day and three in out-of-home child care. In all of the SUID deaths, the baby was found dead in a non-supine position or an environment with hazards for safe sleep. As noted in the past, among these deaths were those occurring on sofas or an adult bed. In addition, in 2015, there were SUID deaths that occurred in baby equipment that was either too old and/or worn to be safe or not designed for safe sleep (to include infant car seats). In the region, no 2015 SUID death occurred in a standard crib.

Figure 2 presents data on the rates of SUID for the region, South Dakota and the U.S. Apparent in these data is how, with the exception of 2008, the region’s rate of SUID in 2015 was the highest that it has been in the past 15 years. Further, it has been increasing over the past seven years. As noted throughout this report, small numbers require caution when observations are made; nonetheless these data must alert the community to a trend that demands attention to prompt its reversal.

Advocacy Issues

Data from the reviews of the 2015 deaths highlight actions that health care professionals, community leaders, and citizens may take to prevent future loss of life of infants and children. Issues that are listed with an asterisk note those that have been discussed in previous reports and require ongoing attention.

1*. Unexpected infant deaths during sleep occur in unsafe sleep environments. Reviews of deaths attributed to SUID continue to document that they are associated with care that violates what is known about safe sleep for infants. Though efforts have been initiated with public media and hospital-based instruction on infant care, SUID deaths are tragic indications that education is not sufficiently impacting the behavior of all parents or caregivers. In 2015, with the exception of one of the seven deaths, all occurred during the day. Education must strive to convey the message that sleep must always be in a safe position and environment. Though uninviting to adult eyes, this safe environment means that a baby is placed on his or her back, in a crib with a firm mattress with no soft material within this space. This means that blankets, quilts, bumper pads, stuffed toys or any other materials must not be in the crib with a sleeping baby. Sleep in car seats or other equipment in which babies are held, sofas or adult beds must be avoided. Further, co-sleeping is not considered safe for babies. Babies are safest when sleeping alone, on their backs and wearing clothing that provides comfort for the temperature. Though the image of baby sleeping in this way may appear “un-cozy” to adults, it is the safest for babies. We understand that parents often want to sleep with their new baby. There are benefits for the baby and parents when the same room is shared, but they should never share the same sleeping surface. We recommend that a safe sleeping surface be provided for

Figure 2. Rates of SUID - RICMRC, South Dakota and U.S., 2000-2015

![Graph showing rates of SUID from 2000 to 2015 for RICMRC, South Dakota, and United States.](image-url)
Great news: In 2015, 36.5% of our enrollees heard about QuitLine services from healthcare professionals. Even better, we’re introducing a new South Dakota QuitLine module on “PROF” (Program and Resource Online Facilitator) at dohprofisd.org, where health professionals like you will learn even more about the effects of tobacco and the steps required to guide those addicted to seek help. You’ll also learn how to visit with patients about their tobacco use and how best to make a QuitLine referral.

The interactive online system tracks progress, so users can log in and out at their convenience and still maintain their place in the training. We encourage all health professionals and providers who interact with tobacco users to participate in this training.
an infant adjacent to the parent’s bed in such a manner that an exhausted sleeping parent could not in any way come in contact with the infant.

While knowledge about safe sleep can be shared in multiple ways, the challenge becomes how it can be best assured among those who care for babies. The public can play a vital role in this effort. Narratives surrounding the events that have occurred just prior to a SUID death not uncommonly include a rushed decision to do what is easiest at a stressed moment. Exhausted parents or harried childcare providers are prone to justifying placing a baby in an unsafe position “just this one time,” and the “one time” can become fatal. Further, babies are known to die as house guests where proper places for them to sleep are not used in an unfamiliar setting. Red Cross manuals from many decades ago describe how “pasteboard boxes” may be made into baby beds. Today, barring use of pillows or other un-firm material on its bottom or side surfaces, this continues to be an acceptable place for infant sleep. Indeed, Finland for generations has issued cardboard boxes to new mothers. The boxes serve as locations for infant sleep and the country experiences a very low infant mortality rate.

Specific to the deaths that occurred in 2015 is the finding that two of these deaths occurred in non-safe baby equipment. In one case, the mattress and frame of a portable crib was worn and broken creating a hazard. In another, a baby was asleep in a device that does not provide a flat horizontal surface for sleep. These observations create important awareness about the need to check previously used equipment to determine if it may no longer be safe. Further, babies should not sleep in care devices, like car seats, that do not have a flat surface.

Community vigilance and advocacy in promoting safe sleep for babies is critical to the prevention of SUID. These questions may guide what this advocacy may include: What happens when one sees cribs displayed in businesses that include soft bumper pads and quilts? What happens when one sees a family member about to nap on a sofa while holding a young infant? What happens when one’s church nursery includes portable cribs filled with soft toys or quilts? What happens when one passes a childcare center where a young baby is asleep on her stomach? These are all opportunities for education and action that may protect not just one baby, but also provide education and safety for all those involved.

2. *Proper seat belt use is vital to survival.* Failure to use seat belts was associated with the deaths of two youth. Persistence in presenting the message that use of seat belts saves lives is essential. Further, the vital role adults play in modeling routine seat belt use is critical in establishing this life saving habit. The role of safety checks by adult drivers before starting a vehicle is emphasized when the tragedy of death occurs when this precaution is not taken.

3. Parents with limited intellectual capacity require intensive surveillance. A 2015 death occurred in the care of a parent known to have an intellectual disability. Though services were provided for this family, an incident of care occurred that was fatal for the baby. This death highlights the challenges inherent when those with limited capacity care for fragile new life. The need for extended social support and on-going supervision of infant care is difficult to provide yet critical for the safety of infants whose parents have limitations that risk the safety of their infants and children. Further, recognized is how making professional judgments regarding the potential wellbeing of infants reared in such families is difficult.

4. Infants and young children place objects in their mouths upon which they may choke. Removing such materials from their reach is demanded. A number of deaths have occurred in the region when infants and young children have choked on small objects. Diligence in considering how any small object is a potential threat to the life of a child is needed. Care must be taken to remove all such objects from an infant or child’s reach.

5. *The Big Sioux River creates safety hazards for the region.* Though no river-related deaths occurred in 2015, the safety risks associated with this scenic area of our region must not be neglected. Education on water safety and the need for parents to be watchful as children are in the vicinity of rivers remain vital to the prevention of tragedies that unfortunately have occurred in this area of beauty and recreation.

6. *Adolescence is a time of vulnerability to social pressures and emotional volatility.* The tragedy of suicide alarms all who work with adolescents. The volatility of teen years presents challenging issues for families and other professional service providers. Assuring that homes have safeguarded teens from access to means of self-harm is a protective step. Firearm safety is needed in all homes. Further, the committee is applauding the state-wide efforts in suicide prevention that are funded by the Substance
Abuse and Mental Health Services Administration. Locally, the Help Line Center is involved in this important effort.

7.* The sleeping environments for all children and adults should be protected by working smoke detectors. The committee supports and encourages the ongoing efforts of local fire departments in educating the public about the need for families to install and service smoke detectors to assure their ability to provide life saving warnings of home fires.

8.* Maternal tobacco and alcohol use are known risk factors for SUID. Maternal smoking, both during and after pregnancy, also represents a risk factor for SUID. Secondhand smoke is an additional SUID risk factor. Parents should make every effort to restrict the use of alcohol, tobacco, and illicit drugs for the well being of their infants, both before and after the baby’s birth. We encourage the creation and use of programs that assist parents in abstaining from tobacco and alcohol use. After adherence to the safe sleep programs for infants, cessation of maternal smoking during and after pregnancy is the next best way to prevent sudden infant deaths.

9*. Care must be taken to assure that all infants and children have periodic physical examinations to detect potentially preventable and treatable illness and immunizations. Vigilance in assuring that infants and children are up to date on immunizations may prevent loss of life from an infectious illness. Encounters with health care providers also provide opportunities for providing guidance on identifying the signs of illness in infants and young children.

10*. Follow-up activities from the 2011 State Task Force on Infant Mortality convened by South Dakota First Lady Linda Daugaard include coordination between the SDDOH, RICMRC and the similar committee that reviews infant deaths in the Rapid City area.

Efforts have continued by the SDDOH to provide coordination of data collection on infant deaths. Statewide meetings to review these data are assisting in establishing their reliability. Data provide the essential foundation for prevention efforts. The development of this effort must continue so that education and services may best address the underlying causes of deaths that may be preventable and end young lives.

Report submitted by the Regional Infant and Child Mortality Review Committee

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REFERENCES

1. 2010-2014 data from the South Dakota Department of Health.

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Blastomycosis and Histoplasmosis in a Patient with Glioblastoma Receiving Temozolomide

By Aiham H. Jbeil, MD; and John Yu, MD

Abstract

Malignant glioblastoma multiform (GBM) is the most common primary malignancy of the brain in the U.S. Temozolomide (TMZ) is the cornerstone of management along with surgical resection and radiotherapy. Because of the reduction in the CD4+ lymphocyte count as a side effect of TMZ use, this patient population is under risk for opportunistic infections like Pneumocystis jiroveci. A male patient with newly diagnosed glioblastoma multiform presented with non-productive cough and chest pain. Before presentation, the patient received the standard therapy including surgical resection, radiation and TMZ. Computerized tomography of the chest showed a very large cavitary lesion in the upper segment of the right lower lobe and multiple nodular lesions with some starting to cavitate. Cytology of the bronchioalveolar lavage with special stain showed large, broad based budding yeast-like cells, morphologically consistent with blastomyces and macrophages filled with yeast-like forms, morphologically consistent with histoplasma. The patient was treated with intraconazole intended for 12 months. To the best of our knowledge, our case represents the first documented case of lung infection with both blastomyces and histoplasma in a patient after receiving TMZ for newly diagnosed GBM.

Introduction

Malignant glioblastoma multiform (GBM) is the most common primary malignancy of the brain (15.7 percent) in the U.S., according to The Central Brain Tumor Registry of the United States report. Surgical resection of the tumor, radiotherapy, an initial course of temozolomide (TMZ), and subsequently, six cycles of adjuvant TMZ result in a statistically improved survival with a relatively safe side effect profile. A severe reduction of the cluster of differentiation 4 (CD4+) count is not uncommon with this regime; in one study, 40 percent of the patients had CD4+ count nadir less than 200. More importantly, opportunistic infections like Pneumocystis jiroveci pneumonia (PJP) are well documented and invasive pulmonary aspergillosis has been reported in patients treated with TMZ.

The following is the first documented case of lung infection with both blastomyces and histoplasma in a patient receiving TMZ for newly diagnosed GBM.

Case Presentation

A 51-year-old male patient with a history of newly diagnosed GBM was admitted to the hospital for evaluation of a non-productive cough for two weeks. The patient was previously treated with surgery followed by concomitant TMZ and radiotherapy and subsequently by six cycles of TMZ.

On the day of admission, he also had right-sided chest discomfort when coughing. He did not give a history of shortness of breath, fever, chills, constitutional symptoms, recent travel or contact with sick individuals. A chest X-ray in the hospital showed a new cavitary lesion in the right lower lobe (Figure 1). Computerized tomography (CT) of the chest showed a very large cavitary lesion in the upper segment of the right lower lobe and multiple nodular lesions with some starting to cavitate (Figure 2). The CT showed bilateral pulmonary embolism (PE). The patient was started on Coumadin and bridged with enoxaparin until therapeutic international randomized
ratio was achieved; he was discharged on Coumadin. The differential diagnosis in this patient was broad including aspergilloma, other fungal lung infections, atypical organisms like Mycobacterium tuberculosis (TB) and PJP, viruses like cytomegalovirus, bacterial lung abscess and non-infectious causes like vasculitis. Lung infarction, necrosis and metastasis were taken into consideration, although, the probabilities of these were considered to be low.

Sputum and blood were sent for culture. Bronchial washing and bronchoalveolar lavage (BAL) were obtained via bronchoscopy early in the course of the hospitalization and sent for bacterial, fungal and viral studies. The patient was empirically started on voriconazole, levofloxacin, vancomycin and piperacillin-tazobactam. Fungal serology for histoplasma, blastomyces, coccidioides and aspergillus antibodies were negative. A negative quantiferon indicated that TB was unlikely. Antinuclear
antibodies and anti-neutrophil cytoplasmic antibody were negative. The CD4+ was decreased to 191 cells/mm³. Human immunodeficiency virus testing was negative. Cultures from the sputum, blood, bronchial washings and BAL failed to isolate any organism. A Gram stain and acid-fast stain were also negative. Aspergillus galactomannan antigen was negative in the blood, sputum and BAL. Cytology of the BAL and bronchial washing was negative for malignancy but showed the typical morphology for both blastomycoses and histoplasmosis. Cytology with special stain showed large, broad based budding yeast-like cells, morphologically consistent with blastomycoses (Figure 3a) and macrophages filled with yeast-like forms, morphologically consistent with histoplasmosis (Figure 3b). The urine was also positive for blastomycoses and histoplasma antigens. On the basis of these finding, the antimicrobial coverage was narrowed to itraconazole intended for 12 months. Unfortunately, the patient was admitted later to another facility with worsening weakness; a repeat magnetic resonance imaging showed progression of the GBM with more edema. The patient was subsequently transitioned to hospice care. He unfortunately passed away two months after discharge from our facility.

Discussion

GBM is the most frequent primary central nervous system malignancy. The current standard of care for patients with newly diagnosed GBM is surgical resection followed by concomitant TMZ and radiation followed by six cycles (each cycle is a 28-day cycle) of TMZ. We presented the first reported case of a combined pulmonary infection with blastomycosis and histoplasmosis in a patient with newly diagnosed GBM receiving TMZ. The diagnosis was confirmed by showing the two organisms in BAL. The patient was treated with itraconazole, which is the drug of choice for both pulmonary blastomycosis and histoplasmosis.

TMZ is an oral alkylating agent with well-demonstrated antitumor activity when used as a single agent in the treatment of recurrent glioma. The approved dosing schedule is 150 to 200 mg/m²/day for five days for a 28-day cycle. Alternatively, a daily dose of 75 mg/m² for up to seven weeks is safe. Before TMZ was shown to be efficacious in GBM, PJP was noted with increased frequency in patients with primary brain tumors who were receiving radiotherapy and glucocorticoids. Follow-up of those patients showed that after six weeks of radiation, 47 percent of patients had CD4 counts less than 300 cells/mm³ and 26 percent of patients had CD4 counts less than 200 cells/mm³, which represents a major risk factor for opportunistic infections.

In 2005, TMZ was introduced as the standard of care in patients with newly diagnosed GBM. Because of the early occurrence with PJP, and because TMZ is known to be toxic to CD4+ lymphocytes, the Food and Drug Administration recommends prophylaxis (trimethoprim-sulfamethoxazole has been considered the first-line agent) for possible PJP infection in this patient population. Grossman et al. showed that TMZ administered to patients with melanoma as a single agent, without radiation therapy or glucocorticoids, produces a profound lymphopenia and a striking reduction of CD4+ count that lasts for months after discontinuing TMZ. This study confirmed the suppression of cell-mediated immunity as a side effect of TMZ, independent of radiation or glucocorticoids.

The primary acquired host defense against both B. dermatitidis and H. capsulatum is cellular immunity mediated by antigen-specific T-cells and lymphokine-activated macrophages. Hence, CD4+ lymphocyte suppression is a predisposing factor for both infections. Progressive disseminated histoplasmosis (PDH) is typically seen in immunocompromised patients with CD4+ T cell counts less than 200/µL. This is one of the most important risk factors for subsequent infections with histoplasmosis.

The spectrum of the PDH ranges from an acute rapidly fatal course to a more chronic course with a focal distribution of cavitary lesions. A productive cough, dyspnea, low-grade fever, night sweats and weight loss, as described above, usually characterize chronic cavitary histoplasmosis. Chest X-ray shows upper-lobe infiltrate, cavitation and pleural thickening. The presentation of blastomycosis is similar to histoplasmosis. The most common radiologic findings are alveolar infiltrates (with or without cavitation), mass lesions that mimic bronchogenic carcinoma and fibronodular infiltrates. The antifungal treatment for both infections is amphotericin B for severe life-threatening cases and itraconazole for non-life threatening infections. The duration of therapy is six to 12 months.

Conclusion

This case represents a new finding that patients receiving TMZ are at risk of combined infections with blastomycosis and histoplasmosis, especially in endemic areas where both immunocompromised and immunocompetent
individuals are at risk of infection. Currently, there are no recommendations for prophylactic antimicrobial treatment for opportunistic infections other than PJP. While awaiting further research and recommendations in this field, it is reasonable to monitor this patient population carefully for opportunistic infections especially in endemic areas. Our case is also a prime example of the fact that opportunistic infections in immunocompromised individuals may be caused by multiple organisms.

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REFERENCES

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A Primer on Bleeding Risk and Management Strategies of Newer Oral Anti Platelet Agents in Cardiovascular Disease

By Jimmy Yee, MD; Vishesh Kumar, MD; Amornpol Anuwatworn, MD; Marian Petrasko, MD; and Adam Styx, MD

Abstract
Aspirin, the first antiplatelet agent, has been around since the 19th century, and is one of the most established drugs in history. With the improvement of coronary interventions in the past few decades, there has been more reliance on oral antiplatelet agents to reduce complications of in-stent restenosis/thrombosis. Clopidogrel was initially introduced in 1997, and within the past seven years, two additional oral antiplatelet agents have been approved by the U.S. Food and Drug Administration. With more potent antiplatelet agents comes increased risks of adverse effects. Physicians of all fields should be aware of the common antiplatelet agents used today, and the basic landmark trials that allowed them to be on the market today. The focus of this review article is to evaluate each oral antiplatelet drug, its brief history, relevant trials, indications and management of complications through evidence based guidelines.

Introduction
There have been two oral antiplatelet agents (prasugrel, ticagrelor) with varying mechanism of action and bleeding risk recently approved by the U.S. Food and Drug Administration (FDA) within the past seven years. The newer antiplatelet agents are used for management of patients with acute coronary syndrome (ACS) with or without percutaneous coronary intervention (PCI) and atrial fibrillation (Afib). This paper will critically review all the oral antiplatelet agents used today, including the two that are recently approved by the FDA. With newer, more potent, and faster acting antiplatelet agents comes with the increased risk of gastrointestinal (GI) bleeding. The aim will be to discuss each drug, its implication regarding GI bleeding, management, possible ways to reverse the antiplatelet agents and surgical recommendations (pre and post operatively) with regards to timing of withholding and resuming the common antiplatelet agents used today.

Antiplatelets
Antiplatelet agents have been around for a long time and are popular today due to their wide use for prophylaxis in cardiovascular events. Approximately 50 million people in the U.S. take aspirin (ASA) daily for the prevention of cardiovascular disease. In-stent thrombosis is mediated by platelet related mechanisms because newly placed stents are similar to unstable plaques until there is a cellular layer covering it, which depending on the type of stents can take varying amounts of time.1 Antiplatelets are used extensively pre and post operatively in patients requiring PCI. GI bleeding related to antiplatelets have been steadily rising with increased usage in patients taking it for primary and secondary prevention of cardiovascular events.2 As clinicians, it is important to recognize GI bleed secondary to antiplatelets, its general mechanism of action and the variety of ways to manage because it is a fairly common occurrence in general practice.

Aspirin
ASA was first marketed in 1899, and is one of the oldest drugs used today.3 It was initially used for analgesic, antipyretic, anti-inflammatory, and later found to have antiplatelet activity. Today, it is used extensively in the prevention of stroke, and patients with ACS requiring PCI. Its main action is in reducing thromboxane A2
synthesis (a prothrombotic agent) through irreversible inhibition of cyclooxygenase (COX), both COX-1 and COX-2. COX also mediates prostaglandin synthesis, and this inhibition is largely responsible for its major side effect of upper GI bleed and peptic ulcers. Other adverse effects include Reye’s syndrome; therefore, its use is discouraged in patients less than 19 years of age. Even though the half-life of ASA is three hours, its effect on platelets is permanent. Thus, bleeding time usually normalizes in approximately three days after discontinuation of ASA as platelets are continually replaced and have a lifetime of approximately seven to 10 days.

Patients who use low dose ASA for prevention of cardiovascular events who present with acute peptic ulcers can be a challenge in clinical practice. The first step is to re-evaluate the need for antiplatelet therapy. Withholding the drug during acute peptic ulcers is recommended, but prolonged withdrawal could increase the risk of strokes and precipitate an ischemic vascular event, especially in patients who are at risk for in stent thrombosis after PCI. Because the effect of ASA in the system lasts for the lifespan of the platelets, it is reasonable to resume once the GI bleeding has resolved (usually three to five days), and all other risk factors have been addressed (i.e., concomitant non-steroidal anti-inflammatory drugs (NSAIDs) use, Helicobacter pylori [H. pylori] infection, smoking, etc). Addition of proton pump inhibitors (PPIs) has been shown to reduce rate of recurrence of bleeding in patients taking low dose ASA after H. pylori has been eradicated (1.6 versus 14.8 percent). Sung et al. showed that patients who present with peptic ulcer disease and had endoscopic hemostasis in addition to intravenous PPIs have increased chances of recurrent bleeding (10.3 versus 5.4 percent) but had a lower all-cause mortality in 56 days (1.3 versus 12.9 percent).

**Clopidogrel (Plavix)**

Clopidogrel was approved by the FDA in 1997 for concurrent use with ASA in patients with ACS and/or requiring PCI to prevent stent thrombosis. It is a second generation thienopyridine after ticlopidine. Due to ticlopidine's poor side effect profile (neutropenia, thrombotic thrombocytopenic purpura (TTP), granulocytopenia, thrombocytopenia), it has largely been replaced clinically by clopidogrel. Thienopyridine derivatives exert their effect by irreversibly inhibiting the purinergic receptor 12 – adenosine diphosphate (P2Y₁₂ ADP) receptors on platelets. By inhibiting the P2Y₁₂ ADP receptors, activation of glycoprotein IIb/IIIa (GpIIb-IIIa) complex on the surface of platelets is impaired. This complex is responsible for bridging platelets together and is a key step in platelet aggregation. Of note, GpIIb-IIIa complex is dysfunctional in patients with Glanzmann’s thrombasthenia. Clopidogrel is a prodrug, and requires two step activation by the cytochrome (CYP) system, CYP P450. As a result, there is a delay in onset of action that could be problematic in patients who require anticoagulation acutely to reduce myocardial injury, such as in patients who present with acute myocardial infarction (MI). The solution is to have a loading dose of 300 mg followed by 75 mg daily that can result in maximal antiplatelet activity in approximately two to five hours from onset of dosing. The key enzyme in the metabolism of clopidogrel is CYP 2C19, which is also the enzyme responsible for metabolism of many PPIs. Administration of clopidogrel and PPIs together have a possibility of unwanted drug interactions. Currently there is mixed results regarding co-administration of clopidogrel with a PPI. Until further studies can be conducted, it is recommended to administer clopidogrel at least 12 hours apart from any PPIs. It is noted that some patients have variable response to clopidogrel, owing in part to the polymorphisms in the genes of CYP P450 enzymes and can vary widely, ranging from 5 to 56 percent in non-responsiveness to clopidogrel in studies.

Monotherapy with clopidogrel for prevention of ischemic events (recent acute MI, recent ischemic stroke or symptomatic peripheral artery disease) was assessed in the clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE) trial. This study overall demonstrates that clopidogrel was superior in reducing ischemic events when compared to ASA, but the most beneficial effect of clopidogrel is in conjunction with ASA as a dual antiplatelet therapy (DAPT) option for patients with ACS. The clopidogrel in unstable angina to prevent recurrent events (CURE) and clopidogrel as adjunctive reperfusion therapy – thrombolysis in myocardial infarction 28 (CLARITY TIMI 28) trial led to the conclusion that DAPT with ASA and clopidogrel in patients with ACS leads to decreased cardiovascular death and recurrent MI. The CURE trial, however, demonstrated that addition of clopidogrel to ASA increased risk of major bleeding (3.7 versus 2.7 percent with aspirin alone), but the number of life threatening bleeds or hemorrhagic strokes were similar. In the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel – thrombolysis in myocardial infarction 38 (TRITON TIMI 38), it was found that clopidogrel with ASA in a subset of patients being treated for moderate to high risk
patients with ACS (MI) undergoing PCI had a 1.2 percent chance of major bleeds defined as TIMI major (↓Hgb greater than or equal to 5, intracranial hemorrhage or cardiac tamponade).²⁻⁷ In patients who experience major GI bleed, it is recommended to stop the drug temporarily, control the bleed with supportive measures such as packed red blood cells (PRBCs) and platelet transfusion if necessary. Like ASA, the thienopyridine derivatives irreversibly inhibit platelet for the lifespan of that platelet, although via a different mechanism. It would seem reasonable to transfuse platelet if the bleed cannot be controlled; although there is no definite clinical evidence to prove that this is useful.¹¹ The decision to resume clopidogrel largely depends on the initial indication for the antiplatelet drugs and will be discussed. It has been shown that discontinuation of antiplatelet therapy, especially clopidogrel during critical periods after PCI is an independent risk factor for development of in-stent thrombosis, a potentially life threatening complication.⁴

**Prasugrel (Effient)**

Prasugrel was approved by the FDA in 2009 for use in patients with ACS requiring urgent PCI in conjunction with ASA to reduce cardiovascular events.³ Its indication is similar to clopidogrel. Like clopidogrel, it is a thienopyridine derivative which exerts its effects through inhibition of the P2Y₁₂ ADP receptors, irreversibly inhibiting platelet activity. The difference between the two is in their pharmacokinetics and the onset of action. Whereas clopidogrel requires two step hepatic conversion (mainly by CYP 2C19), prasugrel requires only one step conversion, making the onset of action faster.¹⁰ This results in 80 percent of the absorbed drug being converted to the active metabolite versus only about 10 to 20 percent with clopidogrel.¹ A usual loading dose of prasugrel (60 mg) achieves 80 percent of its inhibition of platelet activity (IPA) in only 30 minutes, with its maximal IPA at four hours. The platelet inhibitory effect with loading dose of prasugrel at 30 minutes is comparable to the platelet inhibitory effect with loading dose of clopidogrel at six hours.³ This correlates to roughly 10 times more potency than clopidorel and roughly 100 times more potency than ticlopidine.¹ This is clearly an advantage prasugrel has over clopidogrel in patients that require immediate antiplatelet activity, such as patients requiring urgent PCI who presents with ACS. In addition, because it is metabolized by a different CYP enzymes (CYP 3A4 and CYP 2B6), suspected PPI interactions with clopidogrel is not a major concern with prasugrel.³ CYP 3A4 inhibitors (i.e., ketoconazole) and inducers (i.e., rifampin) does not appear to have much interaction with prasugrel, leading to minimized drug and food interactions.³ Previous patients who were labeled as “non-responders” for clopidogrel, when administered prasugrel achieved maximum IPA similar to others who were “responders” for clopidogrel, suggesting that the resistance to clopidogrel is not at the level of the P2Y₁₂ ADP receptors, but in the metabolism to the active metabolites.⁷ In short, there are less “non-responders,” and less drug and food interactions with prasugrel compared to clopidogrel.⁷ TRITON TIMI 38 trial demonstrated that prasugrel had a 24 percent reduction in non-fatal MI versus clopidogrel, lower rate of stent thrombosis (1.1 versus 2.4 percent) in patients with moderate to high risk ACS including unstable angina, non ST-elevation MI, ST-elevation MI (UA/NSTEMI/STEMI) undergoing PCI.⁸⁻⁹

With an increase potency comes increased bleeding as well. In the TRITON TIMI 38 trial, prasugrel had a risk of major bleed (TIMI major) of 2.4 versus 1.8 percent with clopidogrel, with life threatening bleeding of 1.4 versus 0.9 percent, and fatal bleeding, 0.4 versus 0.1 percent.⁸⁻⁹ This is expected and is consistent with prasugrel’s more potent antiplatelet effects. Prasugrel should be avoided in patients who had a previous history of stroke or transient ischemic attack (TIA), as the harm of bleeding outweighs the benefit in these patients. Patients 75 years or older and weighing less than 60 kg should also avoid prasugrel.⁴ In summary, prasugrel’s use over clopidogrel prevents 23 MI, but at the same time will cause five major bleeds out of every 1,000 patients.⁹ There are currently no reversal agents for prasugrel, and like ASA and clopidogrel, its effect on platelets is irreversible. It would seem reasonable to consider platelet transfusion if bleeding cannot be controlled, but currently there are no randomized controlled trials regarding this option.

**Ticagrelor (Brilinta)**

Ticagrelor was introduced in 2011, the first of its kind. It is approved for concurrent use with ASA in patients with ACS with or without PCI.¹² Whereas the thienopyridine derivatives have irreversible binding at the site the of the P2Y₁₂ ADP receptors, ticagrelor is direct acting and reversible.⁴⁻¹² It’s site of binding to the P2Y₁₂ ADP receptor is non-competitive and distinct from that of the other thienopyridines.⁹ Ticagrelor is quick acting, is not a prodrug and does not require metabolic activation.⁹ Its onset of action closely mimics the plasma levels, which is
<table>
<thead>
<tr>
<th></th>
<th>Aspirin (ASA)</th>
<th>Clopidogrel (Plavix)</th>
<th>Prasugrel (Effient)</th>
<th>Ticagrelor (Brilinta)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year Introduced</strong></td>
<td>1899</td>
<td>1997</td>
<td>2009</td>
<td>2011</td>
</tr>
<tr>
<td><strong>Clinical Use</strong></td>
<td>Prevention of stroke, secondary prevention of CV diseases, antipyretic, analgesic, anti-inflamatory</td>
<td>Concurrent use with ASA in pts with ACS and/or requiring PCI to prevent stent thrombosis</td>
<td>Reduction of thrombotic cardiovascular events in pts with ACS and/or requiring PCI</td>
<td>Concurrent use with ASA in STEMI pts treated with PCI, NSTEMI, stable angina</td>
</tr>
<tr>
<td><strong>Therapeutic Dosage</strong></td>
<td>81 to 325 mg daily</td>
<td>300 mg loading dose 75 mg daily</td>
<td>60 mg loading dose 10 mg daily</td>
<td>180 mg loading dose 90 mg every 12 hours</td>
</tr>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>Reducing thromboxane A2 synthesis through irreversible inhibition of COX-1/2</td>
<td>Irreversible inhibition of ADP induced platelet aggregation by antagonizing P2Y12 ADP receptors on platelets</td>
<td>Irreversible inhibition of ADP induced platelet aggregation by antagonizing P2Y12 ADP receptors on platelets</td>
<td>Reversible, direct acting inhibition of ADP induced platelet aggregation by antagonizing P2Y12 ADP receptors on platelets</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Hepatic</td>
<td>Prodrug metabolized by liver. CYP2C19 key enzyme. About 10-20% of absorbed drug converted to active drug</td>
<td>Prodrug, requiring hydrolysis by intestinal esterases and hepatic (CYP3A4, CYP2B6). CYP3A4 inhibitor and inducer do not interact significantly. 80% of orally absorbed drug converted to active drug</td>
<td>Hepatic metabolization by CYP3A with active metabolites. Does not require metabolic activation</td>
</tr>
<tr>
<td><strong>Time to Maximum IPA</strong></td>
<td>Within 1 hour</td>
<td>4 hours (if loading dose given), or 4 days if on maintenance dose of 75 mg daily</td>
<td>80% of max IPA in 30 minutes with loading dose, 4 hours to max IPA</td>
<td>2 hours</td>
</tr>
<tr>
<td><strong>Elimination Half Life</strong></td>
<td>~ 3 hrs</td>
<td>~ 8 hrs</td>
<td>~ 7 hrs</td>
<td>~ 6-12 hrs</td>
</tr>
<tr>
<td><strong>Effect of Drug in System</strong></td>
<td>7-10 days</td>
<td>7-10 days</td>
<td>7-10 days</td>
<td>3-5 days</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Renal</td>
<td>Renal and biliary</td>
<td>Urine and fecal</td>
<td>Fecal, renal excretion minimal</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>Upper GI bleed/peptic ulcers, Reye’s syndrome</td>
<td>GI bleeding, TTP, neutropenia. Possible interactions with PPI. Metabolism highly variable due to polymorphisms of CYP enzymes</td>
<td>GI bleeding</td>
<td>Bradyarrhythmia, breathlessness/dyspnea, increase in serum uric acid</td>
</tr>
<tr>
<td><strong>Incidence of Major GI Bleed</strong></td>
<td>&lt; 1%</td>
<td>1.8% in concurrent use of low dose ASA in ACS pts undergoing PCI (TIMI major)*</td>
<td>2.4% in concurrent use of low dose ASA in ACS pts undergoing PCI (TIMI major)*</td>
<td>2.8% in concurrent use of low dose ASA in ACS pts (TIMI major)*</td>
</tr>
<tr>
<td><strong>Reversal Agents</strong></td>
<td>• Activated charcoal (if recent ingestion) • IV fluids • NaBicarb • Dialysis</td>
<td>Possible platelet transfusion (no evidence)</td>
<td>Possible platelet transfusion (no evidence)</td>
<td>Possible platelet transfusion (no evidence)</td>
</tr>
</tbody>
</table>
Aspirin (ASA)  

### Timeframe for Withholding Antiplatelets Prior to Surgery
- **Primary prevention**
  - 7-10 days prior
- **Secondary prevention**
  - Ideally should not be discontinued unless evidence of bleeding

### During mandatory dual antiplatelets
- **High level cardiac risk**
  - Postpone surgery
  - Elective surgeries
    - c/w ASA
    - d/c clopidogrel
      - If timeframe allows, d/c clopidogrel 5 days prior
  - Intermediate and low level cardiac risk
    - Elective surgeries
      - c/w ASA and clopidogrel
    - If high risk of bleeding
      - Maintain ASA
      - d/c clopidogrel 5 days prior
    - Elective surgeries
      - Maintain ASA
      - d/c prasugrel
        - If timeframe allows, d/c prasugrel 5 days prior
  - Intermediate and low level cardiac risk
    - Elective surgeries
      - Maintain ASA
      - d/c ticagrelor
        - If timeframe allows, d/c ticagrelor 5 days prior

### Prasugrel (Effient)
- **High level cardiac risk**
  - Elective surgeries
    - Postpone surgery
    - Urgent surgeries
      - c/w ASA
      - d/c prasugrel
        - If timeframe allows, d/c prasugrel 5 days prior
  - Intermediate and low level cardiac risk
    - Elective surgeries
      - Maintain ASA
      - d/c prasugrel
        - If high risk of bleeding
        - Maintain ASA
        - d/c prasugrel 5 days prior
    - Elective surgeries
      - Maintain ASA
      - d/c ticagrelor
        - If high risk of bleeding
        - Maintain ASA
        - d/c ticagrelor 5 days prior
    - Elective surgeries
      - Maintain ASA
      - d/c ticagrelor
        - If high risk of bleeding
        - Maintain ASA
        - d/c ticagrelor 5 days prior
  - Intermediate and low level cardiac risk
    - Elective surgeries
      - Maintain ASA
      - d/c ticagrelor
        - If high risk of bleeding
        - Maintain ASA
        - d/c ticagrelor 5 days prior

### Ticagrelor (Brilinta)
- **High level cardiac risk**
  - Elective surgeries
    - Postpone surgery
    - Urgent surgeries
      - c/w ASA
      - d/c ticagrelor
        - If timeframe allows, d/c ticagrelor 5 days prior
  - Intermediate and low level cardiac risk
    - Elective surgeries
      - Maintain ASA
      - d/c ticagrelor
        - If high risk of bleeding
        - Maintain ASA
        - d/c ticagrelor 5 days prior
    - Elective surgeries
      - Maintain ASA
      - d/c ticagrelor
        - If high risk of bleeding
        - Maintain ASA
        - d/c ticagrelor 5 days prior
    - Elective surgeries
      - Maintain ASA
      - d/c ticagrelor
        - If high risk of bleeding
        - Maintain ASA
        - d/c ticagrelor 5 days prior

IPA: inhibition of platelet activation; CV: cardiovascular; c/w: continue with; d/c: discontinue.

* TIMI major: drop of Hgb ≥ 5, intracranial hemorrhage or cardiac tamponade.

^ Dual antiplatelets refers to ASA plus clopidogrel/prasugrel/ticagrelor. Timeframe of mandatory dual antiplatelets is defined in the paper.

^ Recommendations for urgent surgeries are the same for intermediate and low level cardiac risk.

---

**Table 2. Classification Schemes for Predicting Stroke in Patients with AFib**

<table>
<thead>
<tr>
<th>CHA2DS2-VASc</th>
<th>Points</th>
<th>CHADS2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>HTN (or treated HTN)</td>
<td>1</td>
<td>HTN (or treated HTN)</td>
</tr>
<tr>
<td>Age 65-75 years</td>
<td>1</td>
<td>Age ≥ 75 years</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Prior stroke/TIA/TE</td>
<td>2</td>
<td>Prior stroke/TIA/TE</td>
</tr>
<tr>
<td>Vascular disease (i.e., PAD, MI, aortic plaque)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sex category (female)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

consistent with its reversible nature. It is metabolized by CYP 3A to an active metabolite but its contribution is minor compared to the parent drug. Its main advantage over other thienopyridine derivatives is that ticagrelor has a peak plasma concentration at two hours versus four hours for clopidogrel. Due to the reversible nature of ticagrelor, IPA can start to decline as early as 12 to 24 hours since last dose, and is the main reason why ticagrelor is recommended to be dosed twice daily as opposed to once daily. The effect of ticagrelor diminishes quickly (three to five days versus seven to 10 days for clopidogrel).

According to the platelet inhibition and patient outcomes (PLATO) trial, ticagrelor with concurrent ASA therapy in patients with ACS resulted in lower cardiovascular death (4 vs 5.1 percent with clopidogrel), reductions in MI (5.8 versus 6.9 percent), reductions in all-cause mortality (4.5 versus 5.9 percent), and reductions in in-stent thrombosis (1.3 versus 1.9 percent with clopidogrel). Incidence of GI bleeds were very similar to that of clopidogrel with TIMI major bleed of 2.8 percent for ticagrelor versus 2.2 percent for clopidogrel. Life threatening bleeds and fatal bleeds are not statistically significant when compared to clopidogrel. As with other antiplatelet agents, there are no specific reversal agents.

Clinical Indications of Antiplatelet Agents

ASA has been used for decades for primary prevention of cardiovascular disease (CVD) with varying outcomes in clinical trials. As such, there are currently no clear guidelines in the use of ASA in primary prevention for CVD. Despite this, it is still commonly prescribed by physicians today for primary prevention of CVD, in part due the traditional use of ASA and its long history. Varying organizations (American Heart Association, FDA, World Health Organization, etc.) have differing recommendations. It is reasonable to consider ASA for primary prevention in patients that are above 50 with cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, obesity, family history of CVD, etc.) taking into account the patient’s risk of a gastrointestinal bleed and hemorrhagic stroke.

In patients with non-valvular AFib, risk stratification scores such as CHADS$_2$ and CHA$_2$DS$_2$-VASc can be used to help determine whether the risk of stroke necessitate starting anticoagulation. Both classification schemes have been well validated, but CHADS$_2$ has largely been supplanted in clinical practice for the CHA$_2$DS$_2$-VASc due to better stratification of stroke in low risk patients. Please see Table 2 for the classification schemes. With increasing risk factors for stroke (increasing CHA$_2$DS$_2$-VASc score), the annual risk of stroke can range (3.67 percent per year in a patient with CHA$_2$DS$_2$-VASc score of 2, and 8.18 percent per year with CHA$_2$DS$_2$-VASc score of 4), and risks of stroke continues to increase with increasing CHA$_2$DS$_2$-VASc score. For patients who take ASA for stroke prevention in non-valvular AFib with CHADS$_2$ or CHA$_2$DS$_2$-VASc score less than 2, recommendations are to continue ASA indefinitely unless there are contraindications. The dosage of ASA should be 85 to 325 mg daily for stroke prevention in atrial fibrillation. If patients have CHADS$_2$, or CHA$_2$DS$_2$VASc score greater than or equal to 2, patients should be on one of the anticoagulants (i.e., warfarin, pradaxa, apixaban, rivaroxaban). The decision of which anticoagulant is largely determined by patient’s clinical condition and physician’s preference.

For patients who have had a previous cardiovascular event (i.e., ACS, stable ischemic heart disease), recommendations are for the patient to be on lifelong low dose ASA (75 to 100 mg) unless the patient has contraindications (i.e., allergies, GI bleed).

For acute presentation of ACS (i.e., NSTEMI, STEMI, UA), DAPT should be administered as soon as possible. The first antiplatelet agent is always ASA, and should be given with a loading dose of 160 to 325 mg orally. The second antiplatelet agent should be one of the P2Y$_12$ ADP receptor blocker (clopidogrel, prasugrel or brilinta), and the ultimate decision is at the discretion of the treating physician at the time. As mentioned previously, many trials have demonstrated varying efficacy regarding the differences between the three P2Y$_12$ ADP receptor blocking agents. Many interventional cardiologists favor the newer agents (prasugrel, brilinta) in patients presenting with ACS requiring PCI given their more potent antiplatelet activity compared to clopidogrel.

Antiplatelet Therapy Duration and Recommendations for Surgical Procedures

If a patient is considered low risk for thrombotic events and is taking ASA for primary prevention of cardiovascular events, it is recommended that patients discontinue ASA seven to 10 days prior to an elective surgery. In patients who are at higher risk for thrombotic events, American College of Chest Physicians guidelines recommend continuing ASA up to the date of the surgery.

Patients who take ASA for secondary prevention of their
cardiovascular disease should take it for their lifetime, ideally with no interruption and throughout surgery.\(^1\) DAPT (aspirin with clopidogrel, prasugrel or ticagrelor) is indicated for patients who are considered high risk of cardiac events. Current recommendations for mandatory dual antiplatelet therapy is “6 weeks after placement of bare metal stents, 3-6 months after an incidence of MI, and at least 12 months after placement of drug eluting stents.”\(^1\) In these groups of patients, disruption of postoperative MI and possibly death by up to ten-fold.\(^1\) bare metal stents, 3-6 months after an incidence of MI, and at least 12 months after placement of drug eluting antiplatelet therapy in this critical period can increase risk, or low risk:

- **High level cardiac risk:** “Less than 6 weeks after PCI, bare metal stenting, CABG, ACS, or MI (less than 3 months if complications); less than 12 months after drug eluting stenting - maybe longer in cases of high risk drug eluting stenting,”\(^1\) elective surgeries should be delayed until after the patient is deemed an intermediate cardiac risk level. For urgent/vital surgeries, clopidogrel should be withheld during surgery, but ASA should be maintained. If the surgery has a high risk of bleeding, and an urgent/vital surgery is required, P2Y\(_{12}\) ADP inhibitors should be stopped five days prior to surgery and possibly consider intravenous tirofiban or eptifibatide.\(^1\)

- **Intermediate level cardiac risk:** “6-12 weeks after PCI, bare metal stenting or coronary artery bypass grafting (CABG), 6-24 weeks after ACS or MI, more than 12 months after high risk drug eluting stenting,”\(^1\) elective surgery is considered to be permissible, but recommendations are to continue ASA and P2Y\(_{12}\) ADP inhibitors if prescribed. If the surgery is considered high risk of bleeding, elective surgeries should be postponed. For urgent/vital surgeries, maintain ASA, and discontinue P2Y\(_{12}\): ADP inhibitors five days prior to procedure and resume 24 hours after the procedure.\(^1\)

- **Low level cardiac risk:** “More than 3 months after PCI, bare metal stenting, or CABG; more than 6 months after ACS or MI, more than 12 months after regular drug eluting stenting.”\(^1\) It is recommended to continue ASA or P2Y\(_{12}\) ADP inhibitors during surgery, but if the surgery is considered high risk, then the recommendation is to stop P2Y\(_{12}\) ADP inhibitors five days prior to surgery if the patient is on it, and to resume it 24 hours after surgery.

Cardiac risk factors is stratified to high risk, intermediate risk, or low risk:

14. Patti G, Cavallari I. Patients with atrial fibrillation and CHADS2-VASc score 1: To anticoagulate or not to anticoagulate? That is the question! Heart Rhythm. 2015. doi: S1547-5271(15)00899-1 [pii].
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New Age of Treatment for Fecal Incontinence: Sacral Nerve Modulation

By Elizabeth E. Blears, MD; and Kevin Benson, MD, MS

Abstract

Sacral neuromodulation (SNM) is a minimally invasive therapy which is enabled by the implantation of a small neurostimulator in the subcutaneous tissue of the back and a connecting lead placed near the S3 nerve root. This system has been termed a “bowel pacemaker.”

Efficacy has been demonstrated in patients with fecal incontinence (FI), urinary incontinence, anorectal pain, anal fissures, chronic constipation, as well as patients with low anterior resection syndrome, FI related to rectal prolapse or external anal sphincter defects. SNM has become a well-established option for the treatment of FI, regardless of etiology.

Boyd was the first to use SNM for urinary incontinence in 1954 by placing an electrode in the S3 foramina that could pace the detrusor muscle. This intervention was described by Tanago in 1979 for use in FI, and has demonstrated efficacy in human trials since Matzel began implanting the device in 1995. Since approved for use in the U.K. in 2004, it has demonstrated benefit in 75 percent of patients up to 20 years post-implantation for mild to severe FI, and at present, over 2,500 patients undergo treatment with SNM in Europe each year. SNM has improved the management of FI, particularly for patients unresponsive to invasive surgery or aggressive pharmacotherapy.

Since traditional surgical and pharmaceutical options have demonstrated less benefit with higher morbidity, SNM can be considered as a standard of care, rather than an option within the armamentarium of treatments offered to patients with mild to severe FI because of its optimal results in the long term and low side effect profile compared to alternative treatments.

Epidemiology of Fecal Incontinence

Fecal incontinence (FI) is not a life-threatening symptom; however, it conveys a health burden affecting approximately 10 percent of the population over 40 years old, and being present among 50 percent of nursing home patients, it is the second most common indication for nursing home placement. It is a source of disability as most patients with the condition may be unable to work because of pain or choose to avoid social activities because of incontinence. Moreover, only 15 to 45 percent of sufferers receive treatment, perhaps because of such factors as a patient’s embarrassment in disclosing symptoms or because only an estimated 16 percent of physicians are aware of SNM as a treatment option.

FI is more common in women than men, with 8 percent of women in the overall population having symptoms. The rate of incontinence increases in men as age increases with 18 percent of men describing symptoms by age 80. While FI is associated with decreased functional status in men, in women it is associated with other factors, such as urinary incontinence, history of vaginal delivery (especially if traumatic) and major depressive disorder. Several factors, such as history of diarrhea, stroke, dementia, diabetes mellitus and lack of social activities are independent risk factors for both genders. Some studies report that the incidence has been stable over time, but others report an increasing incidence, particularly in countries that have a large proportion of elderly, such as Japan. While certain factors, like diarrhea and diabetes mellitus, are modifiable, many are not, and the problem requires a functional solution.

Physiology, Etiology and Diagnosis of Fecal Incontinence

Understanding the physiology of defecation enables the clinician to elucidate the proper cause of a given patient’s...
Defecation is controlled by three important muscles: the puborectalis (a sling-like muscle that encircles the rectum), the internal anal sphincter and the external anal sphincter. The internal anal sphincter muscle is made up of slow twitch muscle fibers innervated by the hypogastric nerve and pelvic plexi that are found within the S2, S3 and S4 nerves. The internal anal sphincter and the puborectalis are not under voluntary control. Rather, when the rectum fills with stool and the distension reaches a certain threshold, pressure sensory fibers of the internal anal sphincter trigger relaxation of the muscle fibers of the internal anal sphincter and the puborectalis muscle, reflexively allowing stool to be evacuated (Figures 1 and 2). This coordinated relaxation is termed the "rectoinhibitory reflex." Conversely, the external anal sphincter is under voluntary control and is made up of fast-twitch muscle fibers that can hold stool within the anal canal for approximately one minute. The external anal sphincter is under voluntary control by the pudendal nerve, and permits the individual to evacuate stool at his or her discretion. However, these fibers fatigue more quickly than the other two muscles involved in defecation, and the difference in muscle fiber physiology comes into play when assessing the etiology of a patient's FI.

Of note, FI is not a diagnosis itself, but only a symptom for which there are many etiologies. Proper diagnosis of FI involves a thorough history and physical exam, giving attention to the patient’s obstetric and neurologic history as well as a work up for any cause of diarrhea, if present. Patients can be asked to prepare a stool diary and a FI scoring tool can be used to establish baseline symptoms and monitor progress as therapy proceeds (Figure 3). The Cleveland Clinic Florida Fecal Incontinence and Wexner scoring systems are shown in Figures 4 and 5. The most

---

**Table 1. Etiology by Symptom**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Defect</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of stool despite patient’s best effort to control it (sensation is intact)</td>
<td>External anal sphincter</td>
<td>&quot;Urges&quot; or active incontinence</td>
</tr>
<tr>
<td>Loss of stool without patient’s awareness</td>
<td>Internal anal sphincter</td>
<td>Passive incontinence</td>
</tr>
<tr>
<td>Pain, constipation and incomplete evacuation</td>
<td>Puborectalis non-relaxation/rectoinhibitory reflex</td>
<td>Paradoxical contraction</td>
</tr>
<tr>
<td>Not feeling BM complete</td>
<td>Incomplete rectal evacuation</td>
<td>Overflow incontinence</td>
</tr>
</tbody>
</table>
### Figure 3. Stool Diary

**Stool Diary**

<table>
<thead>
<tr>
<th>Date</th>
<th>Time of Bowel Movement</th>
<th>Incontinence</th>
<th>Stool Seepage or Staining</th>
<th>Stool Consistency (Type 1–7)</th>
<th>Urgency – unable to postpone BM for more than 15 Minutes</th>
<th>Use of Pads</th>
<th>Medications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes / No</td>
<td>Yes / No</td>
<td>See Below</td>
<td>Yes / No</td>
<td>Yes / No</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

Use the following descriptors for describing stool consistency:

- Type 1: Separate hard lumps. Type 2: Sausage shaped but lumpy. Type 3: Like a sausage but with cracks on its surface. Type 4: Like a sausage or snake, smooth and soft. Type 5: Soft blobs with clear-cut edges (passed easily). Type 6: Fluffy pieces with ragged edges, a mushy stool. Type 7: Watery.

### Figure 4. Cleveland Clinic Fecal Incontinence Score

<table>
<thead>
<tr>
<th>Type of Incontinence</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>Rarely</td>
</tr>
<tr>
<td>Solid</td>
<td>0</td>
</tr>
<tr>
<td>Liquid</td>
<td>0</td>
</tr>
<tr>
<td>Gas</td>
<td>0</td>
</tr>
<tr>
<td>Wears pad</td>
<td>0</td>
</tr>
<tr>
<td>Lifestyle alteration</td>
<td>0</td>
</tr>
</tbody>
</table>

0, perfect continence; 20, complete incontinence.

Never: 0 (never); rarely, <1/month; sometimes, <1/week and >1/month; usually, <1/day and >1/week; always, >1/day.

### Figure 5. Wexner Scale

<table>
<thead>
<tr>
<th>Type of incontinence</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid</td>
<td>Never</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Liquid</td>
<td>0</td>
</tr>
<tr>
<td>Gas</td>
<td>0</td>
</tr>
<tr>
<td>Wears pad</td>
<td>0</td>
</tr>
<tr>
<td>Lifestyle alteration</td>
<td>0</td>
</tr>
</tbody>
</table>

Never, 0; rarely, <1/month; sometimes, <1/week, >1/month; usually, <1/day, >1/week; always, >1/day.

0, perfect; 20, complete incontinence.
common cause of FI is diarrhea; the volume and frequency of stool overcome the fatigable external anal sphincter, despite properly coordinated defecation. However, problems with anatomy, such as loss of reservoir following surgical resection, muscle tone (due to muscle atrophy, paralysis or inflammation) or sensation (loss of awareness of stool) can cause incontinence. See Box 1 for the patient symptoms and associated causes of FI. It is important in the evaluation to rule out problems that yield a similar history but are not “true incontinence.” Causes of “pseudoincontinence” include anorectal neoplasms, sexually transmitted diseases, poor hygiene, hemorrhoidal prolapse, and others. See Box 2 for a complete differential diagnosis for the symptom of FI. Work up involving colonoscopy or flexible sigmoidoscopy is usually reserved for patients that describe any alarm symptoms indicative of inflammatory bowel disease or neoplasm (See Box 3 for full list of alarm symptoms). In the absence of alarm symptoms, the diagnostic tools available typically have low yield for directing treatment and their primary function is in the academic investigation of defecation. See Box 4 for a list and description of these studies.

Efficacy of Sacral Neuromodulation

Sacral neuromodulation (SNM) begins with placement of a temporary pacemaker device in the subcutaneous tissue of the back, and a tunneled lead that delivers low amplitude electricity to the S3 nerve. An example made by Medtronic and its location are featured in Figures 6 and 7. A two to three week trial gages the patient’s response and

---

**Box 1. Physical Exam Findings**

- Inspect perianal skin for scars from prior surgeries, trauma or birthing injuries, fistulae, chronic soiling excoriation, prolapsed hemorrhoids (Valsalva maneuver can help reveal rectal prolapse)
- Palpation of perineal body in women to see if is atrophied
- Anal canal: check “wink” anocutaneous reflex, sensation to pinprick, check by finger for mass or fecal impaction
- Anoscopy (or flexible or rigid proctosigmoidoscopy): can help diagnose IBD, infectious proctitis or neoplasm

**Box 2. Differential Diagnosis**

- CNS/spinal cord injury
- Congenital malformations (Spina bifida, imperforate anus, myelomeningocele, hirshprung’s)
- Autonomic neuropathies (DMII)
- Neoplasm/radiation therapy
- Iatrogenic injury
  - LIS
  - Fistulotomy
  - Hemorrhoidectomy
  - Transanal advancement flaps
- Obstetric injury
  - Can result in anal sphincter injury (occult tears in 25 to 35 percent of vaginal deliveries and using forceps, mediolateral episiotomy and primiparity are risk factors for tears)
  - Denervation (60 percent of patients with obstetric tear also had evidence of pudendal nerve damage)
- High birth weight is risk factor for compression injury
- Pseudoincontinence
  - Internal/external hemorrhoids
  - Rectal prolapse
  - Incomplete evacuation
  - Poor hygiene
  - Anorectal STDs
  - Anorectal neoplasms
  - Fistula-in-ano

**Box 3. Alarm Symptoms**

- Unintended weight loss
- Hematochezia
- Family history of colorectal cancer
- History of inflammatory bowel disease
- Iron deficiency anemia
- Abrupt change in symptoms or nocturnal symptoms

**Box 4. Diagnostic Tools**

- Endoanal ultrasound: will show scar tissue/traumatic defects as mixed echogenic versus external sphincter is hyperechoic
- Anorectal manometry: no standardized method of manometric evaluation, but can give information about function of anal sphincters
- Rigid anoscopy or flexible sigmoidoscopy or colonoscopy
- Endoanal magnetic resonance imaging
- Cinedefecography/defecography: uses barium paste and fluoroscopic imaging of evacuation to give dynamic measure of muscle function will confirm rectal prolapse
- Electromyography: evaluates transmission of pelvic nerves through contractions of internal and external anal spincters and puborectalis
- Pudendal nerve terminal motor latency: measures speed of nerve conduction, thereby identifying damaged pudendal nerves by slower conduction speeds
provides time for adjustment as the patient records his or her symptoms in a stool diary. Permanent implantation is offered provided a certain threshold of clinical improvement is achieved, typically greater than 50 percent reduction in incontinence episodes from baseline. Different from conventional surgical therapies, such as anterior overlapping sphincteroplasty, SNM offers a prospective evaluation of the final therapy before committing the patient to a permanent alteration in anatomy. Moreover, during this trial phase, adjustments in the amplitude of current delivered through the lead can be made to optimize resolution of the patient’s symptoms prior to permanent implantation. In an early study of SNM, 15 patients demonstrated improvement in muscle strength with increases in resting anal pressure and continence, with 73 percent fully continent after five years.\textsuperscript{15}

Traditional surgical options include anterior overlapping sphincteroplasty (most common), as well as modifications to this procedure such as end-to-end repair, stapled transanal rectal resection procedure (STARR) or the Parks posterior anal repair. A sphinteroplasty is only offered to patients that demonstrate defects with the external anal sphincter by endoanal ultrasound (EUS), so many patients with severe FI are not eligible for treatment because the etiology of their FI involves dysfunction of the nerves of the pelvis or the deeper pelvic muscles. However, SNM may offer hope to these individuals. SNM has remarkably few contraindications: inaccessibility of neural foramina, a history of prior implants, regular need for MRI imaging or active post-sacral sepsis.\textsuperscript{16} SNM has demonstrated efficacy in the treatment of a variety of specialized patient groups, such as those with IBD, spinal cord injury, dual incontinence and anatomic sphincter defects. Remarkably, one study of SNM demonstrated that an intact external or internal rectal sphincter is not a prerequisite for success in patients with chronic FI.\textsuperscript{17}

Although the mechanism of action is not yet precisely defined, SNM is thought to stimulate both sensory and motor arms of the defecation reflex pathway\textsuperscript{18} and help normalize coordination of peristalsis within Auerbach’s plexus or within the spinal cord.\textsuperscript{19} Studies show that SNM improves the regulation of motor stimulation by normalizing colonic transit time; varying degree of improvements are noted with different etiologies of FI, as seen in patients with both FI and chronic constipation.\textsuperscript{20} Interestingly, patients can receive benefits regardless of the etiology and range of symptom severity. The first Cochrane Review of SNM in 2009 reported the efficacy of SNM for both FI and chronic constipation.\textsuperscript{4} This review included three crossover studies that demonstrated a decrease in the number of incontinence episodes when the device was turned “on” compared to when turned “off.” A study of 33 patients in 2014 examined the efficacy of SNM for a variety of causes of incontinence, such as obstetric injury during delivery, rectal prolapse, neurogenic and iatrogenic.\textsuperscript{21} The entire group of patients had failed dietary supplements and antidiarrheal medications, and 73 percent had failed biofeedback therapy. However, with SNM, the patients experienced a mean reduction in the number of incontinent episodes from 19 (range nine to 52) to two (range 0 to 12). Also, less severe episodes of incontinence were
observed after implantation and no complications were associated with either the trial or permanent phases. One patient underwent device explant nine months after permanent placement for chronic pain.

Improving the sensation of defecation is not altered with surgical treatment or pharmacotherapy. This is unlike SNM, which improves defecation sensation and highlights the importance of the sensory pathway which has previously been underappreciated as a factor in restoring fecal continence. Animal models reveal that SNM alters representation of the lower GI tract on the sensory cortex. In humans, SNM has been found to induce changes in the frontal cortex with increased activation of the Vagus nerve, as demonstrated by positron emission tomography (PET) scan. This is perhaps why SNM is more effective in the long term than sphincteroplasty, which only affects the external anal sphincter, while SNM affects the sacral nerves, pelvic floor muscles and central nervous system resulting in proper coordination of defecation. A prospective trial reported five-year results of SNM placement, with 55.6 percent of patients (60 of 101 patients) showing sustained favorable outcomes. A 2011 study of 41 patients receiving SNM for FI were followed for a mean of 51 months, and the results revealed statistically significant improvements in both incontinence episodes and quality of life measures. These data contrast with long-term data for surgical repair: Initial results for overlapping sphincteroplasty reveal improvements in 85 percent of patients in the short term, but only a minority maintains continence over a 10-year period, as demonstrated by several long-term studies. The Parks posterior anal repair is not widely practiced because the continence rates are only 33 percent at five years. A 2013 Cochrane Review of the surgical treatment for FI examined nine trials, with a total sample size of 264 patients, to assess the impact of surgery on change in incontinence, failure to achieve full continence and presence of fecal urgency. The authors’ conclusion was a “striking lack of high quality randomized controlled trials on faecal incontinence surgery” and “still not enough evidence on which to judge whether one type of surgical operation was better or worse than another one or better than different types of treatment for faecal incontinence.”

A compelling case for recommending treatment with SNM is the lack of morbidity compared to its surgical counterpart. Anterior overlapping sphincteroplasty or end-to-end sphincteroplasty are associated with evacuation difficulties, increased rate of fecal urgency, pelvic abscess, wound infection and even sepsis. The STARR procedure, which involves firing circular staplers to remove redundant rectal mucosa, is associated with a high rate of complications such as worsening incontinence, rectal pain, sepsis and rectovaginal fistulae. In contrast, long-term data for SNM published as recently as March 2015 shows sustained improvement in continence without major morbidity. The most common complication is pain around the pacemaker implantation site, occurring at a rate of approximately 13 percent, due to either hematoma or device protrusion. Other complications include failure of symptom improvement in approximately 5 percent of patients in the short term and 16 percent after an approximate two-year follow-up. The rate of adjustment for suboptimal device programming has been reported to be 29 percent in one study after permanent placement. Superficial wound infections are usually amenable to treatment with antibiotics, but deep infection requires removal of the device. Fortunately, the rate of these complications is even lower with superficial infection rates being reported at 10.8 percent, and deeper infections reported as exceedingly rare.

Conclusion

Since its use in humans 20 years ago, sacral neuromodulation has proven to be a safe and effective treatment for FI from a variety of causes, such as obstetric trauma, spinal cord injury or inflammatory bowel disease. Although the physiology of its benefit is still being delineated, SNM has demonstrated improvement in the sensory and motor pathways that contribute to fecal continence, which helps address the underlying pathophysiology causing uncoordinated defecation. Moreover, its benefits are associated with minimal morbidity and long-term efficacy, which is in contrast to traditional surgical and pharmacotherapies, which are accompanied by major morbidities and diminished efficacy over time. Clinicians can begin to help integrate this new, effective therapy to suitable patients for a common problem that so dramatically affects activity levels and quality of life.

REFERENCES


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Autism spectrum disorders (ASDs) are an aggregation of chronic developmental conditions distinguished by impaired verbal and non-verbal communication, repetitive behaviors (also called stereotyped behaviors), and significant inability to socialize and communicate. The prevalence of ASDs has exponentially grown in the past few decades. However, whether this is due to an actual increase, spreading awareness, or the lack of uniform methods used to diagnose these conditions and appraise their prevalence is ambiguous. Although the cause of autism is unknown in most cases, there is a small but vocal minority of people who attribute the rising rates of ASDs to childhood vaccination, despite the fact that there is little scientific evidence to support their argument. Vaccination has been instrumental in the eradication or control of 12 major infectious diseases including such scourges as smallpox, polio, and measles. Thus, vaccinations are essential to promoting a healthy population as determined by public health experts.

The question of what causes autism has plagued families of patients and baffled the medical/scientific communities for nearly 70 years. Although its foundations remain mysterious, a strong genetic component has been identified in those affected with ASDs. For example, it is known that if an ASD occurs in one of a pair of identical twins, there is a 60 percent chance that the other twin will also be affected. The risk of a sibling developing an ASD is 2 to 7 percent, compared to the general population risk of 0.01 to 0.08 percent. Opponents of this hypothesis argue that in most people with ASDs, a specific genetic defect cannot be identified. However, this is because the genetic basis of autism is an active area of research and specific genetic causes have been found in 10 to 15 percent of cases. It is expected that as the field advances, more genes involved in causing these diseases will be recognized. One of the main alternative theories as to what causes ASDs are environmental triggers—of which, vaccinations have garnered the most interest. This is owing to the coincidence that young children receive vaccines at the same age at which ASDs are usually diagnosed. According to Chatterjee and Moffatt, there is absolutely no “rigorous scientific evidence to support this contention.” Albeit, the true origins of ASDs are unclear, coincidental associations do not provide proof for the etiology of autism.

Yet if vaccines are not to blame, then why are ASDs increasing at such an alarming rate? The answer lies in the evolution and understanding of the definition of ASDs. Primarily, the way in which ASDs are diagnosed has changed over the years. The characteristics of autism were first addressed in Leo Kanner's 1943 article, “Autistic Disturbances of Affective Contact.” At this point in time autism was mainly studied in institutionalized children and believed to be a psychiatric disorder. This was later disproven by Bernard Rimland's book Infantile Autism; the Syndrome and its Implications for a Neural Theory of Behavior. Rimland's work then lead to much research in the late 1960's that established the neurologic, rather than psychiatric basis of ASDs. A number of conditions, such as mental retardation and learning disabilities began to be included under the umbrella diagnosis of ASDs, technically referred to as diagnostic substitution. As a consequence, the prevalence of ASDs seemed to increase with a concomitant decrease in other developmental disorders. Other health professionals, school teachers, and even the lay public began to recognize ASDs more easily (which is also referred to as ascertainment bias). Finally, the families of these children began to accept the diagnosis more readily, in part due to the availability of special services and governmental assistance for these patients.

One of the earliest claims that autism might be related to vaccines appears in the 1991 book A Shot in the Dark by Harris Coulter and Barbara Loe Fisher. Coulter and Fisher specifically stated, “With the increasing number of vaccinations American babies have been required to use has come increasing numbers of reports of chronic immune and neurologic disorders… including… autism.” This work did not receive much publicity until the now infamous article by Andrew Wakefield et al. which appeared in the British journal Lancet in 1998. The authors of the article claimed that of the 12 children in
their study with abnormal gastro-intestinal disorders, nine had been diagnosed with autism, and in six of the cases, either a parent or a physician had linked the onset of the developmental regression with the administration of the measles, mumps, and rubella (MMR) vaccine. This was the genesis of the alleged association between vaccines and autism.

Wakefield’s work has been discredited through investigations into his research methods and the discovery of his involvement with a lawsuit against the manufacturers of the MMR vaccine. The scientific limitations of the paper were pointed out shortly after it appeared. Wakefield’s study consisted of a small number of cases with no controls, linked three common clinical conditions, and relied on the recall/beliefs of parents rather than documented medical records. These early criticisms of the Wakefield paper spurred further research into his hypothesis. Numerous studies were conducted in various countries by a slew of different scientists—all of which failed to reproduce the results. Along with the dubious scientific value of his assertions, it was also found that Wakefield had engaged in unethical and fraudulent activities. It is unclear whether or not he had obtained parental consent for some of his procedures and it was shown that he had altered some of the patient data to match his conclusions. Following the revelation of his misconduct, 10 of the original 12 co-authors of this article abrogated the interpretation of their findings. The Lancet went on to retract the entire paper, an extremely rare occurrence in this distinguished journal’s history. For all these reasons his work shows no merit and cannot be cited as a credible source.

Another environmental trigger claimed to be associated with ASDs is exposure to thimerosal, a preservative that used to be added to vaccines. Thimerosal contains approximately 50 percent mercury by weight. While methyl-mercury is a known neurotoxin, the form of mercury present in thimerosal is ethyl-mercury which is far less toxic. Despite this difference, several public health organizations (including the U.S. Food and Drug Administration, the National Institutes of Health, and the Centers for Disease Control and Prevention [CDC]) urged the removal of thimerosal from childhood vaccines. It was only after this recommendation that certain parent groups formed to claim that their children were injured by thimerosal in vaccines. However, it is necessary to note that the symptoms of mercury poisoning and ASDs are distinctly different. Children with mercury poisoning display motor, speech, sensory, psychiatric, visual, and head circumference changes that are dissimilar/not present in children diagnosed with ASDs. Concerns about mercury as a cause of autism are biologically implausible.

A third erroneous theory presented by Dr. Jon Poling and his wife is that multiple vaccinations weaken the immune system. The Poling family received compensation from the U.S. Vaccine Injury Compensation Program for their daughter who was diagnosed with a mitochondrial enzyme deficiency with encephalopathy that was judged to have worsened following the receipt of several vaccines. This theory is flawed for many reasons. While the infant immune system is immature, it is capable of an array of protective responses starting at birth. Vaccines represent only a small fraction of the immunologic challenges that children face. According to a study of 25,000 illnesses in a group of Cleveland families, “the average child is infected with four to six viruses per year, exposing [their] immune system to more antigens than are present in childhood vaccines given simultaneously.” Most people do not recognize that although the number of childhood vaccines has increased, the immunologic load has actually decreased due to advanced technologies that are used to manufacture modern vaccines. Thus, the available data suggest that vaccines do not weaken the immune system or cause ASDs.

Vaccination, primarily a phenomenon of the 20th century, ranks among the greatest achievements of modern medicine. In the pre-vaccine era, human beings had few methods to prevent or treat various plagues and pestilences. As reported by the CDC, vaccination has contributed to the significant decline in illness and death from nine vaccine preventable diseases and their complications in the past century. As a result of their incredible success, most parents and even many health care professionals have limited or no experience with the devastating effects of these infectious diseases. Those who refuse to vaccinate their children assert that their children are healthy despite being unvaccinated. The fallacy of their argument is that their children are at least partially protected by herd immunity (a form of immunity that occurs when the vaccination of a significant portion of a population provides a measure of protection for individuals who have not developed immunity). Some parents perceive a greater risk from vaccines than from the diseases they are designed to prevent, not recognizing that the threat from these diseases is kept in check by effective vaccination programs.

In parts of the world where vaccination rates have fallen,
diseases such as measles and polio have resurfaced. For example, in the U.K. in 2005, the MMR scare resulted in a decline of vaccination rates that then led to a re-emergence of both measles and mumps. As expected, a majority of the cases occurred in inadequately vaccinated or unvaccinated children, sometimes resulting in deaths and permanent injury. This is especially concerning, as the U.K. had gone without a single death from measles in many decades. Clearly, such fears were unfounded and had unforeseen consequences.

In conclusion, vaccines are essential to a healthy society and any assertions that they cause ASDs are fallacious and potentially harmful to the public. In the past few decades, there has been a distressing rise in the number of cases of ASDs, however this is probably due to greater ascertainment bias, parental acceptance, and diagnostic substitution. In tandem, there has been an increase in the number of vaccines administered to children; however this congruence in time is merely coincidental and not causal. There is plenty of scientific evidence refuting many misconceptions regarding vaccines and ASDs, but this information is not readily accessible to the general public. The erosion in public confidence has led to the reappearance of various vaccine-preventable infectious diseases. A concerted effort by experts, health care providers, parents, and public health authorities to reinstate trust in these life-saving interventions is crucial.

REFERENCES


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The incidence of pediculosis capitis, commonly known as head lice, has been estimated between 6 to 12 million infestations each year in children 3 to 11 years old in the U.S. Head lice is estimated to cost as much as $1 billion annually, with a large portion of costs attributed to over-the-counter treatment. Lice are transmitted by direct contact of two people or by direct contact of infected items such as clothing or hair brushes. Lice are diagnosed by visual identification which can prove to be difficult as lice move to avoid light. An adult louse is typically 2 to 3 mm long, appears tan or grayish-white in color and can be found on the hair shaft within 4 mm of the scalp. Eggs may be found behind the ears or along the bottom of the hair line. Empty egg casings (nits) may be easier to identify as they will appear white among darker hair color. Misdiagnosis may occur when dandruff, hairspray, scabs, dirt or other insects are mistaken to be the different life stages of lice.

While non-pharmacologic remedies including nit combing are important components to the management of head lice, pharmacologic treatment with over-the-counter or prescription products remains the mainstay of lice eradication. Because head lice are associated with limited morbidity, the ideal treatment should be void of adverse effects. Treatment should not be used unless there is a clear diagnosis of lice. Pyrethrins and permethrin are inexpensive, easily obtainable without a prescription, and are typically first-line options for treatment of head lice. Their extensive use has led to resistance in lice and increased the need for alternative pediculocides.

**Pyrethrins, Pyrethroids, and Resistance**

Derived from chrysanthemum extract, pyrethrins inhibit closure of voltage-gated sodium channels, preventing nerve repolarization and causing paralysis of the insect. Piperonyl butoxide is added to pyrethrins to prolong effectiveness and is marketed as a shampoo (Rid) which is recommended for patients over 2 years of age. The product should be avoided in those with chrysanthemum allergy and used with caution in patients sensitive to ragweed, though incidence of allergic reaction is rare. The shampoo should be applied to dry hair and left on for 10 minutes before rinsing. Because residual effect is not seen with pyrethrins, a repeat treatment is recommended after seven to 10 days to rid newly hatched lice from eggs that were not killed with the first treatment.

Pyrethroids are synthetic analogues of pyrethrins. Permethrin lotion (Nix) is a commonly used pyrethroid available for over-the-counter lice treatment for children 2 months of age or older, and is associated with minimal toxicity to humans. Adverse effects include pruritus, edema, and erythema. Unlike pyrethrins, permethrin is not associated with allergic reactions in patients with plant allergies. To apply permethrin, the hair should be shampooed (without use of conditioner), rinsed, and towel dried. The lotion is left on the hair for 10 minutes then washed off. About one-third of eggs are not killed with the first application, but remaining permethrin residue in the hair kills lice emerging from the remaining eggs. If live lice are seen, the application may be repeated seven to 10 days after first treatment.

Multiple mechanisms are responsible for the resistance to pyrethrins and pyrethroids, including three genetic mutations also known as knockdown resistance or kdr. The kdr-type mutation results in desensitization of the nervous system to the effects of pyrethrins and pyrethroids. While it remains unclear if this resistance mutation directly predicts clinical failure, increasing rates of treatment failure have coincided with rising rates of kdr-type resistance. Gellatly and colleagues collected lice samples from 138 geographical locations including 48 U.S. states to determine kdr-type mutation frequencies. Of the 138 sites, 100 percent of lice samples collected at 132 of the sites were found to carry all three kdr-type mutations, including the two collection sites in South Dakota. They found an overall increase in kdr-type mutations from 37 percent in 2001 to 98 percent in 2015,
while at the same time correlating a decline in the rate of lice-free patients after use of permethrin from almost 100 percent in 1998 to 25 percent in 2009.

Pyrethrins and pyrethroids are still effective in many cases and remain the recommended first line agents, however these increasing rates of resistance raise the need for providers to be aware of alternative treatment options for patients who fail non-prescription treatment.3

**Malathion**

Available by prescription only, malathion 0.5 percent is an organophosphate that returned to the market in 1999.1 Malathion lotion is applied to dry hair, left to air dry, and then washed thoroughly after eight to 12 hours. A single application is sufficient for most patients, as malathion has high ovicidal activity, but it may be repeated if lice are still seen seven to nine days after treatment. The product marketed as Ovide has 78 percent alcohol content, making it highly flammable. Patients should be instructed not to use hair dryers or other heat styling devices during treatment. Malathion is approved for children age 6 years of age and older, and is not recommended in children less than 2 years of age. Adverse effects include skin irritation and rare second degree burns.

**Benzyl Alcohol**

Benzyl alcohol 5 percent lotion (Ulesfia) is Food and Drug Administration (FDA) approved for children 6 months of age and older. With an alternative mechanism of action compared to pediculocides, benzyl alcohol instead acts by suffocating lice. The lotion is applied to dry hair to fully saturate the scalp and hair, and is then washed out after 10 minutes. One 8 ounce bottle of Ulesfia is needed to treat a child with hair length of 2 to 4 inches, while children with longer hair will require multiple bottles.3 As with pyrethrins, the treatment should be repeated in seven days as it is not ovicidal. Benzyl alcohol should not be used in neonates due to risk of neonatal gasping syndrome if the product is absorbed systemically. Side effects of benzyl alcohol are minimal and include pruritus and erythema. In a randomized, double-blind study, benzyl alcohol resulted in 76.2 percent of patients lice-free after treatment compared to 4.8 percent of patients who were treated with the inactive vehicle alone (p<0.001).5

**Ivermectin**

A prescription-only lotion form of ivermectin 0.5 percent (Sklice) is approved for treatment of children 6 months and older. Ivermectin enhances chloride ion permeability, resulting in hyperpolarization and death of lice due to paralysis. Ivermectin lotion is applied to dry hair and scalp, and is rinsed out in 10 minutes. Lice that hatch from remaining eggs are also paralyzed, thus only one treatment application is required. The most common adverse reactions reported include skin dryness and irritation. In two clinical trials, 765 patients were randomized to ivermectin or vehicle control, with 85.2 percent versus 20.8 percent of patients lice-free on day eight after treatment (p<0.001).6

While not FDA approved for head lice, oral ivermectin has been studied for off-label use.3 A single dose of 200 mcg/kg repeated in 10 days has shown efficacy against head lice, as well as a single dose of 400 mcg/kg repeated in seven days. Oral ivermectin can cross the blood-brain barrier, causing blockade of neural transmission. Oral ivermectin is not recommended for patients weighing less than 15 kg, as younger children are at a higher risk for adverse reactions. Due to the risk of toxicity, oral ivermectin is reserved for treatment failures after other options have been tried.

**Spinosad**

Spinosad 0.9 percent suspension (Natroba) is a prescription product approved for topical use in children over 6 months of age.3 Derived from soil bacterium, spinosad offers both ovicidal and pediculicidal activity by inhibiting neuronal activity in insects and their eggs. Spinosad is applied to dry hair to saturate the scalp and hair, and is then rinsed off 10 minutes later. A second treatment may be given at seven days if live lice remain, though one treatment is typically sufficient. Adverse effects are rare and include skin irritation. Spinosad was compared to permethrin 1 percent in two randomized controlled trials involving over 900 patients with lice. Treatment with spinosad resulted in 84.6 and 86.7 percent of patients lice-free, while permethrin resulted in 44.9 and 42.9 percent of patients lice-free after treatment (p<0.001).7

**Summary**

Over-the-counter lice treatments may be less effective but remain first line for most patients. In the setting of treatment failure, the use of prescription products may be required after ruling out treatment failure from improper product use or reinfestation from another lice contact. In children over the age of 6 months requiring prescription treatment, options include benzyl alcohol, spinosad, or topical ivermectin. For children over age 2 years, malathion can also be considered. An ongoing Cochrane
Review aims to address comparative effectiveness of various treatment options, as well as determining safety and tolerability. The specific agent should be chosen with regard to cost, potential adverse effects, and method of application.

<table>
<thead>
<tr>
<th>Medication</th>
<th>OTC/Rx</th>
<th>Average Cost</th>
<th>Number of Treatments Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrethrins + piperonyl butoxide (Rid)</td>
<td>OTC</td>
<td>$20/kit*</td>
<td>Repeat in 7-10 days</td>
</tr>
<tr>
<td>Permethrin 1% (Nix)</td>
<td>OTC</td>
<td>$20/kit</td>
<td>Single application sufficient; May repeat in 7 days if needed</td>
</tr>
<tr>
<td>Malathion 0.5% (Ovide)</td>
<td>Rx</td>
<td>$216</td>
<td>Single application sufficient; May repeat in 7-9 days if needed</td>
</tr>
<tr>
<td>Benzyl alcohol 5% (Ulesfia)</td>
<td>Rx</td>
<td>$218*</td>
<td>Repeat in 7 days</td>
</tr>
<tr>
<td>Spinosad 0.9% (Natroba)</td>
<td>Rx</td>
<td>$240</td>
<td>Single application sufficient; May repeat in 7 days if live lice are seen</td>
</tr>
<tr>
<td>Ivermectin 0.5% (Sklice)</td>
<td>Rx</td>
<td>$363</td>
<td>Single application sufficient</td>
</tr>
</tbody>
</table>

*Average cash price without insurance, as determined by average of several South Dakota pharmacies.

*May require more than one unit for longer hair.

OTC – available without a prescription.

Rx – requires a prescription

References:

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Dear Participating Provider,

As a participating provider in the DAKOTACARE network, we value your partnership in delivering quality care to your patients.

On Monday, Aug. 22, DAKOTACARE received notice from Sanford Health that they would end their providers' participation in the DAKOTACARE provider network effective Jan. 1, 2017.

DAKOTACARE has a 30-year history of maintaining a broad network of providers, and we value the relationships DAKOTACARE has built with physicians. Avera had hoped to continue negotiations with Sanford and is still open to collaborating with them.

Our top priority is our DAKOTACARE members. We will communicate with our employer groups and insureds to help them understand how Sanford's decision impacts them.

For our members who are in certain active treatment plans with Sanford providers there will be provisions for continuity of care so they can conclude their care regimen. Our customer service representatives are available to assist you and any of your patients who may need to change providers in this transition as we approach the Jan. 1 effective date.

Our goal is to put patients first and find solutions to ensure DAKOTACARE groups and policyholders receive the access and coverage they need. Our commitment to our members and customers does not change.

We ask for your assistance and collaboration in transitioning patients, so they are impacted as little as possible and experience uninterrupted care.

Again, thank you for your partnership in providing quality care to the patients you serve. We will continue to communicate with you to keep you up to date with any new developments.

Sincerely,

E. Paul Amundson, MD
Chief Medical Officer
Despite immunization effectiveness in preventing morbidity and mortality due to infection, there remains a significant percentage of our population that has not received the recommended vaccines. A number of factors can contribute to the low rates. Misconceptions about the need for immunizations as well as concerns regarding effectiveness and safety remain barriers. The cost and insurance coverage of the medications, along with a somewhat complicated dose and timing of administration, can contribute to lower rates. Perhaps the most important issue may relate to the failure of clinicians to recommend and encourage these vaccines.

The Great Plains Quality Innovation Network (QIN) actively works with providers, partners, and patients to implement practices that support the bold national goals of improved immunization. Great Plains QIN has developed a number of evidence-based resources to promote influenza, pneumococcal, and herpes zoster vaccination best practices, guidelines, and tools. We also hope to break down barriers for disparate and underserved populations. Home health agencies are another source of improving access to vaccination. Learning and action networks (LANs) are an interactive communication tool to give providers, community organizations, and patients the ability to share and learn. Great Plains QIN gives information about these options regarding immunizations on their website, www.greatplainsqin.org.

Overcoming misconceptions about vaccination effectiveness and safety is a difficult challenge. It often requires direct conversations and strong recommendations on the part of the clinician to ensure the patient has a clear view of the evidence supporting routine, safe administration of the vaccines. Cost concerns were sometimes a reason why patients did not receive recommended vaccine. The Affordable Care Act requires insurers to cover the cost of immunization recommended by the Advisory Committee on Immunization Practices (ACIP), helping a number of patients overcome that obstacle.

Immunization information systems (IIS) are confidential population-based computerized data bases that record all immunization doses given by participating providers to patients in a given geopolitical area. Submitting information to immunization registries makes that information readily available to other providers and institutions such as public health clinics or schools. When it becomes widespread it offers providers historical immunization data to assist in keeping vaccinations up to date. This will help contribute to public health by reducing vaccine preventable disease and over-vaccination. This is a prime example of the benefit of interoperable EHR data in improving health care delivery.

Another area for patients to access immunizations is participation by pharmacies. This offers a convenience for patients because of availability after hours as well as accessibility in underserved and rural areas. This could represent an effective way to increase vaccination rates.

Ultimately the aim is disease prevention. Evidence supports the use of vaccine and it remains a challenge for providers to increase rates and diminish illness. Achieving the bold goals of the Healthy People 2020 listed below will be the effort of the Great Plains QIN.

1) By 2019, a national absolute immunization rate of 70 percent, 90 percent for pneumonia, and 30 percent for zoster. Also an effort to reduce disparities among racial and ethnic minority and rural Medicare beneficiaries and dual-eligible Medicaid beneficiaries.

2) By 2019, 1 million previously unimmunized Medicare beneficiaries will receive pneumonia immunization.

3) By 2019, an absolute rate of 90 percent for adult immunization status assessment, appropriate immunizations or referrals, and documentation of Medicare beneficiary immunization status to the state or an IIS via CEHRT and other electronic methods.

If you would like additional information or resources, please feel free to contact me at stephan.schroeder@area-a.hcqis.org.
Have you heard the myth of Prometheus, a Greek Titan god, and challenger of Olympian god Zeus? Prometheus stole fire from Olympus, brought it down to humankind, making Zeus furious for sharing with mere mortals the secret of such creative power. Zeus punished Prometheus by chaining him to a rock. Each day birds would eat away his liver, and each night his liver would grow back. Every day Prometheus would suffer again, forever repeatedly punished for his gift to humanity.

There are many interpretations of the myth, but probably the most famous comes with the Frankenstein story, written by 17-year-old Mary Shelley in 1816.

In Shelly's time, science was virtually exploding with new knowledge. Modern medicine was becoming effective, illustrated by how death rates were dropping; Galvani and Volt had just discovered how a dead frog leg would jerk when connected to a battery; chemists were showing how ether and nitrous gasses could make people stay asleep during surgery; and biologists were on the verge of realizing how microscopic bacteria cause contagion and fever, and how cleanliness could prevent such infection following surgery.

Thus, it is understandable why Shelly would create her famous story about scientist Victor Frankenstein. Like Prometheus who brought fire to mortals, her mad scientist brought life back to something once dead using newly discovered breakthroughs in electricity and chemistry. Shelly imagined how a mortal with scientific knowledge could create a superhuman being out of body parts stolen from a graveyard.

However, such a discovery should require responsibility and careful safeguards, or else, like fire that could jump its boundaries and spread destruction, so could creative scientific experimentation get out of control and cause monstrous harm and havoc to people and the environment. One cardinal rule of ethics we are taught in medical school demands, “first of all, do no harm.”

Consider how nuclear power can produce marketable energy and yet could cause explosions of mass destruction; how antibiotics can treat infections that would certainly kill, and yet could cause life-threatening overgrowth diarrhea illnesses; how advancements in genetics could promise to treat chronic diseases like an inherited emphysema-like condition or hepatitis C, and yet could cause potential harm to our society's ability to afford health care. Indeed, great advancements in science can do such good and yet could cause potential danger to public and environmental health.

Thus, the Greek myth of Prometheus and the monster story of Frankenstein both speak to us today. As we seek to advance science we must understand the ethical responsibility of safety, “first of all, do no harm.”
For Your Benefit:

Get Involved in the SDSMA

Thank you for your membership in the South Dakota State Medical Association. As a member, you have several direct opportunities to become more involved in the important work of the SDSMA:

• Doctor of the Day – serve as the physician for the South Dakota State Legislature for one day during session
• Physician lobbyist – serve as a volunteer lobbyist during the legislative session
• SDSMA PAC – help friends of medicine become elected officials and lawmakers
• SDSMA committees and task forces – serve the organization and yourself
• SDSMA appointments to state boards, committees and commissions – the SDSMA is asked to nominate and recommend physicians to fill positions to numerous vacancies every year
• Districts and specialty societies for local involvement

If you’d like to get involved, give us a call at 605.336.1965 or visit www.sdsm.org for more information.

“For Your Benefit” is the SDSMA’s monthly update on programs and services available to physicians through their affiliation with the SDSMA.

SDSMA President Visits Medical Districts

SDSMA President Dr. Tom Hermann’s Presidential District Visits are underway. Dr. Hermann and physicians attending have discussed issues facing physician practices, the challenges faced in health care in South Dakota and nationwide, and the ways physicians can work together toward common goals.

So far, Dr. Hermann has been hosted by the District 6 Medical Society in Mitchell, District 2 and 12 in Watertown, and District 3 in Brookings.

Please consider attending your district’s meeting. Dr. Hermann and SDSMA staff want to hear your concerns about challenges that affect care for South Dakotans and to gather ideas on how to work together to represent physicians both at the state and federal levels.

The remaining Presidential District Visit schedule is as follows:

• Oct. 6 – Districts 1, 6 p.m., Moccasin Creek Country Club, Aberdeen
• Oct. 12 – District 5, 6 p.m., Ryan’s Hangar Restaurant & Ace Lounge, Huron
• Oct. 13 – District 8, 6 p.m., The Landing Restaurant & Lounge, Yankton
• Oct. 19 – District 9, 6 p.m., Rushmore Hotel, Rapid City
• Jan. 10 – District 10, 6 p.m., Frank Day’s Bar, Dallas
• Jan. 11 – District 11, 11:30 a.m., Mobridge Regional Hospital, Mobridge
• Jan. 11 – District 4, 6 p.m., RedRossa Italian Grille, Pierre

Source: SDSMA staff

Support Medical Student Scholarships

Since the establishment of the SDSMA Foundation in 1949, hundreds of medical students have received help through much needed scholarships and low-interest loans.

With the rising cost of education, the need continues.

Please support South Dakota medical student scholarships. Your donation to the SDSMA Foundation has a lasting impact and helps offset the more than $180,000 in debt incurred by medical students upon graduation.

Log in through your SDSMA account at www.sdsm.org to make a donation to the SDSMA Foundation, or send your contribution to SDSMA Foundation, PO Box 7406, Sioux Falls, SD 57117.

Thank you for your generosity and support of the SDSMA Foundation.

Source: SDSMA staff
Sign up to be Doctor of the Day at the State Capitol!

The SDSMA’s Doctor of the Day program is a huge success every legislative session.

During session, the SDSMA commits to providing a physician member to serve as Doctor of the Day for the State Legislature in Pierre. This volunteer commitment involves one day of service at the State Capitol by providing basic medical assistance to legislators and staff as needed.

As Doctor of the Day, you’ll have the unique opportunity to interact with legislators on the House and Senate floors and get a first-hand look at the legislative process and how it affects the practice of medicine. Your presence at the Capitol shows legislators not only your expertise but also your concern for the health of South Dakotans.

The SDSMA is in need of volunteers willing to spend a day to serve as Doctor of the Day. Each year we receive requests from physician assistants and advanced practice nurse practitioners who wish to participate in the program; it is critical that volunteer physicians are serving each day of session.

South Dakota’s 2017 Legislative Session opens on Jan. 10. For more information and to see a listing of available dates, visit www.sdsm.org. If you are interested in volunteering or have questions, please contact Mark East at 605.336.1965 or meast@sdsm.org.

Source: SDSMA staff

2017 SDSMA Membership Dues Renewal Now Available

Annually, SDSMA members must renew their membership to continue receiving many great membership benefits. Membership renewal will take place on the SDSMA website at www.sdsm.org.

To ensure a smooth renewal process for 2017, complete the following today:

Log into your member profile at sdsm.org and enter your username and password. If assistance is needed, contact the SDSMA office at 605.336.1965 or membership@sdsm.org.

Do not create a new account. All members have an account at sdsm.org.

Contact your office administrator to determine if you or your organization will be paying the dues so it’s clear who will be completing this online process.

Once you have logged into your account, proceed to the Pay My Dues link at the top of the page. Payment by electronic check and credit card are both accepted through your account. A receipt will be emailed to you upon completion of the payment.

For step-by-step instructions on how to renew visit the Membership tab at www.sdsm.org and select Renewal.

Those with questions may contact Laura Olson at 605.336.1965 or membership@sdsm.org.

Source: SDSMA staff

Legal Brief Highlight: Physician Employment Agreements

When negotiating an employment agreement, physicians should be mindful of the length of the term of employment, the method and means of termination, how compensation will be determined and paid, the avoidance of conflicts of interest, and the terms of any possible restrictive covenant.

It is recommend that physicians establish goals for the employment relationship before starting contract negotiations with the potential employer. As stated in the preface to the American Medical Association’s (AMA) Annotated Model Physician Employment Agreement, “the time to think about your future and to do something about it is before the contract is signed, preferably before negotiations begin. Know what you want and why you want it; then ask for it.” The SDSMA Center for Physician Resources at www.sdsm.org and the AMA at www.ama-assn.org have several resources available to physicians that can help in establishing goals and reasonable expectations, and potentially avoiding pitfalls as well.

For more information, download the SDSMA legal brief Physician Employment Agreements at www.sdsm.org. Through the SDSMA Center for Physician Resources, the SDSMA has developed more than 50 legal briefs that are available to members. In addition, the Center develops and delivers and programs for members in the area of practice management, leadership and health and wellness.

Source: SDSMA staff
CMS Tool Would Allow Physicians to Determine Possible Impact of MACRA on Their Reimbursement

CMS intends to unveil a new web tool that helps clinicians assess the potential impact of merit-based incentive payment systems (MIPS) on their reimbursement, according to Modern Healthcare.

The tool will help physicians evaluate their performance under the system and provide tips to improve scores. The article explains that MIPS, which is part of the Medicare Access and CHIP Reauthorization Act, requires that physician reimbursement be based on a compilation of quality measures and the use of electronic health records.

Read more at www.modernhealthcare.com.

Source: Modern Healthcare
### CME Events

Continuing Medical Education events which are being held throughout the United States (Category 1 CME credit available as listed)

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<td>Pediatric Grand Rounds: The Up Side to Down Syndrome in the 21st Century</td>
<td>Internal Medicine Grand Rounds: Updates for Nephrology in Four Acts</td>
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<td>Internal Medicine Grand Rounds: Cardiovascular Disease in Women</td>
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<td>Pediatric Grand Rounds: Mom, Potato Oles, and the Patient Experience – One Clinician’s Street Level View</td>
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**DO YOU HAVE A CME EVENT COMING UP? WOULD YOU LIKE TO HAVE IT LISTED HERE?**

*Contact: Elizabeth Reiss, South Dakota Medicine,*

2600 W. 49th Street, Suite 200,

Sioux Falls, SD 57105

Phone: 605.336.1965 • Fax: 605.274.3274

Email: ereiss@sdsmi.org
At MMIC, medical liability is just the beginning. For more than 35 years, we’ve worked directly with physicians and developed a deep understanding of the risks involved with practicing medicine. We’re there for those who are always there, drawing on a wide range of clinical data, insights and best practices from medical experts to help care teams deliver better care. To learn more visit MMICgroup.com.
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