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Both learning and teaching are changing with technology. We seem to now rely less on the didactic real life models many of us have had. Our millennial learners want to know what is expected of them in the way of objectives and goals our schools challenge them with. Then they bring a ménage of tools and savvy to mastering them with our electronic world. Those old lecture formats and our cherished teaching techniques of old have, in many ways, given way to a new academia world. There is so much to learn and so much information, and often, it is compressed in time, and launched outside of lecture halls, with our patient contacts a vestigial last bastion of how our teachers know how to still teach.

Recently our own Dr. Tim Ridgway presented a lecture about the knowledge that comes from those clinical experiences. Attending physician mentors act and handle a multitude of medical scenarios, and students reflect and share their reactions to various clinical teaching scenarios. These shared experiences of insights in clinical situations, and how physicians respond as professionals and as people, are apparent highlights in the learning experiences of our medical students. Let us hope this type of mentoring will never be lost.

What a unique experience for us carrying the banner of the House of Medicine and sticking to our mission to promote the art and science of medicine and protect the health and quality of medical care for our citizens this legislative session has been. With the legislature passing SB 61 allowing independent practice of medicine by advanced practice registered nurses, we venture into potential new scenarios in provision of medical care that many of us consider a time of jeopardy for our patients and a time of uncertainty regarding where this goes from here. The benevolent relationships of the past with collaborative oversight were apparently legislatively deemed to not be meeting the needs of providing primary care across our state. Our SDSMA voices of concern and rationale fell on a majority of deaf ears. We spoke not against the fine APRN individuals who we’ve worked with, who we’ve provided teaching, and who we’ve guided in our own practices, but for the importance of the hours spent completing medical school and the post graduate training of three years, along with certifications along the way, in order to apply for a license to practice medicine as physicians in South Dakota. With Gov. Daugaard signing this bill, what message does it bring to our medical students? What challenges does it bring to the South Dakota Board of Medical and Osteopathic Examiners to adapt and modify the present requirements that physicians must face to practice medicine? Who else may come forward as paramedical professionals to request of the legislature that they, too, can “practice medicine?”

At the time of this writing, we are also facing a legislative battle to protect the provision of maternity care as it pertains to our past support of “nurse midwifery” from the legislatively proposed “certified midwifery,” which means “non-nurse.”

May we continue to work together to serve our patients and our state in providing the highest quality of care and to continue to promote the profession of medicine. There seems to be a new era of learning, new modes of teaching, and legislative transitions away from the steadfast pillars of experience, teaching models, and team-based care that have made medicine what it has been to this point. We must still have courage to be the best physicians, teachers and role models we can be. Let us strive to keep our teams intact and the circles of excellence in care unbroken.
Can I create a tax loss from my vacation home?

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If you used the property for the greater of 14 days or 10% of the total time rented, then it is considered a vacation home by the IRS. You can write off most expenses associated with the vacation home, but you will have to prorate the expenses between personal use and rental use. Oh, and the pesky IRS says that if it’s a vacation home, then you can’t create a loss. So, even if you have a nice depreciation charge or other expense to offset the revenue, you can take your income down to zero, but you can’t create a loss to offset your other income.

There is, however, a way to rent it out for 14 days or less and not report the rental revenue as taxable income.....
In this month’s issue of *South Dakota Medicine*, we have a number of very interesting manuscripts. In this issue, we continue the point-counterpoint discussion of pharmacogenomic testing in the use of specific medications. This month’s feature, by Russell A. Wilke, MD, PhD, and Joseph Fanciullo, MD, is on the utility of SLCO1B1 genotyping for the use of statins. This manuscript illustrates the importance genetics and genomics is having in medicine today.

In this issue, Bruce Vogt, MD, and co-authors discuss the process of peer review for scientific publications including *South Dakota Medicine*. Peer reviewed publication is an important aspect of scholarly activity which allows one to communicate important findings to the scientific community. Peer review itself is a time-honored method of allowing scrutiny of scientific findings by our scientific peers prior to their publication and becoming part of our knowledge base. In this review, the authors discuss the importance of peer review, what to consider before accepting a review assignment, the format of the review, and comments for the author. *South Dakota Medicine* is fortunate to have a number of excellent peer reviewers who volunteer their time and energies to this critical task.

In this issue we also have important articles on pulmonary embolism, meningitis, hepatic adenoma, and the use of paclitaxel following infra inguinal endovascular revascularization. I hope you enjoy this thought-provoking issue of *South Dakota Medicine*. 

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**Editorial**

**So You Want to Be a Reviewer**

By Keith Hansen, MD

*Editor, South Dakota Medicine*
Point-Counterpoint: SLC01B1 Genotyping for Statins

By Russell A. Wilke, MD, PhD, FACP; and Joseph Fanciullo, MD, FACR

Introduction

There is a great deal of interest in understanding genes that predict drug response. In January, South Dakota Medicine began publishing a series of monthly articles dedicated to reviewing the pros and cons of gene-based drug dosing. The first article in this series was a point-counterpoint argument by local content experts exploring the utility of CYP2C19 (cytochrome P450 gene, subfamily 2C19) genotyping for patients taking clopidogrel. The second article explored genotype-guided warfarin therapy. We now present the third article in this series, a discussion of the genes that impact patient risk for myopathy on statins.

Russell Wilke, MD, PhD, FACP: “The SLC01B1 Gene Impacts Risk for Statin Myopathy”

HMG Co-A reductase inhibitors (statins) are among the most commonly prescribed drugs in the industrialized world. Currently there are half a dozen drugs available for clinical use within this class, and they vary in clinical efficacy. While they are also generally regarded as safe, greater than 1 percent of patients exposed to statins develop myalgias. Fortunately, only 0.1 percent of exposed patients have a serum creatine phosphokinase (CPK) level exceeding 3xULN (upper limit of normal) accompanied by muscle pain sufficient to justify stopping the medication. This phenomenon, the development of clinically relevant statin myopathy, is dose-dependent. In fact, the SEARCH Trial (“Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine” Trial) demonstrated that myopathy occurs at a higher frequency (approaching 1 percent) in patients using 80 mg simvastatin daily. The Food and Drug Administration (FDA) therefore issued a warning in 2011, discouraging the use of high-dose simvastatin.

Early studies assessed the impact of several well-characterized candidate genes (e.g., the HMG-CoA reductase gene itself, and multiple CYP genes encoding the cytochrome P450 enzymes) on statin myopathy risk. Although some of these studies revealed statistically meaningful association with statin muscle toxicity, the effect size was small and none of these drug-gene relationships were found to be clinically actionable. Then, in 2008, the SEARCH Trial investigators conducted a genome-wide association study revealing that variation in a hepatic uptake transporter gene, SLC01B1 (solute carrier gene, subfamily 1B1), was a strong predictor of myopathy in patients taking simvastatin (20-fold increase in myopathy risk).

Because the strength of association between SLC01B1 genotype and statin myopathy varies drug-by-drug, this information may be clinically actionable. In 2012, we published a gene-based dosing guideline for statins, and in 2015 we published the automated decision support for this relationship in one of the largest commercial electronic medical records in the U.S. In patients with an abnormal SLC01B1 gene, EPIC can now display kinetic data for various statins, allowing clinicians to balance risk for myopathy against lipid-lowering efficacy when selecting a drug within this class.

As the field of medical informatics changes the landscape upon which we practice, it seems inevitable that genomic data will increasingly be available through wide-scale expansion of electronic medical records. Because statins are the most commonly prescribed drugs in the U.S., and because SLC01B1 gene variants cause a striking elevation in risk for myopathy, gene-based statin dosing will soon be a clinical reality.

Joseph Fanciullo, MD, FACR: “Gene-based Statin Dosing is not Ready for Prime Time”

The FDA currently requires genetic or genomic information in the labels of nearly 200 prescription medications. In some cases, genotyping is mandatory. For most, however, genotyping is optional. Statins are among the latter group. There are at least two reasons why gene-based drug dosing for statins remains optional: 1) some cases of statin muscle toxicity are idiosyncratic, due to autoimmune myositis rather than myopathy, and 2) risk prediction models need
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to be measured against equally accurate models of statin efficacy.

Most human traits are influenced by multiple genetic factors of relatively small effect, and the search for genetic markers of statin efficacy is therefore still in its infancy. Half a decade ago, an international genome wide meta-analysis identified nearly 100 genetic factors contributing to low-density lipoprotein (LDL) cholesterol level. The genetic architecture underlying statin-induced change in LDL cholesterol level is also polygenic. Using a similar design (genome wide meta-analysis), we and others recently published a list of genes impacting the lipid lowering efficacy of statins. In validating previously known determinants of pretreatment LDL cholesterol level, this study identified at least two novel loci influencing the cholesterol response to statins: SORT1 (sortilin gene, subfamily 1) and SLC01B1. So genetic variants in SLC01B1 not only impact myopathy risk, they impact the efficacy of statins. The contributions made by other genes like SORT1 remain poorly understood.

For most clinicians, gene-based dosing guidelines are only desirable when they pertain to preventable effects (e.g., muscle-related side effects leading to interruption of statin therapy, or potentially fatal cases of rhabdomyolysis). While myalgias and myopathy appear to present along a clinical continuum, it is unclear if the SLC01B1 gene variants predict the entire spectrum of statin myopathy. The SEARCH trial defined statin-related myopathy based on clinical symptoms and a threshold elevation in CKP. However, some patients may develop muscle pain and stop their statin therapy irrespective of CKP levels. Furthermore, some of the more clinically severe cases of statin induced muscle damage have been due to a different pathophysiological process, the development of autoimmune myositis. This process appears to be distinct from typical statin myopathy. It is characterized by the presence of anti-HMGCR (hydroxymethylglutaryl-coenzyme-A reductase) autoantibodies, and persistent muscle injury not reversed after cessation of statins. Patients with autoimmune myositis often require immunosuppressive therapy. When patients with this syndrome were studied, there did not appear to be an association with the SLC01B1 gene polymorphism. Therefore, genetic determinants of myopathy may not predict necrotizing myositis, and more research is needed to clarify the immunogenetic contribution to this adverse drug reaction before we are ready to begin using genetics for statin dosing.

Additional layers of complexity include cost and insurance coverage. At present, SLC01B1 genotyping costs approximately $400, and most third party payers are unwilling to reimburse patients for this test. As the field of pharmacogenetics moves forward, insurance providers appear more willing to cover the cost of gene variants associated with outcome for drugs with a narrow therapeutic index (e.g., anticoagulants or antineoplastics). Because statins have a wide therapeutic index, most clinicians simply “start low and go slow” — titrating dose upward while monitoring for adverse effects.

For drugs with a wider therapeutic index, like statins, more information is needed before we proceed. Risk prediction models will need to incorporate information from multiple genes impacting mechanism and metabolism, as well as immune response. Perhaps in the future, these models may be able to predict rare cases of autoimmune myositis in addition to mild myopathy. Until we get there, however, this approach is not ready for prime time.

References


Please note: Due to limited space, we are unable to list all references. You may contact South Dakota Medicine at 605.336.1965 for a complete listing.
Introduction

In this article, we present a case of hepatic adenoma in a 25-year-old female, followed by a brief description of the surgical intervention. We then elaborate on some common benign liver lesions and their clinical characteristics.

Case Report

We are presenting a case of a 25-year-old otherwise healthy female who presented to our clinic for further evaluation of progressive epigastric discomfort. The patient has a past medical history notable for laparoscopic cholecystectomy; polycystic ovarian syndrome on oral contraceptive, hypothyroidism and irritable bowel syndrome. Her physical exam was notable for right upper quadrant pain. The patient underwent ultrasound of the right upper quadrant which showed heterogenous, slightly hyperechoic lesions in the left lobe of the liver with slightly lobular margins. MRI of the abdomen was then obtained and showed a 6.8 cm mass in the left hepatic lobe which correlated to the US finding and consistent with hepatic adenoma. Her laboratory workup included CBC, LFTs and Alpha fetoprotein which all were within normal limits. The patient’s oral contraceptive pills were stopped and a repeat scan in six months showed the mass had gotten slightly smaller in size to 6.1 cm but the patient was still symptomatic. Due to the size of the mass and its failure to adequately regress in size, the patient was advised to pursue surgical intervention. She underwent laparoscopic converted to open resection of the left lobe of her liver.

Figure 1 shows ultrasound of the abdomen obtained, showing heterogeneous, slightly hyperechoic lesion in the left lobe of the liver with slightly lobular margins. These imaging findings represent a differential diagnosis including adenoma, hemangioma, and possibly fatty infiltration but much less likely. MRI of the liver with and without contrast was recommended for further evaluation and is shown in Figure 2. MRI demonstrates a mass in the left lobe of the liver that correlates with ultrasound findings. The mass demonstrates minimal arterial enhancement. This finding is most consistent with hepatic adenoma.

Operative Description

The case was started laparoscopically but due to technical difficulties was converted to open. We proceeded by dividing the left triangular ligament of the liver. The falciform ligament was also divided as far as the suprahepatic inferior vena cava and the rest of the left lateral

Abstract

Although liver lesions in the young population are relatively rare, clinicians can benefit from being familiar with a subset of common benign liver lesions which include hepatic adenoma, hepatic hemangioma, and focal nodular hyperplasia. This a case report of a 25-year-old Jehovah’s Witness female on chronic oral contraception for polycystic ovarian syndrome who presented with progressive right upper quadrant abdominal pain. Ultrasound and MRI findings were consistent with hepatic adenoma. A description of her clinical work up followed by a brief description of the surgical intervention is discussed. We then elaborate on the clinical characteristics and evidence-based interventions of hepatic adenoma, hepatic hemangioma, and focal nodular hyperplasia.

Hepatic Adenoma – A Case Report

By Hasan H. Turaihi, MD; Adam Binneboese, MD; and Thavam C. Thambi-Pillai, MD

March 2017
segment was completely mobilized down to left hepatic vein. The gastrohepatic ligament was then divided and proximal control of the porta hepatis was obtained using Rumel tourniquet. Intraoperative ultrasound was performed to help identify the relationship of the mass to the left portal pedicle. The line of dissection was marked. The hepatic adenoma was found to be involving the left lateral segment as well as segment 4A and the decision was made to perform a left hepatic lobectomy. We used a microwave ablation-coagulation technique at 45 watts along the line of resection, after which we performed the resection. Estimated blood loss was 200 ml; a drain was left close to the cut surface of the liver. The patient tolerated the procedure very well and was extubated in the operating room after which she was transferred to the surgery floor. The patient was discharged on postoperative day six in good condition. The patient returned for her three-week postoperative clinic visit reporting doing well and having complete resolution of her abdominal pain.

Discussion

Hepatic Adenomas

Hepatic adenomas are uncommon benign epithelial tumors of the liver parenchyma. They are most commonly seen in young women ages 20 to 45 years old.1 Histologically, liver cell adenomas are composed of sheets and cords of cells that may resemble normal hepatocytes or have some variation in cell and nuclear size; portal tracts are absent.2 They are typically solitary, and most frequently found in the subcapsular region of the right hepatic lobe. Although less common, they also arise from the deeper liver parenchyma. Hepatic adenomas range in size from 5 mm to 30 cm. They are associated with symptoms such as abdominal pain localized to the epigastrum and/or right upper quadrant. Adenomas are commonly diagnosed incidentally on imaging studies. Occasionally, they are suspected from physical examination findings and subsequently confirmed through follow-up imaging. On unfortunate and rare occasions, hepatic adenomas are discovered following hemodynamic collapse whereupon rupture and intra-abdominal bleeding are found.3

The majority of patients with hepatic adenomas have used oral contraceptives for more than two years prior to diagnosis. In fact, hepatic adenomas were rarely diagnosed before the advent of oral contraceptives in the 1960s.4 Other possible factors linked to the development of hepatic adenoma include androgenic steroids, glycogen storage disease, diabetes mellitus, and pregnancy.5 Unlike other benign liver lesions, hepatic adenomas carry a possibility of rupture and malignant transformation. There is rising school of thought among many surgeons that surgical intervention should be sought out regardless of lesion size, symptomatology, or lack thereof. This notion arises from the increasing use of minimally invasive techniques that have lessened the risks and morbidities of liver surgery.6

The current standard of treatment for asymptomatic hepatic adenomas is based on size. Hepatic adenomas less than 5 cm can be observed and discontinuation of oral contraceptives or androgenic steroids is advised. Surgical resection is considered for hepatic adenomas greater than 5 cm and near the liver surface; transcatheter embolization is also a viable option. Pregnancy should be avoided due to increased risk of rupture.7,8

Hepatic Hemangioma

Hepatic hemangiomas are the most common benign tumors of liver parenchyma. They are also referred to as cavernous hemangiomas because of their hepatocytes regularly-spaced, dilated appearance on histological examination.2 Hemangiomas are typically discovered incidentally at laparotomy, autopsy, or during an imaging test performed for unrelated conditions. Although they can be diagnosed at any age, 60 to 80 percent of hepatic hemangiomas are diagnosed in patients who are between the ages of 30 and 50 years.9 In adults, hemangiomas occur more frequently in women, with a female to male ratio of 3:1. Hemangiomas are often solitary, but multiple lesions may be present in both the right and left lobe of the liver. They range in size from a few millimeters to over 20 cm. The majority are small, being less than 5 cm. Those larger than 5 cm have been referred to as giant hemangiomas.11

The etiology of hepatic hemangiomas is incompletely understood. They are considered to be vascular malformations or hamartomas of congenital origin that enlarge by ectasia rather than by hyperplasia or hypertrophy.11
Hormonal influence over tumor growth is suggested by enlargement during pregnancy and with estrogen and progesterone therapy; regression in tumor size is seen after withdrawal of therapy. Hemangiomas can be recognized on imaging by having a nodular or globular enhancement on arterial phase and centripetal enhancement on venous phase. Hemangiomas are typically not treated unless they become symptomatic. Complications are extremely rare and include spontaneous rupture, abscess formation, and high output heart failure in case of giant hemangioma. Surgical resection is the gold standard of treatment for hepatic hemangiomas.

Focal Nodular Hyperplasia

Focal nodular hyperplasia is the second most common benign hepatic tumor, more common in females, with a ratio of 9:1. Focal nodular hyperplasia is a firm mass that lacks a capsule, a key feature distinguishing it from hepatic adenoma and hemangioma. Fibrous septations at different levels of maturity and organization are present, along with areas of necrosis. These features contribute to the appearance of the classic central stellate scar that is often seen radiographically. Focal nodular hyperplasia is most commonly found in patients between the ages of 20 and 50 years. Wanless et al. suggested that focal nodular hyperplasia is a hyperplastic response of normal liver parenchyma to localized areas of increased arterial perfusion, facilitated by the presence of small arteriovenous malformations. Moreover, focal nodular hyperplasia is known to be associated with vascular diseases associated with arterial hyperperfusion of the liver, including hereditary hemorrhagic telangiectasia or congenital absence of the portal vein. Focal nodular hyperplasia was first described in the early 1900s, long before the advent of oral contraceptives. It is seen in patients who do not use oral contraceptives and its incidence remained steady after the introduction of oral contraceptives in the 1960s. The natural clinical course of a patient with focal nodular hyperplasia is one of stability and a lack of complications, and as such, is managed conservatively.

A diagnosis can be made through a combination of imaging modalities. Tissue diagnosis is rarely required. A triphasic helical CT scan can be done with and without contrast during the hepatic arterial and portal venous phases is highly sensitive in diagnosing focal nodular hyperplasia. It may be hypo or isodense on non-contrast CT with the central scar identified in some patients. The lesion becomes hyperdense during the hepatic arterial phase due to the arterial origin of its blood supply.

Risk Factors for Malignant Transformation of Hepatic Adenoma

The risk of malignant transformation hasn’t been quantified although some characteristics have been postulated in conferring risk for malignant transformation. These risks include a hepatic adenoma greater than 5 cm in diameter, the patient being male, the patient having a glycogen storage disease, and germline mutations in the APC and p53 genes with a history of adenomatous polyposis coli. A consistent increase in size on subsequent imaging and/or an increase in AFP levels should raise concern for malignant transformation.

Conclusion

The most common benign, solid, hepatic lesions are hepatic adenoma, hepatic angioma, and focal nodular hyperplasia. Knowledge of their respective etiologies, compositions, and natural histories guide diagnosis and treatment. Hepatic adenomas are associated with pregnancy, oral contraceptives, and androgenic steroid use. Hepatic adenomas are at risk for rupture and malignant transformation. On gadolinium enhanced MRI, hepatic adenomas are hyperintense during the arterial phase and isointense or hypointense during the venous phase. Given the risk of malignant transformation, most hepatic adenomas should be resected and oral contraceptives and anabolic steroids be discontinued. Hepatic hemangiomas are the most common solid hepatic mass. Hepatic hemangiomas are congenital vascular malformations without significant risk for rupture or hemorrhage. They are characterized radiographically from contrast enhancement from the periphery to center over time. The majority require no surgical intervention. Surgery is indicated for symptoms, consumptive coagulopathy, or rare cases of hemorrhage. Focal nodular hyperplasia results from hyperplasia of all hepatic cellular components secondary to increased perfusion or vascular malformation. It may contain fibrous septae and central necrosis, which will appear as a central scar on contrast-enhanced, cross-sectional imaging. Because focal nodular hyperplasia contain the normal cellular components of the liver, although not arranged in cords and sinusoids, they will uptake sulfur colloid on scintigraphy. Asymptomatic focal nodular hyperplasia should not be resected and do not require follow-up imaging.

REFERENCES


Please note: Due to limited space, we are unable to list all references. You may contact South Dakota Medicine at 605.336.1965 for a complete listing.

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Pilot Study to Determine Safety and Efficacy of Paclitaxel Infusion in De Novo Peripheral Lesions Using the Atrium ClearWay Balloon

By Joseph Anderson; Laura Danielson; Jordan Anderson; Katie Pohlson; Tyler Remund, PhD; Chad Laurich, MD; Greg Schultz, MD; Angelo Santos, MD; Gopinath Mani, PhD; Patrick Kelly, MD; and Andrea Shermann, MSIV

Abstract

Objective: To evaluate the safety and efficacy of a one-time infusion of paclitaxel through an Atrium ClearWay balloon in infra inguinal de novo peripheral lesions.

Methods: This is a single-center prospective study looking at treatment of 50 limbs. Treatment includes standard infra inguinal endovascular revascularization followed by a pre-prescribed infusion of paclitaxel. Control is standard reintervention without subsequent paclitaxel infusion. Patients were followed at one, four, and 10 months with ankle-brachial index (ABI)s, arterial duplex of the treated limb, and Rutherford classification stage measured before and after procedures and at each follow-up. Freedom from binary restenosis was tracked with duplex ultrasound, and freedom from target lesion revascularization (TLR) was also tracked in the treatment group. Binary restenosis and TLR data was harvested from the patient record for the control group.

Results: Average ABI and Rutherford classification stage improved as expected. The treatment group had a freedom from TLR rate of 86 percent and a freedom from binary restenosis rate of 80 percent at 10 months. Average ABI improved from 0.65 at baseline to 0.94 at 10 months in the treatment group. The control group had a 72 percent freedom from TLR and a 58 percent freedom from binary restenosis at 10 months. Average ABI of the control group improved from 0.67 at baseline to 0.85 at 10 months in the control group. There were no amputations, open bypass revascularizations, or hypersensitivity reactions observed in the treatment group.

Conclusions: Infusion of paclitaxel in de novo lesions appears to be a safe and efficacious treatment in the peripheral vasculature when compared to a historical control group. While it is early, it appears that the patients do receive some benefit from this one-time infusion, and this approach should be studied further.

Introduction

Peripheral artery disease (PAD) affects approximately 10 million individuals in the U.S. causing significant morbidity and mortality. For chronic ischemic extremities, there are two general approaches for revascularization; open surgical and endovascular. The increasingly popular endovascular intervention involves the use of stents, stent-grafts, balloon angioplasty and plaque de-bulking procedures. Balloon angioplasty was found to be effective with shorter and non-complex lesions with good clinical outcomes in the short-term, however, restenosis occurs at a rate of 40 to 60 percent after one year due to several mechanisms: acute vessel recoil, chronic remodeling and intimal hyperplasia. Stenting of arterial vessels is used to supplement balloon angioplasty in longer lesions. In the intermediate-term, stents do maintain vessel patency better than angioplasty since they prevent vessel recoil but tend to restenose in the long-term due to neointimal hyperplasia mediated by inflammatory response and subsequent smooth muscle cell proliferation.
prevent the proliferation of smooth muscle cells in coronary arteries, anti-proliferative drugs were used at the site of the lesion by means of attachment to the stent. Stents were coated with polymers which contained drugs (or just the drug without polymers). The drug would then be released into the vessel wall over time, preferably with a sustained release profile. While drug-eluting stents (DES) have significantly reduced the occurrence of restenosis in coronary interventions, first-generation peripheral DES late restenosis rates remain high. Late lumen loss has prompted development of bioabsorbable DES so that the stent does not present a potential ongoing source for inflammation and restenosis. Another method under investigation is the use of drug-coated balloons (DCB) that make use of a burst release perioperatively. This allows the application of anti-proliferative drugs without leaving behind a stent. DCBs have been shown to be successful in the treatment of in-stent restenosis following either bare metal stents or drug eluting stents.

In the U.S., the Bard Lutonix has recently been approved for use in the superficial femoral artery (SFA), and it is anticipated that the Medtronic IN.PACT will be similarly approved in the near future. Despite the excitement surrounding the recent and pending approvals of DCBs in the U.S., some questions remain. There have been some safety issues in below the knee (BTK) use, results have largely been reported in TransAtlantic Intersociety Consensus (TASC) A and B lesions, and reimbursement is not yet fully understood.

We hypothesized that a one-time limited dose infusion of an anti-proliferative agent (paclitaxel) delivered via infusion balloon will aid in the prevention of clinically significant recurrent stenosis secondary to intimal hyperplasia when compared with a control group. A prospective, single-center, non-randomized study was conducted to observe the effects of this infusion on recurrent stenosis and the need for TLR. Here we present our 10-month experience with 50 limbs.

Methods

Prior to the clinical phase we examined the infusion efficiency of two paclitaxel solutions through the Atrium Clearway (Atrium Medical Hudson, New Hampshire) balloon as follows. The two solutions included powdered paclitaxel (Life Technologies Carlsbad, California) in saline solution and a commercially available clinical grade paclitaxel in a cremaphor solution (Hospira Lake Forest, Illinois) diluted with saline solution. Both solutions of paclitaxel were at a concentration of 0.1 mg/mL. The commercially available paclitaxel came from Hospira and was packaged in a concentration of 6 mg/mL. The cremaphor was 527 mg of polyoxyl 35 castor oil, NF, 49.7 percent v/v dehydrated alcohol, USP and 2 mg citric acid USP. A 0.5 mL aliquot of the cremaphor-based paclitaxel solution was mixed with 29.5 mL of saline solution to obtain the desired concentration. Once the two solutions were prepared they were infused through the porous balloon at a rate of 3 mL per minute into separate vials for each minute of a total three-minute period using 2 ATM pressure with a 1.5 mm. The collected infusates were analyzed using high-performance liquid chromatography (HPLC – Waters Corporation Milford, Massachusetts) in order to quantify the amount of paclitaxel that passed through the balloon’s micro-porous wall. After that the balloon was washed with 3 mL of saline solution which was collected and analyzed with HPLC. Then the balloon was flushed with ethanol and de-ionized water several times to retrieve the drug that was precipitated inside the balloon without infusing out. Each of these solutions collected was characterized using HPLC to determine the total amount of drug retained inside the balloon. The HPLC protocol for determining the quantity of paclitaxel in solution was used as previously shown.

Once we had determined that clinically available paclitaxel will in fact infuse through the Atrium ClearWay balloon, we began treating patients. We received an Investigational New Drug (IND) waiver for this study from the Food and Drug Administration (FDA) on Oct. 6, 2010. We then received approval from one of our local institutional review boards on March 14, 2011 for project#. The study was listed on www.clinicaltrials.gov NCT01454778. Patients were referred to our center through our normal regional referral patterns over a three-year period. There were a total of four operators that enrolled patients for this study. Indications for intervention included clinically significant de novo lesions in the SFA, popliteal, peroneal, or tibial arteries in patients with a greater than one year life expectancy. After diagnosis with ABI and arterial duplex, all of the patients who underwent this procedure were clearly informed that the treatment was investigational in nature and gave consent. They were informed of the risks and benefits of having an endovascular procedure with the investigational infusion. The patients did not undergo preoperative angiogram. Our hospital pharmacy prepared a hands-free treatment solution by mixing the cremaphor-based paclitaxel with saline solution to arrive at the desired concentration of 0.1 mg/mL.
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Our administration protocol called for a concentration of 0.1 mg paclitaxel per 1 mL of solution. We based our dosing regimen on the assumption that we wanted to deliver 3 ug of paclitaxel delivered per millimeter squared surface area of target lesion. For the surface area calculation we assumed all SFA arteries were 5.5 mm in diameter, all tibial arteries are 4 mm in diameter, and all tibial arteries are roughly 3 mm in diameter. Beings the balloon we used was 50 mm in length, we could make an easy calculation for the amount of drug we wanted to deliver per inflation.

\[ \text{Dose} = L \times \pi \times D \times \rho \]

Where, dose per inflation: desired dose delivered to the vessel wall per 50 mm balloon = unknown

- \( L \): the infusion length of the balloon = 50 mm
- \( D \): diameter of the balloon = 3 mm, 4 mm, or 6 mm
- \( \rho \): desired dose per unit area = 3 ug/mm²

This calculation leaves us with the SFAs receiving 2.4 mg per inflation, the popliteals receiving 1.8 mg per inflation, and the tibials receiving 1.4 mg per inflation. The solution was delivered in an IV drip bag which was joined in series with sterile tubing. A waste bag was also connected as can be seen in Figure 1 for a hands-free assembly. As paclitaxel tends to adhere to the tubing wall, we first primed the tubing and wasted before use. Then the patient was prepped and draped in a normal sterile manner. Procedures were performed under conscious sedation. Treatment strategy was based on the standard of care and individual preference of the four operators who enrolled under this study.

The Clearway drug infusion balloon (Figure 1 A-B) did not serve as our angioplasty balloon. Instead if balloon angioplasty was performed the angioplasty balloon was exchanged for the Clearway infusion balloon before the inflation process began. A similar sequence was followed if the operator deemed it appropriate to use atherectomy. Following standard infrainguinal endovascular revascularization (which could include angioplasty, atherectomy, or bare metal stenting, a paclitaxel solution was drawn into the indeflator which was used as a delivery chamber. The infusion balloons used varied in diameter from 3 mm to 7 mm in diameter. Most balloons used were 50 mm in length but sometimes a 20 mm long balloon was used. The balloons had a porosity which was also variable based on our evaluation with scanning electron microscopy (SEM). The pore size varied from 5 um to 40 um in diameter and were randomly distributed along the surface of the balloon. Beings we limited the dose to 2.4 mg/inflation in an SFA and 1.4 mg/inflation in the tibia, and the solution concentration was 0.1 mg/mL, the total volume infused was 14 mL in the tibial arteries and 24 mL in the SFA. The rate of inflation was similar to plain old balloon angioplasty. The volume of drug is delivered to the indeflator by turning the stop cock corresponding to the drug solution bag to a point where the fluid flow will be blocked to the waste bag but open to the indeflator. The stop cock between the indeflator and the drug infusion balloon is turned so that the fluid flow is blocked in the direction of the infusion balloon and open to the indeflator. From here the drug infusion volume can be drawn into the indeflator. Once the indeflator has the appropriate volume, the stop cock between the indeflator and the drug infusion balloon is turned to block fluid flow to the IV bags but open to fluid flow to the drug infusion balloon. (Figure 1C) Then the drug solution can be infused. Because the pores of the drug infusion balloon are so small (Figure 1 D-E) and the pressure of the infusate (roughly 2 atm) is higher than systolic blood pressure (roughly 0.15 atm) the drug solution can be infused despite being in tight apposition with the vessel wall. We found the average inflation time was 3 minutes, so this left us with an inflation rate of 4.7 mL/minute in the tibial arteries to 8 mL/minute in the SFA. Since the infusion lumen is also the inflation lumen, the operator monitored the indeflator pressure closely and readjusted as needed. If a patient had a lesion longer than the 50 mm Atrium Clearway balloon or if the patient had multiple lesions, the infusion process was repeated as needed.

We set the maximum dose at 10 mg of paclitaxel for patient safety reasons. We felt that this was an appropriate dosing at which we could test safety. We arrived at this number by assuming our average patient has a body surface area of 2 m². Beings a typical systemic infusion dosing of paclitaxel for breast cancer is 175 mg/m² over three hours, a patient would receive 350 mg dose of paclitaxel systemically. In our case we are infusing locally in a single leg. The foot makes up 1.4 percent of body weight and the leg makes up 5 percent of body weight. The two combine to make up 6.4 percent of body weight. So during a typical breast cancer treatment, the foot receives 4.8 mg of paclitaxel, the leg receives 17.7 mg paclitaxel, and the foot and leg combined receive 22.5 mg of paclitaxel over a three-hour period. When we treated
the patients in the current study, they received their dose of paclitaxel over one to four three-minute inflations. With these numbers in mind, we chose a maximum dose per patient of 10 mg of paclitaxel in order to evaluate safety.

The construct of the clinical trial was a single center, non-randomized prospective study assessing the effect of paclitaxel infusion following revascularization of 50 limbs with de novo infrainguinal lesions. This was a pilot study intended to evaluate safety but not to prove efficacy. Therefore we chose n=50 as a number sufficient for evaluating safety while minimizing risk exposure to the treatment group. Baseline measurements such as ABI and Rutherford scores were taken pre-operatively. The Rutherford classification is a commonly used clinical staging system for descending peripheral artery disease. Stage 0 is asymptomatic, Stage 1 is mild claudication, Stage 2 is moderate claudication, Stage 3 is severe claudication, Stage 4 is pain at rest, Stage 5 is ischemic ulceration of the digits of the foot, and Stage 6 is severe ischemic ulceration or frank gangrene. Length, diameter, occlusive extent, and calcification were measured perioperatively. Patients with tandem lesions were characterized in an additive fashion with the lengths of each of the treated vessels being reported as a sum. Post-operatively the patients were followed at one month, four months, and 10 months. ABI, treatment limb arterial duplex, and Rutherford classification stage were measured at each follow-up. Freedom from binary restenosis and freedom from TLR were tracked for each follow-up period. Binary restenosis was defined as reduction in the percent diameter stenosis of 50 percent or more as measured by arterial duplex. TLR was defined as a reintervention performed for a greater than 50 percent diameter stenosis within 5 mm of the target lesion in either direction which coincide with symptoms of peripheral artery disease. Patients were included if they were able to provide informed consent, were between the ages of 18 and 90, if their baseline Rutherford was between 1 and 6, and if they had an occlusion or stenosis in the infrainguinal vessel. Patients were excluded if the operator was unable to cross the lesion, if the patient was pregnant or lactating, or if the limb had been previously treated with
an endovascular intervention.

A retrospective analysis of patients treated at the same institution from 2010 to 2012 without the investigational infusion was used as a control population. Patient’s electronic records were evaluated in order to collect data for comparison to the treatment group. Patients were selected consecutively, without regard to interventional modality, lesion location, lesion size or operator. There were six patients who had lesions treated in bilateral distal extremities in both the treatment and control groups. For these patients both limbs were evaluated for this study. Over 10 months of follow-up, patients from the treatment group were monitored closely to determine if they had binary restenosis or if they required reintervention. The charts of the 50 patients in the control group were reviewed in order to determine the number with freedom from binary restenosis and that required reintervention. Finally the patients were followed to see if they had amputation in the treated limb, a hypersensitivity reaction to the drug solution, or if they required an open bypass of the target lesion.

Results

Infusing paclitaxel solution with and without cremaphor present to improve solubility was evaluated using HPLC. Through HPLC analysis we learned that only 9 µg of 122 µg of the paclitaxel was infused through the balloon when 0.1 mg/mL of powdered paclitaxel was used. This indicated that the crystalline paclitaxel precipitated inside the balloon effectively clogging the pores so that a significant amount of the paclitaxel never left the balloon. When 0.1 mg/mL of paclitaxel in the presence of cremaphor was infused through the balloon we found that 895 µg of 919 µg paclitaxel came out of the balloon. This indicated that the solubility of the paclitaxel played an important part in proper delivery of the therapeutic agent. We determined that in order to get appropriate post-infusion dosing of paclitaxel we needed to use the cremaphor. (Table 1)

Treatm ent Group

Of the 50 patients in the treatment group, the average age was 71.6 years. In the treatment group, 32 percent of the patients used tobacco. Forty-two percent of patients in the treatment group had diabetes. Sixty-five percent were hypertensive in the treatment group. The average lesion length of the patients in the treatment group was 131.4 mm. The average diameter was 5 mm. Nearly 99 percent of the patients had total occlusions and 26.6 percent of the patients had calcified lesions (Table 2). In the treatment group, 62 percent of patients had a single vessel affected, 34 percent of the patients had two vessels affected, and 4 percent of the patients had three or more vessels affected (Table 3). Interventional modalities varied in the

<table>
<thead>
<tr>
<th>No.</th>
<th>Solution type</th>
<th>Amount of Paclitaxel infused through the balloon at minutes – 1, 2, and 3 and during saline wash</th>
<th>Total amount of Paclitaxel infused through the balloon (µg)</th>
<th>Amount of Paclitaxel extracted from the balloon during the drug retrieval procedure</th>
<th>Total amount of Paclitaxel retained in the balloon without infusing out through the balloon (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Paclitaxel in saline solution</td>
<td>2 3 3 2</td>
<td>9</td>
<td>47 18 11 15 17 3 1 0</td>
<td>113</td>
</tr>
<tr>
<td>2</td>
<td>Cremaphor based commercially available Paclitaxel solution</td>
<td>263 277 284 71</td>
<td>895</td>
<td>8 3 3 2 6 2 0 0</td>
<td>24</td>
</tr>
</tbody>
</table>

Table 1. The characterization of the solution which was passed through the Atrium ClearWay balloon catheter at 2 ATM pressure in the first minute, second minute, third minute, and the amount of Paclitaxel remaining in the balloon based on an ethanol wash for two groups: a 0.1 mg/mL powdered Paclitaxel (PAT) in saline solution and 0.1 mg/mL commercially available Paclitaxel in cremaphor.
treatment group with 40 percent of patients receiving atherectomy, 96 percent of patients receiving balloon angioplasty, and 56 percent of the patients receiving a stent (Table 4).

In the treatment group, 8 percent of patients suffered a pseudoaneurysm at the access site, and 20 percent of patients had a target vessel dissect prior to paclitaxel infusion. The average number of inflations per patient was 3.6. The average total inflation time was 245.12 seconds. The average total dose of paclitaxel was 7 mg (Table 5). Six percent of the patients reached the maximum dose of 10 mg of paclitaxel. Of the patients in the treatment group, 68 percent remained on Plavix through 10 months, 76 percent remained on aspirin through 10 months, and 10 percent were on Coumadin at 10 months (Table 6).

There were no patients lost to follow-up through the 10-month follow-up period. At 10 months, 80 percent of the patients in the treatment group had freedom from binary restenosis (Figure 2), 86 percent of the patients had freedom from TLR (Figure 3), and the average ABI was 0.94 (Table 6). None of the patients that received the experimental treatment had hypersensitivity reactions in response to the paclitaxel administration. There were also no treatment related amputations or open revascularizations in the 10-month follow-up period for any of the patients in the treatment group.

Control Group

The average age of patients in the control group was 76.1 years. Thirty-six percent of patients used tobacco, 44 percent of patients had diabetes, and 88 percent of patients had hypertension. The average lesion length was 152.6 mm and the average diameter was 4.8 mm. Total

<table>
<thead>
<tr>
<th>Table 2. Patient Demographics and Lesion Characteristics in Both the Treatment and Control Groups</th>
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</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Tobacco (%)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
</tr>
<tr>
<td>Right leg/left leg</td>
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<tr>
<td>Length (mm)</td>
</tr>
<tr>
<td>Diameter (mm)</td>
</tr>
<tr>
<td>Occlusion (%)</td>
</tr>
<tr>
<td>Calcification (%)</td>
</tr>
</tbody>
</table>

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<tr>
<th>Table 3. Quantity of Patients Treated with Various Combinations of Vessels Affected in Both the Treatment and Control Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>SFA</td>
</tr>
<tr>
<td>SFA/tibial</td>
</tr>
<tr>
<td>SFA/peroneal</td>
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<tr>
<td>SFA/popliteal</td>
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<tr>
<td>SFA/popliteal/tibial</td>
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<tr>
<td>SFA/tibial/peroneal</td>
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<tr>
<td>Tibial</td>
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<tr>
<td>Popliteal</td>
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<tr>
<td>Peroneal</td>
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<tr>
<td>Popliteal/tibial</td>
</tr>
<tr>
<td>SFA/popliteal/tibial/peroneal</td>
</tr>
<tr>
<td>Tibial/peroneal</td>
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<tr>
<th>Table 4. Intervventional Modality in the Treatment and Control Groups</th>
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<tbody>
<tr>
<td><strong>Atherectomy</strong></td>
</tr>
<tr>
<td>PTA</td>
</tr>
<tr>
<td>PTA/stent</td>
</tr>
<tr>
<td>Atherectomy/stent</td>
</tr>
<tr>
<td>PTA/atherectomy</td>
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<tr>
<td>PTA/atherectomy/stent</td>
</tr>
<tr>
<td>stent</td>
</tr>
<tr>
<td>Pseudoaneurysm</td>
</tr>
<tr>
<td>Dissection after intervention</td>
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</tbody>
</table>

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<tr>
<th>Table 5. Drug Infusion Statistics for the Treatment Group</th>
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<tbody>
<tr>
<td><strong>Average number of inflations</strong></td>
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<tr>
<td><strong>Average time per inflation (seconds)</strong></td>
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<tr>
<td><strong>Average total inflation time (seconds)</strong></td>
</tr>
<tr>
<td><strong>Average total dose of Paclitaxel (mg)</strong></td>
</tr>
</tbody>
</table>

Freedom from binary restenosis is statistically significant at one month to P<0.1 and at four months to P<0.05.
occlusion was noted in 20.1 percent of patients and calcification was observed in 56.3 percent of patients (Table 2).

Forty-four percent of the patients in the control group had only one vessel affected, 34 percent had two vessels affected, and 12 percent had three or more vessels affected (Table 3). The average lesion length was 152.6 mm and the average diameter of the affected vessel was 4.8 mm. Just over 20 percent of the patients had total occlusion of the vessel and 56.3 percent of patients had calcified lesions. Seventy percent of the patients in the control group received atherectomy, 38 percent received balloon angioplasty, and 40 percent received stents (Table 4). At 10 months, 58 percent of the patients in the control group had freedom from binary restenosis (Figure 2), 72 percent had freedom from TLR (Figure 3), and the average ABI was 0.85 (Table 6).

**Discussion**

There are over 800,000 peripheral interventions per year in the U.S. which are performed at a significant cost and burden to society. Thirty to 40 percent of patients who undergo peripheral intervention require subsequent reintervention. While stenting has shown to prevent lumen loss in the early to near term, late lumen loss remains a significant problem. This prompted the industry to shift focus toward drug coated balloons (DCBs). DCBs make use of a burst release to transfer as much paclitaxel as possible to the arterial tissue. Since paclitaxel is a very hydrophobic drug, it is commonly believed that it is retained in the arterial tissue for a long period of time without getting washed away in the bloodstream. So the DCB needs to retain the drug on its surface while the device is being positioned, then transfer it quickly to the target lesion upon deployment. DCBs typically use a variety of coatings to hold the drug onto the balloon surface. Also, the DCBs use various excipients to improve the penetration of paclitaxel in the arterial tissue. However, the bio-compatibility of coating materials and excipients used in DCBs are not known. Here we presented an alternative technique which makes use of an Atrium ClearWay balloon without any coatings or excipients for infusing an already clinically available paclitaxel solution to achieve a drug dosing similar to that of DCBs.

Before we could begin we needed to establish the ability of the delivery system to convey the therapeutic drug to the target lesion. After simulated infusions and serial HPLC analyses we learned that having a commercially available cremaphor based solution was the best approach for delivering a predictable amount of drug through the expanded Polytetrafluoroethylene (ePTFE) micropores of the infusion balloon. Solubility of paclitaxel in excipients is the key factor, because if the paclitaxel is not totally solubilized it precipitates inside the Atrium ClearWay balloon and does not infuse out. For instance, the concentration of paclitaxel used in this study is greater than the solubility limit of paclitaxel in saline solution. This means the undissolved drug (typically existing as small crystals, agglomerates, etc.) may precipitate out and be too large to pass through the micropores of the Atrium ClearWay balloon. Hence, the drug would have been retained within the Atrium ClearWay balloon without releasing into the vessel wall. The cremaphor excipient used in this study is an excellent vehicle for solubilizing and infusing paclitaxel through the microporous Atrium ClearWay.
balloon. As a matter of fact, 99 percent of the paclitaxel present in the solution was successfully delivered during the infusion process when the cremaphor was used as an excipient.

We limited the dose in this study to 10 mg of paclitaxel per patient in order to minimize the risk of a hypersensitivity reaction to the cremaphor occurring. Because of the risk of a hypersensitivity reaction and the need to increase dose and transfer across the endothelial barrier, there is a need to examine more drug, solubility agent, and excipient combinations. The variety of histological profiles in the peripheral vasculature as well as the varying extent of disease in this patient population further complicates this problem. Clearly there is still much work to do. And the infusion platform opens the flexibility to treat these varying arterial structures in different ways. The platform has inherent flexibility because it has the potential to allow the provider to customize the drug solution to the patient’s clinical situation. The drug solution may also need to be customized for the vessel, because what works in the SFA may not work well in the popliteal or tibial vessels.

There is an additional regulatory advantage to drug infusion balloons. As mentioned above, if flexibility in drug delivery catheters is truly a desirable advantage, drug infusion provides a platform by which the regulatory burden is substantially lower. The regulatory burden and cost of development associated with a combination therapy will fix the industry’s attention on recovering the investment made in DCBs. This scenario makes drug infusion a welcome alternative, because as the excipient for a particular target lesion changes, and the drug or excipient is an off-the-shelf item, the operator can use it without the need to wait for it to receive a new indication from the FDA. This variety in the market provides the competition necessary to ensure continuous innovation which only benefits patients over the long term.

The drug infusion balloon we used worked well but we would like to see some design improvements. For instance, the Clearway’s infusion port and inflation port are in fluid communication through a common lumen. This means the operator must monitor closely and continuously adjust the indeflator to keep the infusion pressure static and working properly. If not, the diameter of the catheter will become smaller than the inner diameter of the vessel and high velocity blood flow will pass between the surfaces of the artery and the catheter. This will effectively wash downstream the drug solution before it reaches the vessel wall. We believe a proximal occlusion balloon would prevent this “peripheral washout” but the occlusion balloon would need to have a separate lumen from the infusion port.

There were several limitations for this study. First, we used a retrospective control in the clinical study. This historical control did not include measurements of lesion length, vessel diameter, occlusion, or calcification. In the future we would like to carry out this experiment as a double-blinded study in order to eliminate the possibility of selection bias. Second, our sample size was small, so we were unable to compare the various modes of intervention and different target vessels. This left us with relatively heterogeneous data. In the future it will be desirable to treat a larger sample size so we can segment and analyze the data as appropriate.

Conclusions

Here we presented a novel approach for reducing restenosis in de novo peripheral lesions by infusing paclitaxel through an Atrium ClearWay balloon. Restenosis and subsequent reintervention rates were lower in the treatment group than the control group, and no hypersensitivity reactions were observed. What’s more is there were no amputations of the treated limb and no open bypasses required to revascularize the target lesions. This approach allows a significantly lower regulatory barrier compared to DCBs and provides a platform for flexibility in treatment drugs and excipients. We believe the results presented herein warrant a more thorough investigation of the described technique.

REFERENCES


Please note: Due to limited space, we are unable to list all references. You may contact South Dakota Medicine at 605.336.1965 for a complete listing.

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A Case of IVIG-Induced Aseptic Chemical Meningitis

By Anish Patel, MD; Kalyan Chakravarthy Potu, MD; and Tamera Sturm, DO

Abstract
Intravenous immunoglobulin (IVIG) is a commonly used and generally well-tolerated medication. Common side effects include flu-like symptoms such as fevers, headaches, myalgia, fatigue, and nausea. One of the more rare side effects is aseptic meningitis, with a reported incidence rate of around 0.067 percent of all IVIG infusions.

In this paper, we describe a 47-year-old female patient with a history of myasthenia gravis who presented with a headache, neck pain, and neck stiffness while undergoing IVIG infusions for a myasthenia crisis. On admission day, the patient was afebrile with stable vital signs. A physical examination revealed nuchal rigidity and tenderness with no focal neurological deficits. Cerebrospinal fluid (CSF) cytology noted an elevated white blood cell (WBC) count of 1,138 cells/µL with a neutrophil predominance (96 percent). CSF red blood cell count was unremarkable at 1 cell/µL. The patient’s IVIG infusions were stopped, suspecting chemical meningitis. Given the markedly elevated CSF WBC count with neutrophil predominance, she was started on vancomycin and ceftriaxone to also cover for bacterial meningitis.

The patient’s meningeal signs and symptoms significantly improved 24 hours after admission. Given the clear temporal relationship to IVIG administration and the rapid improvement of symptoms, IVIG-induced aseptic meningitis is strongly suspected. The patient’s antibiotics were discontinued. Forty-eight hours after stopping IVIG and 24 hours after discontinuing antibiotics, her meningitis symptoms completely resolved with the use of analgesics alone. The patient was then discharged uneventfully. CSF viral and bacterial studies, including a gram stain and cultures, did not result in anything noteworthy.

Our case presents an interesting diagnostic dilemma where drug-induced (IVIG) aseptic meningitis mimics bacterial meningitis clinically and on CSF analysis. The clear temporal relationship to IVIG administration and the rapid resolution of symptoms upon stopping the drug can aid in the diagnosis of this rare event and help doctors avoid the use of unnecessary antibiotic therapy.

Introduction
Chemical meningitis, or drug-induced aseptic meningitis (DIAM), is a diagnostic challenge, as it is often a diagnosis of exclusion. Clinical and cerebrospinal fluid (CSF) findings closely resemble that of bacterial meningitis. Several medications are implicated with aseptic meningitis, including nonsteroidal anti-inflammatory drugs, antibiotics, and OKT3 medications such as muromonab. Several case reports and literature reviews implicate IVIG as a causative factor of DIAM. According to one retrospective study, the incidence rate of IVIG-induced aseptic meningitis is reported to be around 0.067 percent of all IVIG infusions. Symptoms of drug-induced aseptic meningitis include fevers, headache, malaise, neck stiffness, photophobia, nausea, and vomiting. Additionally, CSF analysis generally shows pleocytosis with a neutrophilic predominance, often with elevated CSF total protein. Interestingly, the clinical features and CSF findings mimic acute bacterial meningitis. However, unlike bacterial meningitis, IVIG-induced aseptic meningitis responds to
symptomatic therapy alone. Symptoms start improving promptly after stopping the inciting medication. In this paper, we describe a case of IVIG-induced aseptic meningitis that closely mimics bacterial meningitis in its clinical course and CSF findings (Table 1).

**Case Report**

A 47-year-old female with a history of myasthenia gravis presented with a headache, neck pain, and neck stiffness while undergoing IVIG infusions for a myasthenia crisis. Two days prior to admission to our hospital, she went to a neurology clinic with bilateral lower extremity weakness and an inability to walk or talk. She was diagnosed as having a myasthenia crisis and was started on IVIG treatment. On the second day of this outpatient IVIG treatment, her muscle strength improved significantly, but she developed a severe headache. Upon arriving at our emergency department, she complained of the severe headache associated with neck pain, neck stiffness, photophobia, sensitivity to sound, and generalized malaise. She was afebrile, with a temperature of 98.6 degrees Fahrenheit. Her other vital signs were stable.

Upon examination, the patient had nuchal rigidity and tenderness with no focal neurological deficits. Computed tomography imaging of the head without contrast was negative for acute findings. A complete blood count noted a normal white blood cell (WBC) count of 5.5 L/µL with a normal differential. Her red blood cell (RBC) and platelet counts were within normal limits. A lumbar puncture was done in the emergency department. CSF cytology noted an elevated WBC count at 1,138 cells/µL with a neutrophil predominance (96 percent). CSF RBC count was unremarkable at 1 cell/µL. The CSF total protein count was elevated at 63 mg/dL with normal-range glucose. The CSF immunoglobulin (IgG) fraction was elevated at 8.3 mg/dL. The patient’s IVIG infusions were stopped, suspecting chemical meningitis.

Given the patient’s markedly elevated CSF WBC count with neutrophilic predominance, she was started on vancomycin and ceftriaxone to cover for bacterial meningitis. Her meningeal signs and symptoms significantly improved twenty-four hours after admission. Given the clear temporal relationship to IVIG administration and the rapid improvement of symptoms, IVIG-induced aseptic meningitis is strongly suspected. The patient’s antibiotics were discontinued. Forty-eight hours after stopping IVIG and 24 hours after discontinuing antibiotics, her meningitis symptoms completely resolved with the use of analgesics alone. The patient was then discharged uneventfully. CSF viral and bacterial studies, including a gram stain and cultures, did not result in anything of note.

**Discussion**

Immediate adverse effects associated with IVIG infusions include flu-like symptoms such as headache, malaise, fever, chills, myalgia, and fatigue. Serious but rare side effects include thrombosis, anaphylaxis, acute renal failure, and aseptic meningitis. The exact pathophysiology behind IVIG-induced aseptic meningitis remains controversial. Several mechanisms have been proposed. One suggested mechanism is a direct chemical irritation of the meninges by the IgG fraction of the IVIG. The cytokine release from the interaction of the IgG fraction with antigenic determinants along the meninges also seems to play a role.

Common clinical features associated with IVIG-induced aseptic meningitis include headache (96 percent), fever (92 percent), meningeal signs (89 percent), nausea and/or vomiting (86 percent), photophobia (34 percent), and altered consciousness (23 percent). Symptoms occur within 48 hours of the administration of IVIG. Common laboratory findings include CSF pleocytosis with a neutrophil predominance, elevated CSF total protein count, and elevated CSF IgG. Management is largely symptomatic with antiemetics, analgesics, and hydration. Resolution of symptoms occurs in about two to 10 days after removal of the offending medication. Steroids do not seem to alter the clinical course.

| Table 1. Comparison of CSF Findings of Bacterial, Viral, and Fungal Meningitis with our Patient |
|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|
| **CSF WBC (cells/µL)**                     | **Viral Meningitis**                        | **Fungal Meningitis**                       | **Our Case**                                |
| >1000                                      | <1000                                      | <1000                                      | 1138                                       |
| **Differential**                           | **<80% Neutrophils**                       | **<15% Neutrophils**                       | **<15% Neutrophils**                       |
| **CSF Glucose (mg/dL)**                    | **Reduced**                                | **Normal**                                | **Reduced**                                |
| >250                                       | 50-250                                     | >250                                      | 63                                         |
Conclusion

Our case presents an interesting diagnostic dilemma where drug-induced (IVIG) aseptic meningitis mimics bacterial meningitis clinically and on CSF analysis. The clear temporal relationship to IVIG administration and the rapid resolution of symptoms upon stopping the drug can aid in the diagnosis of this rare event and help medical professionals avoid unnecessary antibiotic therapy. We suggest discontinuing antibiotics if the CSF gram stain results are negative and when there is clear temporal relationship of meningitis to recent IVIG administration. Therapy lies mainly in discontinuing the offending agent with resultant rapid improvement of symptoms.

REFERENCES


Please note: Due to limited space, we are unable to list all references. You may contact South Dakota Medicine at 605.336.1965 for a complete listing.

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Pulmonary Embolism Caused by Popliteal Vein Aneurysm: A Case Report

By Kevin Marquez, MD; Kalyan Chakravarthy Potu, MD; Chad Laurich, MD; and Randall Lamfers, MD

Abstract

In this case report, we describe an unusual episode of bilateral submassive pulmonary embolism (PE) caused by a popliteal vein aneurysm (PVA). The development of PE stems from many risk factors including obesity (BMI $\geq 30$ kg/m$^2$), hypertension, cigarette smoking (greater than 25 cigarettes per day), increasing age, surgery, immobility, malignancy, and inherited thrombophilia. A PVA is a rare but significant cause of PE.

A 28-year-old male presented to the emergency department with progressive shortness of breath. He had no significant past medical history, no family history of deep vein thrombosis or PE, and no recent surgeries, travel, or trauma. A physical exam revealed he was saturating 96 percent on 2 L/minute oxygen through a nasal cannula and was noted to have a heart rate in the 90 beats per minute range that quickly increased to 150 beats per minute with minimal exertion. An initial laboratory workup was unrevealing except for an elevated D-dimer. A chest radiograph demonstrated no cardiopulmonary abnormalities. Computed tomography angiography of the chest was performed and revealed multiple bilateral pulmonary emboli. An urgent echocardiogram then revealed evidence of right heart strain with a dilated right ventricle. A subsequent bilateral venous duplex scan of the lower extremities was performed, which revealed a left PVA. Vascular surgery was performed, specifically emergent catheter-directed lysis with the placement of a temporary inferior vena cava (IVC) filter. The patient was started on rivaroxaban oral anticoagulation therapy and then discharged home without incident. Several months later, he underwent uncomplicated surgical repair of his left PVA.

This case illustrates PVA as a rare but noteworthy cause of PE. Doctors should consider this diagnosis in patients with recurrent PE or when the cause of PE is unknown. Although the exact etiology is not known, inflammation, trauma, degenerative changes, and congenital weakness of venous wall have all been proposed as causes of venous aneurysms. The definitive management of a PVA is surgical repair. Some studies suggest recurrent PE in as high as 80 percent of patients on oral anticoagulation alone. Therefore, an IVC filter is often placed to prevent further thrombi progression until definitive surgical treatment of the aneurysm has been performed.

Introduction

Pulmonary embolism (PE) occurs in about 900,000 individuals per year in the U.S. and is responsible for approximately 100,000 deaths. The development of PE can stem from many risk factors including obesity (defined as BMI greater than or equal to 30 kg/m$^2$), hypertension, cigarette smoking (greater than 25 cigarettes per day), increasing age, surgery, immobility, malignancy, and inherited thrombophilia. A rare risk factor is venous aneurysms. Dahl et al. first reported a case of recurrent PE due to a popliteal vein aneurysm (PVA) in 1976. Treatment of PVAs is primarily surgical.

Case Presentation

A 28-year-old male with no significant past medical history presented to the emergency department with a three-day history of progressive shortness of breath. On the day of admission, he became very short of breath after trying to mow his lawn, which prompted him to seek further evaluation in the emergency department. He had no fever, chills, cough, phlegm, or lower extremity
swelling. He also had no significant past medical history, no family history of deep vein thrombosis or PE, and no recent surgeries, travel, or trauma. A physical exam revealed he was saturating 96 percent on 2 L/minute oxygen through a nasal cannula and was noted to have a heart rate in the 90 beats per minute range that quickly increased to 150 beats per minute upon ambulating less than 20 feet. All lung fields were clear upon auscultation, and the patient’s heart rate was regular but tachycardic without murmurs. There was no jugular venous distention or lower extremity edema. His laboratory workup was unrevealing except for an elevated D-dimer. A chest radiograph demonstrated no cardiopulmonary abnormalities.

Computed tomography angiography (CTA) of the chest was performed and revealed multiple bilateral pulmonary emboli, the right side greater than the left, with a high clot burden (Figure 1). An urgently ordered echocardiogram revealed a normal ejection fraction with evidence of right heart strain. The echocardiogram findings also showed a moderately dilated right ventricle and elevated right ventricular systolic pressure at 67.2 mmHg. The exact cause of the patient’s submassive PE was unclear, so a bilateral duplex scan of the lower extremities was performed, which revealed a left popliteal vein aneurysm with a 2.8 x 3.6 cm thrombus. Vascular surgery was consulted, and the patient then underwent emergent catheter-directed lysis of the pulmonary emboli with placement of a temporary inferior vena cava (IVC) filter.

Following this, the patient’s dyspnea on exertion significantly improved, and he was discharged with stable vital signs and given rivaroxaban oral anticoagulation therapy. Post-discharge CTA of his left lower extremity was later performed and revealed a 6.0 x 4.2 cm popliteal aneurysm with a 2.0 x 1.8 x 2.5 cm thrombus (Figure 2). He eventually underwent uncomplicated left PVA repair with an interposition saphenous vein graft and eventual removal of the temporary IVC filter.

Discussion

PVA is a rare but notable cause of pulmonary embolism. Isolated PVAs were first described by May and Nissl in 1968. Since then, a total of 181 cases of isolated PVAs
have been described.\(^7\) However, about three-quarters of patients with PVAs develop pulmonary emboli.\(^8\)

Although the exact etiology is unknown, inflammation, trauma, degenerative changes, and congenital weakness have all been proposed as causes of venous aneurysms.\(^9\) The best initial diagnostic modality for the diagnosis of PVAs is venous duplex scanning.\(^10\) Newer modalities such as CTA or magnetic resonance imaging (MRI) have been used as diagnostic tools as well.\(^11\) In symptomatic patients with PE, surgical repair of the PVA remains the treatment of choice.\(^6-11\) The risk of recurrent PE with oral anticoagulation alone is estimated to be as high as 80 percent.\(^10,12\) Therefore, an IVC filter is often placed to prevent embolic complications until definitive surgical repair of the aneurysm has been performed.

Aneurysmectomy and lateral venectomy are surgical options to treat saccular venous aneurysms. Resection with end-to-end anastomosis and an interposition graft with bypass or ligation of the proximal and distal veins are options to treat fusiform venous aneurysms. Endovenous ablation techniques are usually not feasible to treat PVAs.\(^13\) The role of long-term oral anticoagulation treatment following aneurysm repair remains controversial. Several studies, though, recommend at least three months of oral anticoagulation following aneurysm repair.\(^14\)

**Conclusion**

While PVAs are rare, physicians should consider this diagnosis in patients with recurrent pulmonary emboli or when the cause of a pulmonary embolus is unknown. Of all cases of PVAs, nearly three-quarters result in PE. While the exact etiology is not known, inflammation, trauma, degenerative changes, and congenital weakness of venous wall have all been proposed as causes of venous aneurysms. A PVA can be diagnosed by utilizing several different imaging modalities, including venous duplex ultrasound, CTA, MRI, or venography. The definitive management of a PVA is surgical repair. Some studies suggest recurrent PE in as high as 80 percent of patients on oral anticoagulation therapy alone. Therefore, an IVC filter is often placed to prevent further embolic complications until definitive surgical repair of the aneurysm has been performed.
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<td>Membership Meeting with Presentations from AMA Chair-Elect Dr. Gerald E. Harmon and SSOM Dean Dr. Mary Nettleman</td>
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<td>SDSMA PAC Lunch: Clinician Health and Wellbeing – Reducing the Cost and Impact of Physician Burnout</td>
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Abstract

Peer review is a process for evaluating the quality of “work” of a scientist or professional as judged by others in the same or related field. In the context of the biomedical and health sciences, it primarily pertains to review of manuscripts submitted to journals for consideration of publication, abstracts for proposed presentations at professional meetings, and competitive research grant applications. Serving as a reviewer is a scholarly pursuit and a worthwhile endeavor, assuming it is approached in a conscientious, responsible manner. The purpose of this article is to define peer review and its various forms, suggest reasons for serving as a manuscript reviewer, discuss considerations prior to accepting a review assignment, and provide guidelines for the process.

Introduction

Publication in a peer-reviewed journal, particularly of the results of one’s original research, is generally accepted as the pinnacle of scholarly activity. This is not to say that authorship is the only measure of scholarship. For example, papers presented at international, national, and regional meetings of major organizations, which were selected via a refereed review process, certainly qualify as scholarship. We submit that manuscript review for peer-reviewed biomedical, health science, and social science journals is also a scholarly pursuit, assuming it is approached in a conscientious, responsible manner. Not only do we contend it is scholarship but believe it is a worthwhile exercise for a variety of reasons.

The purpose of this article is to define peer review and its various forms, suggest reasons for serving as a manuscript reviewer, discuss considerations prior to accepting a review assignment, and provide guidelines for the process. We hope this primer will encourage clinicians, researchers, and students to participate in manuscript review, and that it will provide the guidance necessary for novice and even seasoned reviewers to approach the task in a more confident manner.

Peer Review

Peer review is a process for evaluating the quality of “work” of a scientist or professional as judged by other scientists or professionals in the same or related field. In the context of the biomedical and health sciences, it primarily pertains to review of manuscripts submitted to journals for consideration of publication, abstracts for proposed presentations at professional meetings, and competitive research grant applications to obtain funding for research. The content of this article focuses most specifically on the review of manuscripts submitted to journals but much of it can be applied to critical review of other scholarly works.

The peer review process seeks to assess the validity, relevance, and potential impact of a manuscript. To describe it in a phrase common in industry, it can be considered an academic term for “quality control.” Its ultimate goal is to maintain and enhance the quality of research. Further, however, peer review can help establish a method for the evaluation of research and facilitate networking among scientists and clinicians with similar research interests.

The first journal considered to have established a “formal” process of peer review was the Philosophical Transactions of the Royal Society. First published in 1665, it is the oldest continuously-published science journal in the world. When in 1752, the Royal Society of London (RSL) assumed responsibility for what was then titled the Philosophical Transactions, the RSL constituted a
Peer review is not without criticism and its value is vigorously debated. Many maintain that it is an unreliable process, which fails to assure the authenticity or guarantee the integrity of scientific work. Others argue that it is laborious, slow, inefficient, subject to bias (of many types), and expensive. Despite these criticisms, most authors and reviewers believe it to be crucial given the increasing complexity of scientific subject matter and the need for quality in published scientific literature. It is generally accepted as the best method for research validation and the recognized standard of journal quality.

Peer review can take the form of open, single-blinded, and double-blinded review. In an “open” review, the reviewer and author know each other's names. Open reviews are less likely to be laced with unprofessional comments whether discourteous, sarcastic, or acerbic in nature. But there is also greater potential for an open review to be less than candid and for appropriate criticism to be withheld in the name of being polite or for concern of reprisal. Some editors maintain that this results in bland, cautious, and even timid reviews.

With single-blinded reviews, the name of the reviewer is hidden from the author, but the reviewer knows who authored the manuscript. This is the most common method of peer review, and as with any method there are pros and cons. This method prevents an author from attempting to influence a reviewer. The anonymity of the reviewer, however, can allow for the expression of bias against and needlessly harsh criticism of the author, particularly if the work is inconsistent with the reviewer's viewpoint. On the contrary, but just as concerning, knowledge of who the author is, particularly when he or she is renowned, can result in the manuscript being judged on the basis of the author's reputation rather than the manuscript's merit.

In the case of double-blinded reviews, the author and reviewers are unknown to each other. Although this does not eliminate bias (e.g., a reviewer may be biased because the author's findings are inconsistent with the reviewer), it does decrease the likelihood of bias against an author's country of origin or a specific author's work when it has been controversial in the past.

Why Serve as a Reviewer

There are several reasons to consider serving as a reviewer of manuscripts and other scholarly works. As a reviewer, one assists in assuring the quality of published articles. Further, through one’s critical review and commentary, the reviewer may be providing his or her expertise to the body of knowledge or, at least, making authors aware of other sources in the literature of which the author may be unaware. Manuscript review also helps the reviewer maintain currency in and abreast of advances in his or her own field. Participating as a reviewer adds to one’s professional profile, particularly important to academicians, although it is generally acknowledged that such activity does not lead to career advancement. When done often enough, however, an editor may gain confidence in a reviewer’s work ultimately leading to an invitation to join the editorial advisory board. Such recognition may well make a favorable impression on a promotion and tenure committee. It may also be beneficial when one submits his or her own manuscripts to a journal to be considered for publication. Granted, this motive would not be considered pure. A more highly-principled view is that manuscript review is a service, even a responsibility or duty to one’s profession and is, in fact, a privilege. For someone who is early in his or her career, the opportunity to review manuscripts can be invaluable in helping one learn the process of peer review and improve one’s own critical thinking and writing. It may also suggest methodological approaches for one’s own research interests.

What to Consider Prior to Accepting a Review Assignment

When agreeing to provide a peer review of a manuscript, one must first determine if one is a suitable reviewer of the material. When a solicitation to review is received, many journals will send along the title, authors, and abstract so that the reviewer can make an informed decision regarding his or her expertise as it relates to the article under

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consideration. The potential reviewer can best determine his or her expertise within the field, and the article subject matter should be carefully considered before deciding to provide a peer review.

In addition to the subject matter, one should determine the style of review to be provided. Traditionally, reviews have been provided as free text, where a reviewer could provide context for their decision, and recommend edits that would improve the quality of the manuscript. While most journals provide the opportunity to present specific concerns to the authors in written form, many are now requesting that reviewers provide responses to key questions either in addition to, or in place of, the free text review. Reviews that limit the potential for comments may be undesirable to certain reviewers and fields of study, and the structure of the review being provided should be considered.

While being an expert in the field is greatly encouraged, one must also ensure that the review can be provided without substantial personal bias. The review process relies on critical evaluation of the work presented, and the reviewer must ensure that the review will be fair to the author. If for some reason there is a bias against one of the authors, or the work itself, the reviewer must decide whether a fair review can be provided. The issue of perceived conflict of interest is discussed below, and personal bias can go beyond conflicts of interest. If a personal bias exists, and there is potential for an unfair review, the reviewer should decline review of the manuscript.

As mentioned above, many journals will provide a list of the manuscript’s authors with the solicitation for the review. The reviewer should identify any potential conflict of interest due to past or current association with authors of the manuscript in a timely manner. Potential conflicts of interest include collaboration with the authors, in particular a history of funding or shared publications, as well as potential financial conflicts of interest that could result in a biased review of the manuscript. It is better to identify these potential conflicts of interest early in the review process, disclose them to the editor handling the manuscript, and decline handling the manuscript if the conflict would be perceived as influencing a decision on the fate of the manuscript.

When considering a review assignment, the reviewer should pay attention to the type of review that is being conducted. For example, is the review open, single-blinded, or double-blinded? As mentioned above, each has its strengths and weaknesses and the reviewer must determine which type of review he or she is most comfortable providing. In some cases, the option to disclose a reviewer is left at the reviewer’s discretion, and that can allow the reviewer to complete the review prior to deciding whether to assign his or her name to the review itself. If the review is to be provided on an open basis, the reviewer must consider the implications of the feedback on the scientific community. Feedback should be provided in a manner consistent with publishing the best science from the author, and whether the identity of the reviewer is disclosed or not, the feedback provided should be directed toward increasing the overall quality of the publication.

One final thing to consider before accepting a request to act as a reviewer is the ability to complete the review in a timely manner. It can be discourteous to the editor and authors, and even unprofessional, to not meet a deadline. The process of review is already lengthy, and inability to rapidly evaluate the manuscript can hinder the process. If it is likely that other commitments will delay review of the manuscript, it may be better to decline the invitation rather than delay the process. When making this decision, the reviewer should also consider the fact that feedback on revised versions of a manuscript is often requested. Thus, there may be a future time commitment to the review process beyond providing the initial review. If one does not feel that he or she is an appropriate reviewer for a manuscript, he or she can assist the editor by suggesting potential alternative reviewers. As experts in the field, reviewers often have knowledge regarding who might be able to act as an alternative reviewer.

**Format for Review**

As noted above, the traditional review involves free text while a number of current journals have a combination of specific questions related to important scientific queries as well as an area for free text. In evaluating a manuscript one must determine if it will be of importance and interest to the readership of the specific journal. Usually this already has been accomplished by both the author who has carefully evaluated the readership of a specific journal prior to submission and the responsible editor who has appraised it prior to sending it to the reviewer. Occasionally, especially in journals with broad or general readership, a reviewer who is an expert in the field will find that the submitted manuscript is better suited to a more focused journal for that area of research.

In providing a review one first supplies a brief synopsis of what the authors have accomplished and the significance of these results to the scientific community. Are these
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ground-breaking Nobel laureate type of results, or more commonly are these results that add to the current scientific discourse. As innovative, statistically significant results are always interesting, it is important to remember that the scientific method requires proof of replication of results. Hence, it is vital to the scientific community to have well designed studies that replicate previous research. What about the study with negative results, i.e., no statistically significant difference between groups? These studies are also important in adding to the general scientific information and many times are difficult to get into publication. This difficulty in getting negative results in press can potentially lead to publication bias. Efforts to overcome the difficulty of publication bias include the requirement by many journals to prospectively register a trial prior to initiation in one of the trial registries developed for this purpose. The U.S. National Library of Medicine sponsors a registry at www.clinicaltrials.gov.

Following a brief review of what was accomplished with this trial and how it added to scientific knowledge, one needs to discuss the type of study; was it an experimental or observational trial? If this was an experimental study, did the investigators randomize the subjects and controls or was it a non-randomized trial. If the study was an observational study was it a cohort study, case-control study, cross sectional study or was it a case report or case series? Other types of manuscripts in the medical literature include systematic reviews, meta-analyses, review articles, personal perspective manuscripts, editorials and letters to the editor. In using the literature for evidence-based medicine there is a hierarchy of types of studies designs for making clinical treatment decisions and preventive therapy. In this hierarchy the randomized, placebo-controlled trial (RCT) is at the pinnacle supplying some of the strongest evidence supporting the therapy. Systematic reviews with meta-analysis of RCTs are also powerful in supporting a particular therapy. Next in the hierarchy are systematic reviews of observational trials and then single observational trials. Finally clinical observations have the lowest strength in supporting a particular therapy in evidence-based medicine. However, even the lowly case report/series has significantly added to scientific knowledge. An example of a case series that significantly added to medical scientific knowledge was published in 1970 when Dr. A.L. Herbst described seven cases, six of which were clear-cell, vaginal adenocarcinomas, which are a very rare cancer. Based on this unusual clustering of cases, Dr. Herbst conducted a case-control study and unearthed the association of diethylstilbestrol and clear-cell adenocarcinoma of the vagina. From these initial observations further studies were conducted with the ultimate result of diethylstilbestrol use in pregnancy being halted.

To assist the aspiring scientific author, a number of guidelines with checklists have been developed for each type of study to ensure that the manuscript has all the required elements of a good scientific paper. These guidelines are meant to reflect the minimum requirements to allow the study’s effective use in evidence-based medicine. Many journals now require that a completed, appropriate checklist accompany a submitted manuscript. These guidelines include the CONSORT statement, an abbreviation for Consolidated Standards of Reporting Trials, which was designed to reduce difficulties related to publication of randomized controlled trials. The CONSORT statement with checklists are available at www.consort-statement.org.

Other guidelines include Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) available at www.prisma-statement.org; Guidelines for Meta-Analysis and Systematic Reviews of Observational Studies (MOOSE) available at http://edmgr.ovid.com/ong/accounts/moose.pdf; Standards for Reporting Diagnostic Accuracy (STARD) statement available at www.stard-statement.org; Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) available at www.strobe-statement.org/index.php?id=strobe-home; Consensus-based Clinical Case reports (CARE) available at www.equator-network.org/reporting-guidelines/care; and others. These guidelines were all developed to assist investigators in submitting their manuscripts for publication.

In reading and reviewing the manuscript an author should evaluate the various parts of the manuscript to ensure that each portion contains suitable information. In reviewing a manuscript, a first quick read helps evaluate for originality, appropriateness for the journal, and for basic writing including spelling, grammar and syntax.

One of the first steps in reviewing a manuscript is to evaluate the title. Does the title of the manuscript reflect the content of the article? Most journals require that the title also reflect the type of study, whether it is a RCT, observational trial, or case report or series.

The abstract is a vitally important part of the manuscript as it is often the only part of the manuscript that is read by a busy clinician. The abstract should be a synopsis of the manuscript giving a short, detailed summary of the introduction, materials and methods, results and conclusion sections. Depending on the journal the abstract may be structured or unstructured. The structured abstract...
highlights each section of the manuscript: introduction, material and methods, results, conclusion and sometimes other categories to make it easier for the reader to find and interpret information. From a reviewer’s point-of-view, one wants to review the abstract and make sure that its components and whole give a summary of the manuscript.

The Introduction should give a brief summary of the state of scientific knowledge about the topic being studied. Following this summary of information the author needs to discuss the specific purpose of the study in terms of answering his or her stated hypothesis(es).

In the Material and Methods section, one expects to find details about the study design and how it was implemented. In this portion of the manuscript the details of the study should be comprehensive enough to allow another investigator to replicate the study. The authors should also describe the type of study: randomized controlled trial, observational study, case series or report, or other type of study and the specifics they used to carry out this study. As a reviewer, one should evaluate whether the chosen study design is appropriate to answer the investigator’s questions. Also, how did the authors measure their outcome of interest? Did they use a 12-inch ruler to measure a mile, or did they use an appropriate method of measurement for what they were trying to evaluate and how reproducible was the method of measurement? An example of a method of measurement, which needs to be fully discussed in the manuscript is an immunoassay. The authors also need to state that this study was approved or given exempt status by an appropriate, identified institutional review board and that the subjects gave informed assent/consent. The authors should provide information about the statistical analysis that was performed on the data. The authors should give details on how their ‘n’ was determined and their study’s power. This is an opportunity for the reviewer to determine if the study was appropriately executed and if appropriate statistical analyses were applied to the data. There are a number of references available to refresh the reviewer on different study designs, the appropriateness of a study design to answer a specific question and on biostatistics. A helpful reference for evidence-based medicine is JAMA’s Users’ Guide to the Medical Literature: Essentials of Evidence-based Clinical Practice.16

In the Results section the reviewer needs to determine if the author has clearly stated the results of the study. In this section it is important that the author has organized the results in a method that allows the reviewer, and ultimately the reader, to follow the information throughout the manuscript in a logical fashion. There are a number of methods that an author can use to organize results including parallel design, subsections, or along themes or patterns. In a parallel design the results are organized in parallel with the introduction, the materials and methods, and discussion sections, which allows for a coherent flow of information. With the subsection method, the author organizes results in various subsections, which flow from the Materials and Methods section. Other types of organization along themes or patterns can also be used. The reviewer needs to confirm that the authors have organized data in an understandable, coherent fashion. One also needs to confirm that data analysis is accurate and that findings are clearly presented. Figures and tables are often used in the results section and can enhance the delivery of complex results in a coherent, understandable fashion. The reviewer should assess the figures and tables to decide if they are succinct and easy to understand. One must be on guard for the overuse of tables and figures which can disrupt the flow of the manuscript, as well as safeguard against repeating everything recorded in tables and figures in the text of the manuscript. Similarly, it is important to review the tables and figures to confirm that the results are accurately recorded throughout the manuscript.

In the Discussion, the author should start with the conclusion clearly stated discussing what has been learned with the study and how it may affect clinical care. As noted earlier it is important that the entire manuscript flows in an organized, coherent fashion. In other words, the conclusions should follow the material and methods as well as the results section. The reviewer also wants to see that the author has put the results in the context of current scientific knowledge. It is also important that the Discussion describe the strengths and limitations of the study and how these results can be generalized to the population as a whole. The reviewer should determine if the conclusions the author makes are reasonable and fit with the results in the current study as well as in up-to-date literature. It is also important to assure that the authors discuss the general implications of the research and how it will assist in guiding future research.

The reviewer needs to appraise the references to determine if they are current, high quality and sufficiently reference previous scientific research. The references need to be listed according to the “Instructions for Authors” for the specific journal.

Comments For/To Author and Editor
When providing a review, it is important to remain thoughtful, fair, and constructive in the evaluation of the
manuscript. As an expert in the field, the reviewer should be aware of the direction of the author’s research, and where the findings fit in the context of what is known to other experts in the field. Providing a thoughtful, fair, and constructive review of a manuscript will help authors relate their findings, if they have not already done so. Additional efforts that ensure clarity of the comments, and justification for the feedback provided, will help the authors interpret the intent of the comments provided. Reviewers should remember the comments they themselves have received as authors, and be considerate to their colleagues when providing their review.

Feedback provided by a reviewer should be objective in nature, with the goal of helping authors present their findings in a way that truly impacts the field. When provided in an objective way, this feedback can help authors improve upon their findings, especially if the comments will lead to additional experiments. One way to provide an objective review is to point out both the strengths and weaknesses of the experimental design and interpretation of results. Reviews that provide both positive feedback and constructive criticism of the manuscript will allow the authors to determine the parts of their work that advance the field and the parts that can be improved upon, and to appreciate the evaluation of their efforts to help them design experiments and critically evaluate their own data. Reviews should avoid the use of negative comments that are not relevant or constructive, especially if they do not move the authors toward improving the impact of their findings in the field.

When submitting a review, the reviewer should once again consider any personal bias that may affect the review provided. If there is a personal or professional bias, this should be disclosed to the editor so that any potential impact of this bias can be considered when a final decision is made. These biases should not include perceived conflicts of interest, as those should be disclosed when agreeing to act as a reviewer.

As mentioned above, comments to authors should provide general feedback related to experimental design and interpretation of results as well as specific suggestions for improvement of grammar and overall presentation of findings. Comments should clearly indicate areas that can be clarified by the authors, including those that could be strengthened by additional text and/or reformatting of figures and tables to improve data presentation. The review provided can reference both broad sections for improvement as well as specific areas that need minor editing. For example, if a specific section needs clarification, the section can be directly referenced within the review using page, paragraph, and line numbers. Specific comments can include grammatical errors and spelling errors that the author needs to correct. Also, as an expert in the field, a reviewer should state whether a manuscript will benefit from significant additions or deletions to the content, or if there are key references that have not been cited. Specifically, if the authors have included information that does not directly support their findings, suggestions to remove this additional information can be made. Finally, if the reviewer feels that the overall interpretation of the findings presented warrants a recommendation of rejection by the journal, reviewers should make an effort to not only provide justification for this decision but also, if indicated, to suggest another journal that may be more appropriate for publication of the study.

Conclusion

Peer review remains the most accepted process for evaluating work submitted for either publication or grant funding, and it relies on the use of experts in a specific field of study. Individuals that choose to participate in this process should determine whether they are the right person to provide the review, whether the review format will allow them to provide critical feedback to the authors, and if their feedback will yield the best possible publication on the field of study. This feedback will improve the quality of the manuscript. The ultimate decision to accept or reject a manuscript will be made by the editor based upon the feedback provided by the reviewers with the ultimate goal to produce a manuscript that may help advance the specific field of study.

REFERENCES


Please note: Due to limited space, we are unable to list all references. You may contact South Dakota Medicine at 605.336.1965 for a complete listing.

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Torsades de Pointes (TdP) is a specific type of polymorphic ventricular tachycardia associated with prolongation of the corrected QT interval (QTc). TdP is life-threatening and may result in sudden cardiac death. The incidence of TdP is difficult to determine since few individuals are monitored at the time of death. There are many risk factors associated with developing TdP including many medications that have the potential to prolong the QTc interval. Based on adverse drug case reports from the World Health Organization Monitoring Centre, the overall risk of TdP due to medications was estimated to be 4 in 100,000 in Sweden. Many medications have been removed from the market due to ventricular arrhythmia and sudden cardiac death adverse drug events.

One surrogate marker commonly used to assess the risk of developing TdP is the QTc interval. It has been estimated a 10 ms increase in the QTc interval from baseline is associated with a 5 to 7 percent exponential increase in risk for TdP. When the QTc interval exceeds 500 ms, the risk of TdP is estimated to increase by two to three fold. A threshold for the QTc interval has not been established to predict when TdP is certain to occur. Current risk assessment tools suggest utilizing 500 ms or greater than 60 ms from baseline as a threshold for the QTc interval.

Other patient specific and/or drug specific factors may also contribute to the risk of developing TdP. Known patient risk factors include advanced age, female gender, the acute myocardial infarction setting, heart failure with a reduced ejection fraction, current therapy with diuretics, hypocalcemia, hypomagnesemia and hypokalemia. Elevation in drug concentrations of medications with potential to increase the QTc interval may also increase the risk of TdP. Special attention should be made to avoid drug interactions that may result in increased levels and ensure proper dosing adjustments in patients with impaired kidney function for renally eliminated drugs. In general, strong inhibitors of QTc prolongation medications should be avoided in patients at any level of risk for TdP. The Food and Drug Administration (FDA) has published comprehensive tables of substrates, inhibitors and inducers of various CYP P450 enzymes.

Clinical research data for drugs thought to increase the risk of TdP is limited. Most information is based on case reports and postmarketing surveillance through the FDA. A research article published in 2016 by Wisniowska et al. provides an extensive overview of clinical studies of medications and the risk of TdP. The website crediblemeds.org is a valuable website which provides real time information on medications associated with a risk of TdP. CredibleMeds is the website for the nonprofit organization Arizona Center for Education and Research on Therapeutics (AZCERT). CredibleMeds categorizes medications into “known risk,” “possible risk,” “conditional risk,” and “drugs to avoid in congenital long QT.” Representative drugs associated with a “known risk” of TdP are shown in Table 1. “Known risk” is defined as those medications that “prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended.” It should be noted this list of medications does not encompass all medications with a “known risk” of TdP.

In 2013, a risk score for QTc interval prolongation was developed by Tisdale et al. to help guide monitoring and treatment decisions for hospitalized patients. The score was developed based on an observational study of 900 patients in a cardiac critical care unit. The threshold for the QTc interval prolongation was defined as greater than 500 ms or greater than 60 ms from baseline. After the risk score was developed, the score was applied to a validation group consisting of 300 patients and found to have a high level of sensitivity and specificity.

Factors included in the QTc risk score developed by Tisdale were as follows: age greater than or equal to 68 years of age, female sex, loop diuretic prescribed (1 point each); QTc interval upon admission greater than or equal
Table 1. Drugs Associated with a Known Risk of Torsades de Pointes

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Known Risk</th>
</tr>
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<tbody>
<tr>
<td>Antiarrhythmics</td>
<td>Amiodarone</td>
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<tr>
<td></td>
<td>Disopyramide</td>
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<td></td>
<td>Dofetilide</td>
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<td>Dronedarone</td>
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<td>Flecaïnide</td>
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<td></td>
<td>Ibutilide</td>
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<td></td>
<td>Quinidine</td>
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<td></td>
<td>Sotalol</td>
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<tr>
<td>Antibiotics</td>
<td>Azithromycin</td>
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<td>Clarithromycin</td>
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<td></td>
<td>Erythromycin</td>
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<td>Ciprofloxacin</td>
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<td>Levofloxacin</td>
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<td></td>
<td>Moxifloxacin</td>
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<tr>
<td>Antidepressants</td>
<td>Citalopram</td>
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<td></td>
<td>Escitalopram</td>
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<tr>
<td>Antifungals</td>
<td>Fluconazole</td>
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<td></td>
<td>Pentamidine</td>
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<td>Antiemetics</td>
<td>Ondansetron</td>
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<tr>
<td>Antimalarials</td>
<td>Chloroquine</td>
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<td></td>
<td>Halofantrine</td>
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<td>Antipsychotics</td>
<td>Chlorpromazine</td>
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<td></td>
<td>Haloperidol</td>
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<td>Cholinesterase inhibitors</td>
<td>Donepezil</td>
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<td>Opiates</td>
<td>Methadone</td>
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<td>Phosphodiesterase-3 inhibitors</td>
<td>Anagrelide</td>
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<td></td>
<td>Cilostazol</td>
</tr>
</tbody>
</table>

to 450 ms, serum potassium less than or equal to 3.5 mEq/L, acute myocardial infarction (2 points each); one QTc interval prolonging medication, greater than or equal to 2 QTc interval prolonging medications, heart failure with reduced ejection fraction, sepsis during hospital admission (3 points each). The total possible QTc score is 21 points with high risk greater than or equal to 11 points, moderate risk 7 to 10 points and low risk less than 7 points. For patients taking greater than or equal to 2 QTc interval prolonging medications, a patient would receive a score of 6 points (3 points for one QTc interval prolonging medication and 3 points for greater than or equal to 2 QTc interval prolonging medications).

Although the risk score for QTc prolongation established by Tisdale et al. was based on hospitalized patients in a cardiac critical care unit, this risk score may have utility to assess non-cardiac patients and outpatients. This tool may underestimate the QTc score since specific risk score parameters, such as serum potassium or QTc interval, may not be available in outpatient settings. But consider for example, an outpatient who is a 72-year old female with a recent acute myocardial infarction and taking metoprolol succinate, furosemide, azithromycin and donepezil. This patient would be high risk which would alert the clinician to modify therapy.

TdP is a life threatening event which can lead to sudden cardiac arrest. Several medications are known to cause QTc prolongation and may contribute to the development of TdP. The resource, crediblemeds.org, provides drug information to help clinicians identify medications which may cause QTc prolongation. In addition to being aware of medications which may cause QTc prolongation, clinicians should understand risk factors, drug-drug interactions and renal function which may place patients at risk for TdP. The QTc risk assessment tool developed by Tisdale et al. can help clinicians determine if patients are at increased risk for TdP. Whenever feasible, risk factors for TdP should be minimized or eliminated to decrease the risk of developing TdP.

References


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SDBMOE Announces New Administrative Rules Affecting the Practice of Medicine

The medical documentation rules are provided in this article and can be viewed on the Board website using the New Rules link on the homepage, or by clicking on the Statutes and Rules tab in the right hand menu on the homepage.

Medical Documentation Rules (commonly referred to as the “opioid prescriber rules”). However, this documentation rule covers more than just opioids in that it is for any controlled substances (including tramadol).

More accurately described as the medical documentation rules “when prescribing controlled substances for the treatment of chronic, non-cancer pain”

- When treating chronic, non-cancer pain as defined in the second rule
- Provides a definition of chronic pain

The South Dakota State Medical Association (SDSMA) provided input and recommendations

- The SDSMA created an ad hoc committee to study the issue.
- Board member Dr. Laurie Landeen was the Board’s liaison to the ad hoc committee.

Dr. Landeen would like to provide this guidance on the new rules:

- The intent of this rule is for providers to have a sense of what is expected in the medical chart.
- This will be a tool for investigators to use when there is a complaint about over-prescribing controlled substances.
- The board will not be utilizing this new rule to randomly screen the medical records of providers who prescribe controlled substances.
- Please remember that this rule applies to the use of controlled substances for chronic, non-cancer pain, and does not apply when treating acute or post-operative pain!

The New Administrative Rules

20:47:07:01 Standards for medical records when prescribing controlled substances for the treatment of chronic, non-cancer pain. The standards for medical records when a physician prescribes controlled substances for the treatment of chronic non-cancer pain include each of the following listed items:

1. Copies of the signed informed consent and any treatment agreement required by the physician;
2. The patient’s medical and psychosocial history;
3. The results of all physical examinations and all laboratory tests;
4. Confirmation that the appropriate state prescription drug monitoring programs have been accessed, and the date of that access, or an explanation why they were not accessed;
5. The results of all risk assessments, including results of any screening instruments used;
6. A description of the treatments provided, including all medications prescribed or administered, with the date of prescription or administration, the name and type of the medication, and the dosage and quantity of medication prescribed or administered. The medical records must include all prescription orders for opioid analgesics and other controlled substances, whether written, telephoned, faxed, or electronically transmitted;
7. Instructions to the patient, including discussions with the patient and, if appropriate, significant others of the risks and benefits of opioid analgesics, including the risks of addiction, overdose, and death; proper use and storage of medication; proper disposal of unused medications; and the use of naloxone products to reverse overdose;
8. Results of ongoing assessments, including, when appropriate, urine drug tests, of patient progress or lack of progress in terms of pain management and functional improvement;
9. Notes on any evaluations by and consultations with specialists;
10. Any other information used to support the initiation, continuation, revision, or termination of treatment. Any steps taken in response to aberrant medication use by a patient and aberrant behaviors related to a prescription for an opioid analgesic;
11. Medical records of past hospitalizations or treatments by other providers, to the extent obtained by the physician;
12. Authorization for release of information to other treatment providers; and
13. Name, address, and telephone number of the patient’s pharmacy.
Quality Focus:
March is Colon Cancer Awareness Month

By Stephan D. Schroeder, MD
Medical Director, South Dakota Foundation for Medical Care

Colonoscopy continues to be a vital tool in all colorectal cancer (CRC) control programs. It often serves as the primary screening tool for CRC in adults and for evaluation of any positive screening test including fecal immunochemical test (FIT) for occult blood, fecal DNA test, flexible sigmoidoscopy and CT colonography.

Since 2000, the rate of death from CRC has dropped by 3 percent per year. Despite the success of CRC control programs, like all medical services, colonoscopy is undergoing increasing scrutiny with regard to quality. A number of studies show colonoscopy reduces deaths from CRC. The studies also reflect a great variation in quality between providers in the performance of colonoscopy and relate the direct impact on the effectiveness of colonoscopy in preventing death from CRC.

There are a number of quality indicators for colonoscopy, and there are three key, or priority, indicators for colonoscopy quality identified by the American Society for Gastrointestinal Endoscopy (ASGE)/American College of Gastroenterology (ACG) Task Force on Quality in Endoscopy: 1) Adenoma detection rate (ADR); 2) Use of recommended intervals between colonoscopies performed for average-risk screening and colon polyp surveillance; and 3) Cecal intubation rate with photo-documentation of the cecum.

ADR is an important measure to understand for both primary care providers and endoscopists performing colonoscopy. ADR expresses the rate at which an endoscopist finds at least one adenomatous polyp in a patient of average risk undergoing screening colonoscopy. The rate varies by endoscopist from as low as 7 percent to over 50 percent. ADR is thought to be the central measure of colonoscopy quality as it is a direct reflection of the thoroughness of the inspection of the colonic mucosa.

More importantly, two studies have demonstrated interval colon cancers, cancers occurring soon after colonoscopy and thought to arise from missed lesions, occur at a significantly lower rate after colonoscopy by an endoscopist with a high ADR compared to an endoscopist with a low ADR. For every 1 percent improvement in ADR, the risk of developing an interval colon cancer decreases by 3 percent.

Adherence to guidelines when making recommendations for follow-up colonoscopy is important to the overall cost-effectiveness of a CRC control program. When low-risk patients receive instruction to repeat colonoscopy at too short an interval, they are subjected to the risk and expense of unnecessary colonoscopy and the CRC control program becomes overly expensive. When high-risk patients receive a recommendation to repeat their colonoscopy at too long an interval, they are left at risk for CRC and the effectiveness of the program is diminished.

CMS has included a number of colonoscopy quality measures for reporting in 2017 as part of the Merit-Based Incentive Payment System (MIPS): 1) Appropriate follow-up interval following a normal colonoscopy in average-risk patients; 2) Appropriate follow-up interval for patients with a history of adenomatous polyps; and 3) Screening colonoscopy adenoma detection rate (ADR).

Endoscopists from all specialties now need to measure their ADR and document they are providing appropriate recommendations for follow-up colonoscopy. There are a number of endoscopy-specific software packages that allow one to track ADR and provide documentation for follow-up recommendations given to patients. Further, most of these software packages will interface with reporting software to allow reporting of these measures to CMS, thus fulfilling requirements for participation in MIPS. Given the difficulty in monitoring these endoscopic quality activities manually, investment in software reporting packages is essential for all sites performing colonoscopy.

Further reading:

REFERENCES
7. MACRA: MIPS & APMs - Centers for Medicare & Medicaid Services
   https://www.cms.gov/Medicare/Quality...MIPS.../MACRA-MIPS-and-APMs.html

"Quality Focus" is a monthly feature sponsored by SDFMIC, South Dakota’s Quality Improvement Organization. For more information about the SDFMIC, visit their website at www.sdfmic.org.

This material was prepared by the Great Plains Quality Innovation Network, the Medicare Quality Improvement Organization for Kansas, Nebraska, North Dakota and South Dakota, under contract with the Centers for Medicare & Medicaid Services (CMS), an agency of the U.S. Department of Health and Human Services. The contents presented do not necessarily reflect CMS policy. 1550-F-GPQIN-SD-SIP1-2010217
Mr. D, a diabetic patient of mine, came into the clinic with exercise induced leg pain which would go away if he stopped a minute, but lately it’s been coming on while walking less than a block. He said, “Now the pain is meaner and lasts longer after I stop.”

The diagnosis of Mr. D’s condition is claudication, a condition where arterial flow to the legs is blocked. I immediately called the vascular specialist for an urgent appointment. Two weeks later the patient returned to the office after having had his blocked arteries dilated with a balloon followed by the placement of stents to hold them open. Happily, he told me he could once again walk for miles without pain.

His vascular doctor had started artery dilating meds, lipid meds, and daily baby aspirin. I renewed my encouragement for Mr. D to eat fewer calories, exercise daily, keep his blood sugars controlled, and the most important advice, “Stay away from sitting long on that darn couch. It’s like smoking.”

The narrowing process, called atherosclerosis, can be the result of genetic tendencies, diabetes, smoking, high blood pressure, high blood lipids, and even normal aging. Arteries usually narrow gradually, but atherosclerosis can sometimes trigger a clot and a sudden complete blockage resulting in a sudden, and devastating event. It can occur in coronary arteries of the heart, cerebral arteries of the brain, renal arteries of the kidneys, and peripheral arteries of the legs. And, in general, when it’s happening in one, it’s happening in all.

Narrowing of blood flow can deprive muscles, skin, ligaments, and nerves downstream of precious blood flow and oxygen, resulting in an aching and agonizing hurt that would bring anyone to their knees. When it happens in the legs, like what happened with Mr. D, the pain symptom is called claudication and the condition is called peripheral artery disease, or PAD.

PAD affects 5 percent of all people over 50, but more than 30 percent of all diabetics in the same age group. There can be a curve ball with diabetes or with aging, as these people sometimes lose feeling in their legs and feet due to nerve destruction, setting them up for PAD without pain. The presenting sign then would be painless sores on the feet which won’t heal. This is especially treacherous because, without good blood flow, the healing is very slow and the patient, having no pain, is not as motivated to do the work required to heal ulcers.

Leg pain that goes away with rest may not sound so bad, but peripheral arterial disease is one of the most formidable challenges in modern medicine.
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“For Your Benefit” is the SDSMA’s monthly update on programs and services available to physicians through their affiliation with the SDSMA.

Register Today for the 2017 SDSMA Annual Leadership Conference

The 2017 SDSMA Annual Leadership Conference heads to Deadwood at the SpringHill Suites & Cadillac Jacks on Friday, June 2.

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

Tickets for the banquet and SDSMA PAC lunch are available for purchase online.

Do you have a policy issue you’d like to bring to the SDSMA’s attention? Schedule a time to address the Council by contacting the SDSMA office at 605.336.1965 or visit www.sdsm.org for a submission form.

The Annual Leadership Conference is a benefit of your membership. For the latest details about exciting events taking place during the 2017 SDSMA Annual Leadership Conference, visit www.sdsm.org.

SCHEDULE

8 am
Membership Meeting with presentations from the AMA Chair-Elect
Gerald E. Harmon, MD and SSOM Dean Mary Nettleman, MD

9:15 am
Open Membership Forum

10:45 am
Panel Discussion: Physician Burnout

12 pm
SDSMA PAC Lunch: SDSMA PAC Lunch: Clinician Health and Wellbeing – Reducing the Cost and Impact of Physician Burnout

1:30 pm
Council of Physicians Meeting

4:30 pm
Policy Council Meeting

6 pm
Membership Mixer

7 pm
Awards Banquet & Scholarship Recognition

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2017 SDSMA Annual Leadership Conference – Sponsorship & Advertising Opportunities

The SDSMA Annual Leadership Conference is a perfect opportunity for organizations of all sizes to advertise their products and services to current and potential customers. The 2017 Annual Leadership Conference will be held on Friday, June 2 at the SpringHill Suites and Cadillac Jacks in Deadwood. As a sponsor or advertiser, you will have the opportunity to market your technologies, services, pharmaceuticals and other products. This is a valuable opportunity to reach key health care leaders from across South Dakota.

Diamond sponsors have the opportunity to attend the Membership Mixer and Awards Banquet on Friday evening to visit with physician members. Sponsorship and advertising options are available in many varieties to meet the needs of all organizations.

Check out the all of the sponsorship and advertising opportunities for 2017 at sdsm.org where you will find the registration form along with a description of each sponsorship category and advertising option.

Those with questions may contact Laura Olson at 605.336.1965 or lolson@sdsm.org.
The Issue Is...

CMS extends deadline for 2016 PQRS electronic submissions

The Centers for Medicare and Medicaid Services (CMS) is extending the deadline for submission of 2016 Physician Quality Reporting System (PQRS) data through all mechanisms except claims — including reports submitted through EHR, qualified registries, and qualified clinical data registries.

The original submission deadline was Feb. 28, and claims-based reporters were to be submitted by that date. Eligible professionals who do not satisfactorily report 2016 quality measure data to meet the 2016 PQRS requirements will be subject to a downward PQRS payment adjustment on all Medicare Part B Physician Fee Schedule services rendered in 2018.

A complete list of 2016 data submission timeframes is as follows:

**March 13 deadlines**
- EHR Direct or Data Submission Vendor (ORDA I or III)
  - January 3 - March 13, 8 p.m.
- ET Qualified Clinical Data Registries (ORDA III)
  - January 3 - March 13, 8 p.m. ET

**March 17 deadline**
- Web Interface – Jan. 16 - March 17, 8 p.m. ET

**March 31 deadlines**
- Qualified Registries (Registry XML) – January 3 - March 31, 8 p.m. ET
- QCDRs (QCDR XML) – January 3 - March 31

An Enterprise Identity Management (EIDM) account with the “Submitter Role” is required for these PQRS data submission methods. If reporting through the EHR, it is recommended that practices work with their EHR vendor to submit data on practices’ behalf and not for practices to submit data directly to CMS.

Those with questions may contact the QualityNet Help Desk at 866.288.8912 or Qnetsupport@hcqis.org from 8 a.m. through 8 p.m. ET. Complete information about PQRS is available at cms.gov.

Source: AMA

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Legal Brief Highlight: Medical Marijuana

Although there are different schools of thought concerning the efficacy of marijuana to treat certain medical conditions and whether its possession and use ought to be decriminalized altogether, the fact remains that it is a violation of federal law and South Dakota law to possess or distribute it. Writing a prescription for marijuana, even to a patient living in a state where its use and possession is legal, could result in a disciplinary proceeding brought by the South Dakota Board of Medical and Osteopathic Examiners.

It is recommended that the practitioner not prescribe (either using a traditional prescription or a certification) marijuana unless and until changes in the law make it clear that doing so is legal, and then only when it is medically-necessary and appropriate.

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

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Send photos to ereiss@sdsma.org.
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