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Pictured left to right:
Johnathan Cohen, MD, Andrew Terrell, MD, Chad Spanos, MD, John Lee, MD

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Two years ago, your acting president Dan Heinemann, MD, initiated a governance task force to study various options for structure to assure our organization meets the needs of its members and conducts its business in a way that decisions are made that are understandable and supportable.1 At the time, the South Dakota State Medical Association (SDSMA) had been operating with its current structure of governance for 15 years. He argued that change was needed to increase involvement of members in an efficient manner. Under the capable leadership of Chris Dietrich, MD, a governance task force worked diligently over the ensuing two years and presented its recommendations to the Council of Physicians. At our recent Council meeting on Sept. 18, a new governance structure was approved.

As many of you know, the Council of Physicians was becoming larger and cumbersome because of the formula to add Councilors based on membership. One consequence of this increased size was disengagement and inefficiency. Council meetings became less productive, and as a result increasing authority for needed timely decisions was placed on our smaller Executive Committee. This created tension and conflict. By downsizing the Council, authority for decision-making would stay in the appropriate body. Position statements, policy and bylaw changes would be the sole responsibility of the Council. As acting president, I can assure you I feel much more confident giving the SDSMA’s positions on important issues when they have been fully vetted and supported by the entire Council, as opposed to the Executive Committee alone. The association’s strength is not a function of how many individuals are on the Council but the quality, commitment and participation of those who serve.

Balanced representation is important to an organization. Prior to the new governance model, larger districts had the ability to have a louder voice and smaller districts had less of a voice. This is not healthy for an organization. Our largest district, the Seventh, contained 30 percent of the entire Council membership. By evening the playing field, the Seventh District will still have a strong voice, but not any stronger than any of the other districts. There are those who may argue a smaller Council will make it easier for individuals to advance a special agenda. Evidence shows the opposite to be true. If someone was attempting to advance a special agenda, it would become more evident, and a smaller, stronger Council is more likely to confront this individual because it is less uncomfortable doing so in a smaller group. A large Council is much more vulnerable to political maneuvering than a small one.

Giving up our traditional larger Council structure, what do we get in return? We get initiatives with higher impact because we spend more time on the issues and less time on planning meetings. I particularly recall a recent meeting I chaired in March. We spent the better part of an hour trying to invite people to join by phone so we could reach a quorum and conduct business. We had 77 people on the Council, and had to scrap and claw to come up with a quorum of 39!

At our recent Council of Physicians meeting, the governance task force proposed a number of revisions to the SDSMA’s articles and bylaws to streamline governance to better meet the needs of members, and to engage more members in policy development. The Council of Physicians will be renamed the Policy Council and will have a more purposeful role in policy work. Its role will be to set policy by adopting position and policy statements, and will retain the sole power to amend the articles and bylaws. The Executive Committee will be renamed the Board of Directors, and will be the governing body of the association.

Our standing committees will be replaced by issue-specific committees on health care topics of the day. The ad hoc committees will be shorter-term or time-limited and will provide more opportunity for involvement of members on a variety of topics to address timely issues. Beginning in 2016, the Policy Council will transition to two meetings per year – one to coincide with the SDSMA Annual Meeting, and a November meeting.

My sincere appreciation goes to Drs. Heinemann and Dietrich, as well as all the members of the task force who helped guide us to the present changes. Our association’s work, however, has just begun. We now need to act on the principles outlined above to make this form of governance efficient. Our members on the Policy Council, as well as the Board of Directors, need to be involved, engaged and receptive. In addition, we need to hear from all our constituents about issues that are important to them. Only then can we truly enjoy the fruits of a healthy organization. To quote Albert Einstein: “Life is like a bicycle. You have to keep moving forward so as not to lose your balance.”

REFERENCES

Take the next step to financial freedom.
Update on the New Medical School Clerkships

By Mark Beard, MD, MHA; Paul Bunger, PhD; and Janet Lindemann, MD, MBA

Two years ago, when starting a new curriculum across the four years of medical school, the University of South Dakota Sanford School of Medicine (SSOM) adopted the Longitudinal Integrated Clerkship model for its clinical training year. What? Our third-year medical students are no longer doing block clerkships? This is the question asked of schools like ours that have replaced our block clerkships with longitudinal integrated clerkships. A longitudinal integrated clerkship (LIC) is where students: 1) participate in the comprehensive care of patients over time; 2) develop continuous learning relationships with faculty; and 3) accomplish core clinical clerkships across multiple disciplines simultaneously. Since making this change, faculty and campus leaders have worked hard to make the LIC model work. And while the road to this point has not been without its bumps, the school and faculty alike are beginning to see glimpses of what the future may hold in regard to the expected successes of the LIC.

Our initial results are consistent with publications showing the following outcomes in longitudinal integrated clerkships:1,2

Students in LICs perceive better clinical learning opportunities and access to patients, and are more likely to report longitudinal exposure to disease than students in traditional clerkships. Our students at SSOM are logging significantly more multiple visits with patients and learning more about the course of disease from their patient’s experience. They also follow “Panel Patients,” seeing them three or four times in various clinics through the LIC. These encounters provide students an opportunity to see medical foundation concepts across multiple settings, thus providing an opportunity to layer learning within their clinical training.3

Continuity with patients promotes patient-centered attitudes and prevents the erosion of idealism that occurs among traditional clerkship students. Students function in more of a doctor-like role. Initial feedback indicates students have retained the empathy they entered medical school with during the LIC. Toward the end of their LIC year, students write a professionalism paper about events they observed and many of these experiences support the caring and compassionate service students and faculty provide to their patients.

LIC students have continuity with supervising faculty and are more likely to report receiving feedback and mentoring than traditional students. SSOM physician coordinators who monitor students at monthly meetings report knowing LIC students better than they did in the previous block clerkships. Another tangible result that benefits students is the expanded narrative evaluations submitted by faculty. This has led to additional meaningful comments for inclusion in the students’ Medical Student Performance Evaluation provided to prospective residency program directors. Comments now go beyond “did a good job in the rotation.” Instead, there are more statements like “this student comes prepared to the hospital or clinic by reading up on their case before the visit,” or “this student demonstrates advanced technical and surgical skills – more like those of a resident.”

LIC students’ academic performance on written and clinical skills examinations is equivalent to or slightly better than the performance of students in a traditional curriculum. The clinical knowledge and clinical skills board exams (Step 2 CK and Step 2 CS) are the important parts of the USMLE licensing examination that test student learning in their medical school clinical programs. Scores for our two recent classes, who were the first to complete the new curriculum, are showing encouraging trends. Across the nation, students’ scores typically increase between the Step 1 basic science exam and the Step 2 exam, and we are seeing our students’ scores similarly increase. Furthermore, the new curriculum schedule allows our students to take these exams five months earlier than the prior schedule, positioning them to better compete for outstanding residency positions.

None of this would be possible without the commitment of medical school faculty physicians across the state of South Dakota. We are truly grateful to all of you. As expressed above, we are beginning to catch glimpses of what the future will hold and it does look promising for students and faculty alike.

REFERENCES


About the Authors:
Mark Beard, MD, MHA, Assistant Dean, Medical Student Education and Director of the Longitudinal Integrated Clerkship at the University of South Dakota Sanford School of Medicine.
Paul Bunger, PhD, Dean of Medical Student Affairs at the University of South Dakota Sanford School of Medicine.
Janet Lindemann, MD, MBA, Dean, Medical Student Education at the University of South Dakota Sanford School of Medicine.

November 2015

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Renal Cell Carcinoma Metastases to Thyroid and Pancreas: A Rare Occurrence

By Kalyan Chakravarthy Potu, MD; Brandy Pownell, MD; Hemalatha Devi Ananthaneni, MD; and Vishal Bhatia, MD

Abstract

Objective: To report on a case of late metastases of clear cell renal carcinoma to the thyroid and pancreas.

Methods: A 51-year-old female with a history of nephrectomy 15 years prior for renal cell carcinoma presented with new metastases in the thyroid and pancreas, which were surgically excised.

Results: Pathology noted that both lesions were clear cell carcinomas, and the immunohistochemistry was consistent with metastases from clear cell renal carcinoma.

Conclusion: 1) Renal cell carcinoma can present late metastases to unusual organs like the thyroid and pancreas. 2) A prior history of renal cell carcinoma should raise suspicions of metastases when evaluating a thyroid or pancreatic mass. 3) An ultrasound-guided fine needle aspiration biopsy of the thyroid may not be diagnostic. 4) The treatment of choice is surgical resection.

Introduction

Renal cell carcinoma (RCC) accounts for 2 to 3 percent of all cancers in adults. The clear cell variant accounts for 70 to 80 percent of renal cell carcinoma cases. Several molecular pathways (namely, the hypoxia-induced pathway, the mTOR pathway, the ERK pathway, and the ubiquitin proteasome pathway) are involved in RCC tumorigenesis and progression. These pathways serve as the source for novel treatment strategies based on the design of small molecule inhibitors directed against their targets.

Renal cell carcinoma rarely presents late metastases to unusual sites like the thyroid and pancreas. In this case, we describe a patient with renal cell carcinoma metastases to the thyroid and pancreas 15 years after unilateral nephrectomy for renal cell carcinoma. According to a case series of 36 patients, metastases to the thyroid developed in 1 percent of patients with renal cell carcinoma. In a large published series, metastasis from primary renal cell carcinoma to the pancreas comprised 0.25 percent of all resected pancreatic specimens. In one case series of eight patients with renal cell carcinoma metastases to the thyroid, the metastases occurred after a median interval of 12 years after nephrectomy. On the other hand, the average time for pancreatic metastasis from renal cell carcinoma to present is 9.2 years after the initial nephrectomy.

Surgery is recommended for the treatment of solitary metastases of renal cell carcinoma to the thyroid. Renal cell carcinoma is more commonly associated with solitary metastasis to the pancreas, therefore making it more amenable to surgery.

Case Report

The patient is a 51-year-old female with a past medical history of renal cell carcinoma status post left nephrectomy 15 years prior. She has a recent history of metastatic renal cell carcinoma to the pancreas post-pancreatectomy two years ago. The patient has no known family history of renal cell carcinoma.

Two years ago, she presented for un-resolving left-sided abdominal pain. Subsequently, CT imaging of the abdomen/pelvis showed eight hyper-enhancing lesions in the head, body, and tail of the pancreas. The patient was referred to surgery for evaluation for a pancreatectomy. She was then taken to the operating room for a
pancreatectomy. The pathology from the pancreas showed metastatic clear cell renal cell carcinoma forming multiple nodules up to 0.9 cm in the head, body, and tail of the pancreas.

A perioperative CT chest scan with contrast identified a hypo-dense lesion in the right thyroid lobe. A follow-up neck ultrasound revealed a right thyroid nodule measuring around 3 cm, complex and vascular. A fine needle aspiration biopsy of the right lobe of the thyroid was negative for malignancy. Thyroid function tests (TSH, free T4) were within normal limits.

A follow-up neck ultrasound done six months later noted a stable right thyroid nodule. A follow-up neck ultrasound after one year revealed an enlarged right thyroid nodule now replacing much of the right lobe of the thyroid and measuring approximately 4.5 x 3.2 x 2.5 cm. The patient also complained of pain in the right neck and difficulty swallowing. Thyroid function tests (TSH, free T4) were within normal limits.

A fine needle aspiration biopsy of the thyroid was obtained, given rapid enlargement of the nodule now replacing most of the right lobe of the thyroid. Though the FNAC resulted negative, the pretest probability of malignancy was high, given recent renal cell carcinoma metastases to the pancreas. The patient was referred to surgery for evaluation for a right hemithyroidectomy. Restaging CT scans of the chest, abdomen, and pelvis prior to the surgery did not show any evidence of metastasis. The patient was taken to surgery and underwent a right thyroid lobectomy and isthmusectomy. Much to the doctors’ surprise, there was evidence of un-encapsulated clear cell malignancy. Therefore, a total thyroidectomy was performed.

A histopathologic analysis of postoperative pancreatic and thyroid tissues revealed clear cell renal carcinoma as detailed in Figure 1.

**Conclusion**
Renal cell carcinoma can present late metastases to...
unusual organs like the thyroid and pancreas. We described a patient with renal cell carcinoma metastases to the thyroid and pancreas 15 years after unilateral nephrectomy for renal cell carcinoma. A prior history of renal cell carcinoma should raise suspicions of metastases when evaluating a thyroid or pancreatic mass. An ultrasound-guided fine needle aspiration biopsy of the thyroid may not be diagnostic. The treatment of choice is surgical resection.

Figure 2. H&E (A) and confirmatory immune stains showing strong expression of RCC (B) and CD10 (C) and negative synaptophysin (D) at 40x. Microscopic examination of both the pancreatic and thyroid malignancies reveals well-circumscribed nodules of clear epithelial cells, with distinct cell boundaries and a net-like array of delicate capillaries. The nodular appearance varies, with some hinting at neuroendocrine differentiation. Because neuroendocrine tumors are well known to have the potential for clear cell differentiation, immunohistochemical stains were utilized to aid in the classification of the pancreatic tumor. CD10, RCC, CD56, and synaptophysin were performed on paraffin-embedded tissue. RCC (or renal cell carcinoma marker) is both sensitive and specific in renal cell carcinoma. RCC marker is positive for 93 percent of primary renal cell carcinomas and 67 to 83 percent positive in metastatic disease. Eighty-five percent of clear cell carcinomas have detectable surface membrane staining for RCC, and 94 percent are positive for CD10. Both RCC and CD10 showed strong surface membrane-staining in the pancreatic lesion. CD56 and synaptophysin are neuroendocrine markers. Interestingly, the tumor cells displayed focal areas of membrane-staining of CD56. However, the synaptophysin stain was negative, which is consistent with metastatic clear cell renal cell carcinoma.

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.

About the Authors:
Kalyan Chakravarthy Potu, MD, Resident, Department of Internal Medicine, University of South Dakota Sanford School of Medicine.
Brandy Powell, MD, Resident, Department of Pathology, University of South Dakota Sanford School of Medicine.
Hemalatha Devi Ananthaneni, MD, Associate Professor, Department of Physiology, Siddhartha Medical College, Andhra Pradesh, India.
Vishal Bhatia, MD, Associate Professor of Medicine, Division of Endocrinology, University of South Dakota Sanford School of Medicine; Sanford Diabetes & Thyroid Clinic, Sioux Falls.
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Introduction

Most practicing physicians have long forgotten the scourge of syphilis. Unfortunately, “the great imitator” has been on the rise since 2001 with an estimated 55,000 new cases in the U.S. in 2014. South Dakota is not immune to this resurgence which prompted the South Dakota Department of Health (SDDOH) to encourage increased practice awareness, prevention and early treatment strategies. In 2014, the state had 46 cases (June 2014) with 65 percent being primary or secondary syphilis and most contracted through heterosexual transmission. The most worrisome news in South Dakota was the reports of sporadic cases of congenital syphilis in infants born to untreated mothers. Misdiagnosing or failing to treat this spirochete infection has extensive consequences, especially in pregnancy. This case presentation reminds the reader that congenital syphilis is still present today and provides guidelines for diagnosis, treatment and prevention of this devastating disease.

Syphilis, caused by the spirochete Treponema pallidum, is typically a sexually transmitted infection that causes a wide array of clinical manifestations in multiple stages (Table 1). Syphilis can be readily treated if detected in the early stages (first year after exposure). However, infection is not always recognized and may progress to late stages causing irreversible end organ damage. Acute infection is difficult to diagnose because the spirochete cannot be cultured or stained by typical methods. Syphilis is especially devastating during pregnancy. Indeed 76 percent of mothers with untreated syphilis during pregnancy have adverse outcomes including spontaneous abortion, prematurity, low birth weight, stillbirth or neonatal death. A pregnant woman may be infected without knowledge and transmit the infection to her baby. Furthermore, surviving infants with congenital syphilis have serious long-term sequelae. Fetal transmission is usually trans-placental from maternal spirocheteremia, but it may also occur during birth by contact with infected lesions. The risk of transmission is dependent on the stage and timing of maternal disease and may occur as early as nine to 10 weeks of gestation (Table 1). Early syphilis, including primary, secondary and early-latent disease, occurs in the first year after exposure and is infectious even when clinical symptoms are not present. Late syphilis, including late-latent and tertiary syphilis, occurs more than one year after primary exposure and although late-latent syphilis is typically not transmitted to partners, it may be transmitted to the developing baby if untreated in the first four years after exposure. For these reasons, universal screening for syphilis at multiple times during pregnancy (first prenatal visit, 28 weeks gestation and close to delivery) is strongly advocated in areas of high prevalence, including South Dakota. Women who have stillbirths after 20 weeks gestation should also be re-screened.

The rapid plasma regain test (RPR) is the screening test used during pregnancy and when results are positive one should evaluate the titer (Table 2). The RPR titer is used to ensure adequate treatment which is confirmed by a decrease in RPR titer four-fold (1:16 to 1:4). When the RPR results an elevated titer, confirmatory testing should
Table 1. Clinical Course of Syphilis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Symptoms</th>
<th>Timing</th>
<th>Transmission</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Painless chancre</td>
<td>1-12 weeks after exposure</td>
<td>High</td>
<td>Disappears in 1-3 weeks</td>
</tr>
<tr>
<td>Secondary</td>
<td>Dermatologic: maculopapular rash on palms and soles, condyloma lata</td>
<td>2-8 weeks after chancre</td>
<td>High</td>
<td>Resolves within a few weeks</td>
</tr>
<tr>
<td></td>
<td>(intertrigenous white lesions), mucous patches</td>
<td>disappears</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>General: fever, headache, pharyngitis/lymphadenopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Early neurosyphilis: meningitis, cranial nerve deficit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early latent</td>
<td>Asymptomatic with reactive serology</td>
<td>&lt;1 year after exposure</td>
<td>High</td>
<td>1 year after exposure</td>
</tr>
<tr>
<td>Late latent</td>
<td>Asymptomatic with reactive serology</td>
<td>&gt; 1 year after exposure or</td>
<td>Unlikely except to fetus (80% transmission up to 4 years after exposure)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>unknown</td>
<td></td>
<td>Variable, years after exposure</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Endarteritis</td>
<td>Clinical symptoms after &gt;1 year latency</td>
<td>Unlikely</td>
<td>Variable, years after exposure</td>
</tr>
<tr>
<td></td>
<td>Neurologic: general paresis, dementia, tabes dorsalis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiovascular: aortitis, myocardial ischemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gummatous: destructive lesions of skin, soft tissue and bone</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table developed based on information from Cohen, et al.6

Table 2. Common Assays for Syphilis Detection

<table>
<thead>
<tr>
<th>Non-treponemal Assays</th>
<th>Treponemal Assays</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening, monitoring disease activity</td>
<td>Confirmation, detection specific for T. pallidum</td>
</tr>
<tr>
<td>RPR, VDRL</td>
<td>FTA-ABS, TP-PA</td>
</tr>
</tbody>
</table>

Rapid Plasma Reagin, RPR; Venereal Disease Research Laboratory, VDRL; Fluorescent Treponemal Antibody Absorption, FTA-ABS; T. pallidum particle agglutinin, TP-PA.

Table 3. Clinical Findings in Congenital Syphilis

<table>
<thead>
<tr>
<th>Systemic</th>
<th>Mucocutaneous</th>
<th>Hematologic</th>
<th>Musculoskeletal</th>
<th>Neurologic</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Condyloma lata*</td>
<td>Anemia**</td>
<td>Periostitis</td>
<td>CSF abnormalities</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Maculopapular rash</td>
<td>Thrombocytopenia</td>
<td>Wegner sign***</td>
<td>Pneumonitis</td>
<td></td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Vesicular rash</td>
<td>Leukopenia</td>
<td></td>
<td></td>
<td>Rhinitis</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Jaundice</td>
<td>Leukocytosis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
be done by sending the fluorescent treponemal antibody absorption (FTA-ABS). The FTA-ABS will remain positive for life with infection.

**Clinical Manifestations of Congenital Syphilis**

Although most infants born to mothers with syphilis are asymptomatic at birth, fatal cases are reported especially in untreated mothers. Symptoms may be present at birth or in the first two years of life and include: dermatologic findings (68 percent), multifocal periostitis/osteochondritis (78 percent), hepatosplenomegaly (71 percent), Coomb's negative hemolytic anemia (58 percent), fever (42 percent), thrombocytopenia (40 percent), meningitis (23 percent), proteinuria/hematuria (16 percent), rhinitis (snuffles) (14 percent) and lymphadenopathy (14 percent) (Table 3). Vesiculobullous lesions may be present at birth or in the first weeks of life; they desquamate and crust over in one to three weeks. Condylomata lata and/or mucous patches (shallow ulcers with grey exudate) may be present on genitalia, mouth or other mucous membranes. Profuse rhinitis or “snuffles” does not develop until after the first week of life. Any discharge that comes from the nose or skin lesions is teeming with spirochetes, so precautions should be carefully observed. Most cases of meningitis are asymptomatic, highlighting the need for evaluation in all at-risk infants. Bony lesions often include demineralization of the tibial metaphysis (“Wimberger sign” on X-ray) and are painful even potentially resulting in “pseudoparalysis of Parrot” (lack of extremity movement due to bone pain). These lesions typically resolve by six months of life, but vascular insult to the developing bone may result in late manifestations including “saddle nose deformity,” frontal bossing, “saber shins” (tibial bowing), scaphoid scapula, “Clutton’s joints” (painless effusions) and “Hutchinson teeth.”

**Case**

The patient is a 31\(^\text{st}\) week gestation male born via emergent cesarean section to a 27-year-old G8P7 at an outside hospital due to fetal distress and placental abruption. The pregnancy was complicated by late prenatal care at 28 weeks gestation, polyhydramnios, cigarette use during pregnancy, and positive maternal RPR with a titer of 1:32 with unspecified penicillin allergy. No further work up of the positive RPR had been initiated or therapy initiated at the time of delivery.

The patient's birth weight was 1.7 kg (50th percentile), length 40 cm (20th percentile), and occipito-frontal circumference 28.6 cm (40th percentile). Additional maternal labs were group B streptococcus unknown, HIV negative, hepatitis B surface antigen negative, blood type B positive, antibody screen negative. The infant's blood type was O positive, antibody negative.

The infant required resuscitation at delivery due to placental abruption and avulsion of the umbilical cord from the placenta at the time of delivery. He received bag-mask ventilation followed by nasal cannula immediately after birth. His Apgar scores were 2, 6 and 7 at 1, 5 and 10 minutes, respectively. During the initial assessment by the neonatal intensive care unit (NICU) transport team, he began to develop white papular lesions with an erythematous base on the soles of the feet and palms of the hands (Figure 1). He was also noted to have significant hepatomegaly and splenomegaly on physical exam (Figure 2).

During transport back to the NICU, he developed worsening respiratory distress requiring continuous positive airway pressure. Upon arrival in the NICU, he was intubated and given a dose of surfactant as his radiograph findings were most consistent with respiratory distress syndrome. He developed a pulmonary hemorrhage two hours following surfactant administration and

![Figure 1. Lesions on Soles of Feet in Congenital Syphilis](image-url)
gastrointestinal bleeding in the first 12 hours of life. He also developed petechiae on his chest and purpuric lesions on his lower extremities.

Laboratory evaluation revealed a hematocrit of 29 percent (nl 30-48 percent), platelet count of 5,000 (nl 140,000-400,000), and absolute neutrophil count of 817 (nl >1500). He required multiple packed red blood cell and platelet transfusions throughout his course. A cranial ultrasound was negative for intraventricular or intraparenchymal hemorrhage. Bone radiographs revealed lower extremity long bones with metaphyseal irregularity in a “sawtooth” pattern and slight cupping (Figure 3).

The infant’s mother failed a glucola screening test in pregnancy, but did not follow-up to obtain a three-hour glucose tolerance test. The baby had multiple episodes of severe hypoglycemia with whole blood glucose values less than 30 mg/dl requiring dextrose boluses and excessive glucose infusion rates in the first week of life. He also sustained acute renal failure with hematuria on day of life one through three.

His serum RPR resulted positive with a titer of 1:16. The confirmatory FTA-ABS was positive in the serum and CSF-Venereal Disease Research Laboratory (VDRL) was positive (titer 1:2). Additional CSF studies revealed red blood cells (RBC) of 1095 and white blood cells of 28 (nl 0-20) with protein 293 mg/dl (nl 12-60) and glucose 43 mg/dl (nl 50-80). The elevated RBCs in the CSF are attributed to a slightly traumatic tap. He also underwent a thorough evaluation for herpes simplex virus (HSV) and human immunodeficiency virus (HIV) due to the positive syphilis status. Both work ups for HSV and HIV were negative. The placenta revealed ascending infection but the Warthin-Starry stain for spirochetes was negative.

He was weaned from the ventilator on day of life five but showed evidence of chronic lung disease with a persisting need for supplemental oxygen. He was treated with intravenous penicillin G for 14 days. An ophthalmologic exam was negative for chorioretinitis. He passed bilateral auditory brainstem evoked response test. At the time of this writing, he is stable in the NICU with developmental delay in nipple feeding at 36-weeks postmenstrual age. He continues to have hepatomegaly with elevated liver function tests. He will be discharged home, likely on supplemental oxygen, with follow-up in the pediatric infectious disease clinic, neurodevelopmental clinic, and formal audiology testing.
Evaluation of Infant for Congenital Syphilis

The ability to diagnose congenital syphilis is complicated by the transfer of maternal IgG antibodies to the fetus, making interpretation of serologic tests more difficult. All serologic testing should be done on infant serum as umbilical cord blood can be contaminated with maternal blood yielding a false positive result. An infant RPR/VDRL titer which is fourfold or higher than a similar maternal titer, suggests infection. Although our infant had a lower RPR titer than maternal titer (1:16 vs. 1:32), which suggests against infection, his serum treponemal test (FTA-ABS) was positive and is the confirmatory test in congenital syphilis.

The diagnosis and therapy are dependent on: 1) identification of maternal syphilis; 2) adequacy of maternal therapy; 3) maternal response to therapy; 4) comparison of maternal and infant non-treponemal serologic titers using the same test (RPR, VDRL) (mother should also have more specific treponemal testing such as FTA-ABS, FTA-PA); and 5) physical exam, laboratory, and radiologic findings compatible with syphilis.

The most important evaluations in infants suspected of congenital syphilis include complete blood count (CBC) with differential and platelet count, liver function tests, CSF for VDRL, protein, and cell count (elevated cell count and protein with positive VDRL suggest neurosyphilis) and chest and long bone radiographs. Neuroimaging, auditory brain stem response (ABR), and an ophthalmologic exam may also be indicated in the first month of life.

The following scenarios help depict the evaluation needed and treatment or non-treatment options:

Scenario (1): Highly probable disease:
- Abnormal exam; b) serum quantitative non-treponemal serologic titer fourfold higher than mother’s; c) positive darkfield test of body fluid.

Evaluation:
- CSF for VDRL, protein, cell count
- CBC with differential and platelets
- Long bone and chest radiographs
- Cranial ultrasound
- Liver function tests
- Ophthalmologic exam
- Auditory brainstem response test
- Treatment: 10-day course of penicillin

Scenario (2): Highly probable disease:
Normal physical exam and non-treponemal serologic titer the same or less than fourfold maternal titer:

a) Mother not tested or inadequately treated; b) mother treated with erythromycin or other non-penicillin drug; c) mother received treatment less than four weeks prior to delivery.

Evaluation:
- CSF for VDRL, protein, cell count
- CBC with differential and platelets
- Long bone radiographs
- Treatment: 10-day course of penicillin

Scenario (3): Unlikely disease:
Infant with normal physical exam and serum quantitative non-treponemal serologic titer the same or less than fourfold maternal titer:

Mother’s treatment was appropriate during pregnancy greater than four weeks prior to delivery.

Evaluation: None
Treatment: None

Scenario (4): Unlikely disease:
Infant with normal physical exam with serum quantitative non-treponemal serologic titer the same or less than fourfold maternal titer:

(a) Mother’s treatment adequate before pregnancy (b) mother’s non-treponemal serologic titer remains low and stable before and during pregnancy and at delivery (VDRL less than 1:2, RPR less than 1:4)

Evaluation: None
Treatment: None

Because T. pallidum cannot be cultured and is difficult to stain, diagnosis is dependent upon serologic testing. Non-treponemal tests include VDRL and RPR assays that detect antibodies to a non-specific cardiolipin-cholesterol-lecithin reagin antigen produced by the host in response to infection. This test has a rapid turn-around time, but may be falsely negative with newly acquired syphilis that has not resulted in an immune response.

Non-treponemal tests are 86 percent sensitive in detecting primary syphilis and 100 percent sensitive in secondary syphilis. These tests, primarily the titers, should be used to screen and monitor treatment effectiveness because they correlate to disease activity. Unfortunately, because they
are non-specific they may be associated with false-positive screens especially in patients with other infections (endocarditis, rickettsia), autoimmune disease, chronic liver disease, intravenous drug use or even recent vaccination. In fact, the state of pregnancy alone can result in a positive RPR. Thus, initial diagnosis should be confirmed with more specific treponemal tests that detect antigens specific to T. pallidum. These include FTA-ABS, TP-PA and T. pallidum hemagglutination assays. Confirmatory testing can be sent to the South Dakota state health lab which will perform the testing on a priority basis.

Treatment
Treatment for infants who are highly suspected of having congenital syphilis require 10 days of therapy with parenteral penicillin G. Despite no recent published data available to compare various penicillin treatment regimen for neonates, case reports have identified treatment failures when benzathine penicillin has been used. Despite no recent published data available to compare various penicillin treatment regimen for neonates, case reports have identified treatment failures when benzathine penicillin has been used.7

Infants with clinical, laboratory, or radiologic evidence of congenital syphilis (Table 3), are presumed to have central nervous system involvement. Obtaining cerebrospinal fluid studies does not alter the recommended treatment, but are critical in determining the need for future monitoring and assessing response to therapy.

For asymptomatic infants whose mothers were adequately treated during pregnancy but follow up cannot be confirmed, benzathine penicillin 50,000 units/kg given intramuscular in a single dose is recommended by experts. The single-dose regime can be used only if neurosyphilis can be excluded.7

Furthermore, any infant at risk for congenital syphilis should undergo a full evaluation for HIV infection. International adoptees must undergo syphilis testing regardless of background.8

Follow-up
Infants with congenital syphilis should have repeat nontreponemal tests 3, 6, and 12 months after treatment. Nontreponemal immunoglobulin G antibodies of maternal origin should clear by 6 months of age if the infant did not have infection but treponemal antibodies of maternal origin may persist for 12 to 15 months with reactivity beyond 18 months indicative of congenital infection. As such, the infant with congenital syphilis should have RPR/VDRL titers decline by 3 months of age and become nonreactive by 6 months of age if treatment was successful. Treatment failure is indicated by RPR/VDRL titers which do not decline or increase after 6 to 12 months of age. In this case, the infant should undergo a lumbar puncture to obtain CSF for VDRL and be treated with intravenous penicillin for 10 days, even if treated previously.

Infants with congenital neurosyphilis should have CSF evaluations every six months until indices have normalized for at least three years.8

Infants with congenital syphilis should undergo a thorough developmental assessment at age 2. Annual hearing evaluations are recommended as hearing loss can occur as late as 8 to 10 years of age. Likewise, ophthalmologic abnormalities, such as corneal scarring and glaucoma, can appear after age 5 so annual eye exams are recommended.9

Outcome
Many cases of congenital syphilis result in stillbirths. Of those delivered, a case fatality rate of 6 to 8 percent is reported.9 A majority of the fatal cases are associated with minimal or lack of prenatal care. Although early treatment prevents most of the sequelae of congenital syphilis, anterior tibial bowing and interstitial keratitis may develop despite adequate treatment. Indeed, syphilis infection may persist for life and a history of infection or treatment provides little protection against later infection.10

Conclusion
South Dakota has seen a marked increase in cases of syphilis in the last year. According to the SDDOH, the state has not documented this many cases of syphilis in over 50 years. A concentrated effort to diagnose and treat patients with syphilis, as well as their partners, may prevent many cases of adult and congenital syphilis. It is critical for the physicians of South Dakota to screen pregnant women for syphilis multiple times during pregnancy by obtaining an RPR. If the RPR is positive, treat the woman while awaiting confirmatory testing with the FTA-ABS.

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.

About the Authors:
Susanne Reuter, MD, Sanford Children’s Specialty Clinic; University of South Dakota Sanford School of Medicine.
Michelle Baack, MD, Sanford Children’s Specialty Clinic; University of South Dakota Sanford School of Medicine; Children’s Health Research Center, Sanford Research; Sioux Falls.
David Munson, MD, Sanford Children’s Specialty Clinic; University of South Dakota Sanford School of Medicine.
On average, smokers with serious mental illness will die 25 years sooner than people in the general public.

You can help us change that.

- In South Dakota, 40.8% of persons with mental illness smoke, compared to 23.2% of those with no mental illness.

- About one-fifth of QuitLine participants report having a mental health condition.

- From 2011 to 2014, the SD QuitLine 7-month quit rate for participants who self-report having a mental health condition was 37.0%.

- 30% of SD QuitLine participants with a mental health condition heard about the QuitLine from a healthcare provider.

And if it can add years to patients’ lives, your constant referral and encouragement are well worth the extra effort.

Remember...
Ask. Advise. Refer.
<table>
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<th>Antibiotic</th>
<th>Staphylococcus aureus</th>
<th>Methicillin-susceptible S. aureus (MSSA)</th>
<th>Methicillin-resistant S. aureus (MRSA)</th>
<th>Group A Streptococcus</th>
<th>Group B Streptococcus</th>
<th>Streptococcus pneumoniae</th>
<th>Enterococcus faecalis</th>
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*Urine isolates only
†From laboratories which did not separate MRSA and MSSA. Data included in this column is not included in the MSSA or MRSA columns.
‡Only reported oxacillin and penicillin for Staph. aureus based on CLSI guidelines

CLSI recommends reporting data only if 30 or more isolates analyzed, less than 30 isolates are reported for completeness

July 2015 (ZI)
# Antibiogram of Selected Pathogens, South Dakota 2014

## Gram negative organisms

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*Urine isolates only

†Data only from four laboratories.

>5% increase in susceptibility from last year
>5% decrease in susceptibility from last year

North Central Heart, a Division of Avera Heart Hospital, is shaping heart care in the region by providing comprehensive care to patients and their families. With more than 30 years of service in the region, we know hearts.

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- Vascular medicine and surgery
- Electrophysiology – rhythm management
- Cardiac surgery

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A Division of Avera Heart Hospital

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Screening and Treatment of Osteoporosis

By Andrea Seurer, MD; and Mark K. Huntington, MD, PhD

Abstract
Osteoporosis is a disease affecting millions of Americans, especially elderly women, and resulting in significant health care cost, as well as morbidity and mortality. Screening tests are available but patients and primary care physicians alike should consider their utility in the context of individualized patient care. When osteoporosis is diagnosed, all of the available treatments should be considered when choosing the best option for each patient. A systematic review of the evidence for osteoporosis screening and treatment was conducted to assist primary care physicians with caring for patients at risk for osteoporosis.

Introduction
An estimated 12 million Americans are known to have a disease that can dramatically affect their morbidity and mortality as they age. This disease is osteoporosis, defined as low bone mass and deterioration of bone microstructure which can progress to higher susceptibility of fracture as the bone becomes increasingly fragile. As the population of the U.S. continues to age, an increasing number of the patients seen daily in primary care offices will be affected by osteoporosis, and primary care physicians will have the task of caring for these patients. At least half of post-menopausal women will have an osteoporosis-related fracture during their lifetime. As of 2005, the cost to the U.S. health care system for osteoporosis-related fractures reached a staggering $17 billion annually. This is expected to double by the year 2025 as more and more patients are affected by osteoporosis, approaching over 3 million fractures annually with an estimated cost of $25.3 billion each year. There is significant mortality, especially following a hip fracture; almost one-quarter of these patients will die in the first year after the fracture. If patients are able to survive, their morbidity is also significantly affected as more than three-quarters of patients will require placement in long-term care despite being previously ambulatory. Primary prevention can have a significant impact on the incidence of osteoporosis.

What can primary care physicians do to prevent osteoporosis-related fractures? What are the screening options? Is counseling being provided to our patients on screening and using risk-assessment tools to aid the discussion? If low bone mineral density is found, are these patients being treated to reduce their fracture risk? These questions will be addressed in the following pages.

Evidence Selection
The literature was searched via the PubMed database for evidence-based guidelines and recommendations on osteoporosis screening and treatment. Citations for this article were specifically selected from the database based on their utility and accessibility to primary care physicians seeking self-education on osteoporosis.

Screening for Osteoporosis
The U.S. Preventative Services Task Force (USPSTF) recommends screening for osteoporosis in women greater than 65 years of age as a Grade B recommendation. This recommendation is focused on primary prevention, excluding patients who have a history of fracture and therefore require treatment of the fracture as well as secondary prevention of future fractures. At this level of recommendation, the benefit is seen as moderate, if not substantial; therefore, this service should be offered or provided to all eligible patients. Using the strength of
recommendation taxonomy, the recommendation for screening all women over 65 years of age would be strength of recommendation (SOR) grade B.8

Assessment of Risk
Research on osteoporosis screening has created multiple tools for assessing patient’s risk of osteoporosis-related fracture. The USPSTF used the Fracture Risk Assessment (FRAX) tool created by the World Health Organization (WHO) to assess risk in female patients as this tool uses easily obtainable patient data from a routine clinic visit.1 By combining age, body mass index, tobacco use, alcohol use and family history of fracture, FRAX can identify a patient’s risk of osteoporosis-related fracture in the following 10 years (SOR C). The results of a previous DXA scan can be added to the tool to better assess risk (SOR C). The FRAX has been validated as an effective tool for assessing osteoporosis risk and is advised by the WHO to be utilized in primary care assessment of patients’ risk. The USPSTF has used the FRAX tool to produce guidelines regarding female patients below age 65, specifically those between the ages of 50 and 64. The FRAX could also be used prior to obtaining a DXA to aid the physician’s discussion with the patient greater than 65 years of age. If the FRAX identifies the patient as high risk, perhaps a DXA scan is not needed to determine if the patient needs treatment for osteoporosis. If the FRAX identifies the patient as low risk, the physician-patient discussion could shift to why a DXA scan may not be indicated.

Screening Tests
There are a few options for screening tests to be used to assess for osteoporosis. Although the USPSTF recommendation statements come from DXA of the hip and lumbar spine results only, quantitative ultrasonography of the calcaneus, quantitative computer tomography radiography and biochemical markers have also been studied.3 The USPSTF found sufficient evidence that screening tests for bone density, with dual-energy X-ray absorptiometry or qualitative ultrasonography of the calcaneus, can predict short-term risk for osteoporosis-related fractures.1 Screening should begin at 65 years of age (SOR B), but an upper age limit for screening has not been determined.3 The decision of when to discontinue osteoporosis screening should be a mutual decision between the physician and patient and should account for the patient’s other co-morbidities and life expectancy.

The DXA is considered a proven method of measuring bone mineral density (BMD) (SOR B).1,3 The DXA is non-invasive, takes less than 15 minutes to complete and exposes patients to less than one-tenth of the radiation of a standard chest X-ray.1 After obtaining a DXA scan, the results are reported as a “t-score.” A t-score of greater than or equal to -1 is considered normal BMD. Osteopenia is diagnosed at a t-score of -2.5 to -1. Osteoporosis is diagnosed when the t-score is reported as less than or equal to -2.5. DXA scans are limited by their inability to adequately identify bone architecture; therefore, patients with osteoarthritis, previous fracture, osteophytes and/or vascular calcification may not be accurately assessed. A 2004 study found that primary care physicians in the U.S. have high variability in ordering dual X-ray absorptiometry (DXA) screening for osteoporosis ranging from 38 to 62 percent.3

The quantitative ultrasonography of the calcaneus (QUS) has been studied as a new screening test to replace the DXA scan because it is a portable screening tool, it does not expose patients to radiation and it is inexpensive.1 Several studies have compared QUS to DXA results and noted the sensitivity of QUS is 21 vs. 45 percent with specificity of 88 vs. 96 percent; therefore, QUS currently has limited application for osteoporosis screening compared to the DXA. If QUS can be used in the future, a tool to convert QUS results to a useful scale like the t-score produced by the DXA scan will need to be created.4

The quantitative computer tomography (QCT) has been proposed as a screening method as well. The QCT has the benefit of being able to assess bone architecture, a limitation of DXA, and therefore is less affected by degenerative disease.2,3 There are concerns, however, as the QCT is more expensive and has more radiation exposure than the DXA scan. Additional research is required to determine if QCT results can be validated when compared to DXA t-scores.

Researchers have begun pursuing serum and urine markers of bone turnover for use in osteoporosis. The serum and urine markers indicate when bone turnover is occurring, but they cannot estimate bone mass or fracture risk.1 The markers are not meant for large population testing of bone density, but could be useful for monitoring the response to osteoporosis treatment.

Screening Interval
Researchers have yet to determine the optimal screening interval for osteoporosis. If a patient’s original osteoporosis screening was normal, the potential benefit of repeat
screening is to improve the prediction of fracture risk before it occurs. A minimum of two years between screening is required to reliably measure a change in BMD (SOR C).\textsuperscript{3} A study of more than 4,000 patients reported that repeat screening beyond the initial two years, and a change in BMD on repeat screening, was not any more predictive of fracture risk than the original BMD measurement.\textsuperscript{3} Further research is needed to determine the potential benefit and outcome of repeated DXA scanning to assess osteoporosis risk.

Benefits of Screening
Osteoporosis is seen as a potential preventable condition if screening is performed. Although there are no randomized controlled studies of direct fracture outcome after osteoporosis screening, there is evidence that after initiation of treatment for osteoporosis, bone mineral density improves.\textsuperscript{1} Screening for bone mineral density will provide patients and providers with the necessary knowledge about patient's health to seek treatment for osteoporosis. Abundant research has supported the use of osteoporosis treatment in preventing fractures, especially in women. When treatment for osteoporosis is initiated, morbidity and mortality from osteoporosis-related fractures can decline.

Harms of Screening
As with all screening tests, a potential harm to patients is the anxiety that follows after the screening finds risk of future morbidity and mortality.\textsuperscript{1} Osteoporosis screening can increase patients’ concerns regarding their vulnerability to fracture. Screening also has a risk of false-negative results, which causes patients who should be treated for osteoporosis risk to be advised otherwise. On the contrary, false-positive results can result in patients who do not have osteoporosis risk to be begin treatment and therefore, be at risk for treatment side effects. The screening tests pose their own risk as repeated DXA scans have a risk of radiation exposure. Finally, the potential harms of the treatment options to the patient after osteoporosis is diagnosed will be discussed later.

Cost Effectiveness
There are financial considerations of using DXA more routinely in primary care for osteoporosis screening. The cost of purchasing the DXA machine can vary from $25,000 to $85,000.\textsuperscript{1,4} The American Journal of Preventive Medicine has found evidence that BMD screening is cost-effective for women over age 65.\textsuperscript{7} Cost saving was also documented for women from 85 to 95 years of age when assessed with a screen-and-treat strategy. The Agency of Healthcare Research and Quality has found that universal BMD and subsequent alendronate therapy, assuming medication cost of less than $500 per year, is highly cost effective beginning at 65 years of age.\textsuperscript{5} Medicare does cover biennial BMD screening for all patients at risk for osteoporosis, even less than 65 years of age if risks are identified.\textsuperscript{5}

Treatment
The American College of Preventive Medicine has set forth guidelines for prevention as well as treatment of osteoporosis with lifestyle measures. Adequate calcium (total 1,200 mg/day) and vitamin D (800 IU daily) intake is necessary for bone health (SOR C).\textsuperscript{7} In addition, patients also need to have an exercise regimen of at least 30 minutes three times per week (SOR C). Both non-weight bearing high-force exercise and mixed exercise programs have been found to be beneficial for femoral neck as well as lumbar spine bone mineral density. Patients should also be educated on the importance of smoking cessation, counseling on fall prevention and avoidance of heavy alcohol use. If possible, medications that can affect bone loss, such as glucocorticoids, should be avoided. Other considerations for certain patients include diet, as celiac disease is a major contributor to bone density loss.

Pharmacologic therapies are recommended for post-menopausal women with osteoporosis diagnosed by history of hip or vertebral fracture, or with diagnosis based on BMD testing with DXA scanning resulting in a t-score less than or equal to -2.5 (SOR B). Patients who are diagnosed as osteopenic based on t-score of -1.0 to -2.5, but are considered high risk, are also candidates for pharmacologic treatment based on National Osteoporosis Foundation recommendations in conjunction with the FRAX guidelines.\textsuperscript{7}

There are no high-quality studies comparing pharmacologic therapies therefore, the choice of therapy should be reached after a shared decision-making discussion between the patient and the physician. The choice of therapy will depend on several factors including efficacy, safety, cost, and convenience, just to name a few. The recommended first line therapy is oral bisphosphonates, typically alendronate or risedronate (SOR C).\textsuperscript{7} Intravenous forms of bisphosphonates are available as zoledronic acid and ibandronate for patients who cannot tolerate the gastrointestinal side effects of the oral
## Summary of evidence about drugs and fracture risk

**Effect on risk and level of evidence**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Vertebral fracture</th>
<th>Hip fracture</th>
<th>Adverse effects</th>
<th>FDA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bisphosphonates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate</td>
<td>↓: strong evidence</td>
<td>↓: strong evidence</td>
<td>Mild upper GI effects: esophageal ulcerations, perforations, and bleeding events</td>
<td>Prevention or treatment</td>
</tr>
<tr>
<td>Etidronate</td>
<td>↓: strong evidence</td>
<td>↔: fair evidence</td>
<td>Mild upper GI effects: esophageal ulcerations, perforations, and bleeding events</td>
<td>Not FDA-approved for prevention and treatment</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>↓: strong evidence</td>
<td>↔: strong evidence</td>
<td>Esophageal ulcerations, perforations, and bleeding events</td>
<td>Prevention or treatment</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>↔: weak evidence</td>
<td>↔: weak evidence</td>
<td>Mild upper GI effects: esophageal ulcerations, perforations, and bleeding events</td>
<td>Not FDA-approved for prevention and treatment</td>
</tr>
<tr>
<td>Risedronate</td>
<td>↓: strong evidence</td>
<td>↓: strong evidence</td>
<td>Esophageal ulcerations, perforations, and bleeding events</td>
<td>Prevention or treatment</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>↓: strong evidence</td>
<td>↓: strong evidence</td>
<td>Muscular and joint pain</td>
<td>Prevention</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>↓: fair evidence</td>
<td>↔: strong evidence</td>
<td>No clinically significant adverse effects</td>
<td>Treatment</td>
</tr>
<tr>
<td><strong>Estrogen</strong></td>
<td>↓: strong evidence</td>
<td>↓: strong evidence</td>
<td>Thromboembolic events; cerebrovascular accident, stroke, and breast cancer (when combined with progestin); gynecological problems (endometrial bleeding); breast abnormalities (pain, tenderness, and fibrocystosis)</td>
<td>Prevention</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>↓: strong evidence</td>
<td>↓: fair evidence</td>
<td>↔: weak evidence</td>
<td>No clinically significant adverse effects</td>
</tr>
<tr>
<td><strong>SERMs: selective estrogen receptor modulators</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td>↓: strong evidence</td>
<td>↔: strong evidence</td>
<td>Pulmonary embolism, thromboembolic events</td>
<td>Prevention or treatment</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>↔: strong evidence</td>
<td>Not studied</td>
<td>Pulmonary embolism</td>
<td>Not FDA-approved for prevention and treatment</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Not studied</td>
<td>Not studied</td>
<td>No clinically significant adverse effects</td>
<td>Not FDA-approved for prevention and treatment</td>
</tr>
<tr>
<td>Calcium &amp; Vitamin D</td>
<td>Modest effect, strong evidence</td>
<td>Modest effect, strong evidence</td>
<td>Modest effect, strong evidence</td>
<td>No clinically significant adverse effects</td>
</tr>
</tbody>
</table>

↓ = decreased, ↔ = no effect

U.S. Food and Drug Administration (FDA); Gastrointestinal (GI)

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Monitoring patients’ response to therapy is very important. Further research has shown that osteonecrosis of the jaw usually only occurs in patients taking higher than normal doses of bisphosphonates. Other options include parathyroid hormone for its stimulation of bone formation and activation of bone remodeling and calcitonin for its anti-resorptive effects.  5

Benefits of Treatment
The most desirable benefit from treatment for osteoporosis is the decreased risk of fracture. Table 1 outlines the risk reduction and level of evidence available for each treatment option utilized for osteoporosis treatment as published by the American College of Preventative Medicine. 3

Harms of Treatment
The harms of osteoporosis treatment are mainly related to their side effects. As outlined above, the side effects of these medications can change patient compliance and, therefore, limit their benefit in treating osteoporosis. The most extensively studied medications are the bisphosphonates. The most common side effects of these medications are gastrointestinal adverse events including esophageal perforations, ulcerations and bleeding. 1,5 The USPSTF states that there is no evidence to demonstrate a definitively increased risk of these side effects when taken as prescribed. The evidence is conflicting regarding the risk of atrial fibrillation while taking bisphosphonates. The most concerning side effect of this class of medications is osteonecrosis of the jaw and other severe musculoskeletal symptoms such as mid-femur fracture. Further research has shown that osteonecrosis of the jaw has only been found in a small number of case reports and usually only in patients taking higher than normal doses of bisphosphonates for cancer related osteoporosis prevention. Other osteoporosis treatment options such as raloxifene and estrogen are noted to have a side effect of risk of thromboembolic events. 1,5

Monitoring of Treatment
Monitoring patients’ response to therapy is very important in determining if there is benefit to the patient from osteoporosis treatment following initiation. Up to one-sixth of women taking alendronate continue to lose bone density. 7 Currently, there is no evidence to explain the optimal approach to monitoring bone mineral density after therapy is begun. Generally, it is recommended that the patient obtain a follow up DXA of the hip and spine after two years on therapy (SOR C). This recommendation is endorsed by the International Society for Clinical Densitometry, the National Osteoporosis Foundation, American Association of Clinical Endocrinologists, and the North American Menopause Society. Future options could include measuring markers of bone turnover, but further research is needed.

Conclusion
Osteoporosis is known to affect millions of Americans, especially females. As such, the patients’ primary care physicians can have a significant impact on diagnosis and treatment of patients with this disease. In years past, osteoporosis was under-recognized as loss of bone mineral density was thought to be a consequence of aging and unavoidable. There is a high burden of this disease in the morbidity and mortality that follows an osteoporosis related fracture. At this time, screening with a DXA scan is our best option for early diagnosis and treatment of osteoporosis. Overall, the harms of treatment are minimal compared to the potential benefit of reduction in osteoporosis-related fractures and associated morbidity and mortality. In the future, better diagnostic tools may be developed for diagnosing osteoporosis. Research can also focus on the optimal duration of treatment to affect a patient’s risk of fracture. Primary care physicians, have the opportunity to discuss the risk of this disease with patients and help the patient determine if screening and treatment of osteoporosis is appropriate for them.

REFERENCES

About the Authors:
Andrea Seurer, MD, Sioux Falls Family Medicine Residency Program; Department of Family Medicine, University of South Dakota Sanford School of Medicine. Mark K. Huntington, MD, PhD, Sioux Falls Family Medicine Residency Program; Department of Family Medicine, University of South Dakota Sanford School of Medicine.
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The Seventh District Medical Society and Alliance wish to thank Dr. Wilson and Rose Asfora for opening up their restaurant, Carnaval Brazilian Grill, to host the district’s annual fall kickoff October 5.

The meal was superb, and the fellowship between students, residents, physicians and spouses made it an enjoyable evening for all.
There are many risk factors for the development of osteoporosis. Some of the key ones include age, low body weight, previous fracture, high risk medication use, and diseases/conditions associated with bone loss. Osteoporosis should be screened for in patients who are women aged 65 and older, post-menopausal women less than 65 or men during menopausal transition if they have a clinical risk factor for osteoporosis, men 70 and older, men less than 70 with risk factors, adults with fragility fractures or a disease/condition associated with bone loss, adults taking medications associated with bone loss.

Duel-energy X-ray absorptiometry (DEXA) is the preferred scan for screening and diagnosis of osteoporosis where typically the scan is performed on the lumbar spine and/or hip. Once diagnosis of osteoporosis has been made, treatment should be begun to reduce the risk of fracture. Treatment can include calcium/vitamin D supplementation, weight-bearing exercise and medications. Possible pharmacologic therapy includes bisphosphonates, selective estrogen receptor modulators, recombinant parathyroid hormone (PTH), and human monoclonal antibody to receptor activator of nuclear factor kappa-B ligand (RANKL).

Introduction

Osteoporosis is a disease that effects millions of men and women throughout the U.S. Patients may never notice that they have it but the consequences of it not being discovered can be financially and physically devastating to their quality of life. Osteoporosis is frequently under diagnosed and an overlooked problem. In 2012, the total direct medical costs of fall injuries for people 65 and older, adjusted for inflation, were $30 billion. By 2020, the annual direct and indirect cost of fall injuries is expected to reach $67.7 billion (in 2012 dollars). Osteoporosis increases a person’s risk of fractures due to both trauma (e.g., falls) and non-trauma (e.g., bumping into things). Among community-dwelling older adults, fall-related injury is one of the 20 most expensive medical conditions. Certain populations are at higher risk to develop osteoporosis and thus need to be more carefully monitored.

What It Is

Osteoporosis, and its milder companion osteopenia, is characterized by decreased bone mass and a change in the microarchitecture of bones which leads to increased fragility. The World Health Organization (WHO) has defined osteopenia and osteoporosis in terms of bone mineral density (BMD). An individual’s bone mineral density is compared to the mean of young adults using standard deviations (SD), as seen below where SD is the variation of a number from the average.

Normal bone mass: BMD within 1 SD of young adult mean
Osteopenia (low bone mass): BMD greater than 1 SD but less than 2.5 SDs below the young adult mean

Osteoporosis: BMD greater than or equal to 2.5 SD below the young adult mean

Severe osteoporosis: BMD greater than 2.5 SD below the young adult mean with the occurrence of 1+ fragility fractures.

Osteoporosis occurs in both men and women but is more common in women. In some countries, including the U.S., the incidence in women is twice that of men. Historically the focus of osteoporosis diagnosis, prevention and treatment has been focused on women but in recent years, attention has shifted to include the assessment and treatment of men.8,9

Symptoms are rarely present in individuals with osteoporosis; thus, it can be considered a silent disease that may not be discovered until a fracture has occurred unless specifically sought in screening. Those symptoms that are rarely present include a decrease in height and back, hip, or neck pain from fractures.

Risk Factors
Osteoporosis risk factors can stem from a variety of areas.10 They include genetic background, weight, hormonal status, diet, smoking status, activity level, medications, diseases and more. Table 1 summarizes some of the various risk factors.11 The more risk factors a patient has, the greater their risk for fracture is.

Women are at an increased risk for developing osteoporosis relative to men – related to the bone loss that occurs after menopause when women have a decrease in estrogen. In addition, the amount of bone mass an individual has at their peak also influences their risk. Men have a 10 to 15 percent greater bone mass than women at peak levels; they have more bone mass to lose before clinical effects can be seen but still are not immune to the effects of osteoporosis.12 Both men and women are susceptible to the bone loss that comes with aging.13,14

Diagnosis
Diagnosis of osteoporosis is primarily based on testing bone mineral density with Dual-Energy X-ray Absorptiometry (DEXA).15 DEXA is considered the gold standard for measuring bone mineral density. Testing bone density allows early diagnosis and intervention before fractures occur and yet is typically underutilized.

Patients may have medical conditions that can limit the

<table>
<thead>
<tr>
<th>Table 1. Risk Factors for Osteoporosis by Category</th>
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</thead>
<tbody>
<tr>
<td><strong>Endocrine Disease, Metabolic Causes</strong></td>
</tr>
<tr>
<td>Hypogonadism</td>
</tr>
<tr>
<td>Hyperadrenocorticism</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
</tr>
<tr>
<td>Systemic mastocytosis</td>
</tr>
<tr>
<td>Porphyria</td>
</tr>
<tr>
<td>Adult hypophosphatasia</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Thalassemia</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
</tbody>
</table>
utilization of DEXA for the diagnosis of osteoporosis as some conditions can impair interpretation of the results. These typically involve alterations to bones but can include human factors involved in the DEXA technique. Table 2 shows some of the possible sources of confounding factors.

The WHO has established criteria for diagnosing osteoporosis in women using the t-score generated by DEXA. The t-score is the number of SD a patient’s BMD is different from a young-adult BMD used as reference. Table 3 shows the association between t-score, relative bone mass and the risk of fractures of the spine and hip. The Z-score is the number of SD a patient’s BMD is different from a BMD reference of similarly aged patients. If the Z-score is greater than -2, evaluation for secondary causes of osteoporosis should be considered.

Once the diagnosis of osteoporosis has been made using DEXA, follow-up scans can be considered one to two years after beginning treatment, or six months after glucocorticoid therapy. Serial scans may not be necessary if minimal change in BMD is expected or if the results will not affect management. For patients without osteoporosis at baseline DEXA and who cannot be pharmacologically treated, follow-up DEXA sans can be considered as follows. In patients with low bone mass (t-score -2.00 to -2.49) or risk factors for bone loss follow-up scans can be done every two years while risk factors continue. In patients with low bone mass of t-score -1.50 to -1.99 and no risk factors, follow-up scans can be considered for every three to five years. In patients with normal or slightly low bone mass (t-score -1.01 to -1.49) and no risk factors for increased bone loss, follow-up scans can be done every 10 to 15 years. Ideally, follow-up scans should be performed on the same DEXA machine their baseline measurement was done on.

Lumbar spine and proximal femur are the best locations to scan as they are the most likely locations of fragility fractures. Forearm scans can be used if the hip/spine cannot be measured, individuals who weigh too much for the DEXA scan table and in the setting of hyperparathyroidism.

There are multiple other techniques that can be utilized to assess bone status. These include peripheral DEXA quantitative computed tomography (QCT), digital X-ray radiogrammetry and quantitative ultrasound techniques. They are less commonly used than DEXA in the U.S. Peripheral DEXA is used to measure bone density at peripheral sites and while low t-scores at peripheral sites has been shown to be related to increased fractured risk, it is not very good for following the effects of therapy due to the slow response of peripheral sites to therapy. QCT is superior to DEXA in its ability to distinguish trabecular bone from cortical bone and is currently primarily a research tool. Radiogrammetry compares cortical thickness with total bone width mid-shaft of at least two metacarpal

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Table 2. Limiting Factors for the Use of DEXA in the Diagnosis of Osteoporosis

<table>
<thead>
<tr>
<th>Medical Conditions</th>
<th>Technique/Technician</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteomalacia</td>
<td>Inadequate reference ranges</td>
<td>Overlying metal objects</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>Inadequate operating procedures</td>
<td>Contrast media</td>
</tr>
<tr>
<td>Soft tissue calcification</td>
<td>Calibration, region selection,</td>
<td>Recent technecium-99m</td>
</tr>
<tr>
<td></td>
<td>acquisition mode, positioning</td>
<td>bone scan</td>
</tr>
<tr>
<td>Previous fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe scoliosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extreme obesity or ascites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertebral deformities (due to osteoarthritis, Scheumann disease etc.)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Criteria for Diagnosis of Osteoporosis Based on Femoral Neck T-score

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>≥ -1</td>
</tr>
<tr>
<td>Osteopenia (low bone mass)</td>
<td>≥ -2.5, ≤ -1</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>≤ -2.5</td>
</tr>
<tr>
<td>Severe osteoporosis</td>
<td>&lt; -2.5 AND 1+ fragility fractures</td>
</tr>
</tbody>
</table>
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Please activate your 2016 AMA membership through the South Dakota State Medical Association by calling (605) 336-1965.
bones from standard X-rays of the hand\textsuperscript{1}. Quantitative ultrasound is typically used on the calcaneus and has been found to be a good predictor of fracture risk.\textsuperscript{20}

The FRAX tool was developed by the WHO and uses multiple risk factors to assess the 10-year probability of osteoporotic fracture. The risk factors included in the FRAX algorithm are age, sex, rheumatoid arthritis, secondary osteoporosis, prior osteoporotic fracture, parental history of hip fracture, current smoking, BMI, alcohol intake, steroid use and ± femoral neck BMD.\textsuperscript{21} The FRAX algorithm produces two numbers: the 10-year probability of hip fracture and the 10-year probability of major osteoporotic fracture. FRAX is designed for use in postmenopausal women and men less than 50 years who have not previously been pharmacologically treated for osteoporosis.\textsuperscript{22} The FRAX score can be used to determine cost-effective appropriate treatment of osteoporosis.\textsuperscript{23}

**Treatment**

Upon diagnosis of osteoporosis there are several modalities of treatment. The first step is to ensure adequate calcium and vitamin D intake. This can be accomplished with oral supplementation so the patient receives 1,500 mg of calcium daily and 2,000 to 4,000 units of vitamin D daily. Patients should be encouraged to have a well-balanced diet. If there is adequate dietary intake of calcium, supplementation is not necessary.\textsuperscript{24} Calcium and vitamin D supplementation has been shown to increase the risk of kidney stones in postmenopausal women so it is important to not overdo the supplementation.\textsuperscript{25} The influence of calcium and vitamin D supplementation on cardiovascular event risk has been controversial with some studies showing no effect and some showing an increased cardiovascular risk.\textsuperscript{26–29} Increased activity, and specifically increased weight-bearing exercise, should be encouraged, as well as additional lifestyle changes such as decreasing alcohol and no tobacco products.\textsuperscript{30–33}

Pharmaceutical treatment of osteoporosis should be considered in patients whom lifestyle changes and calcium/vitamin D supplementation has not improved bone density or who meet the National Osteoporosis Foundation (NOF) guidelines for pharmacologic treatment (postmenopausal women and men 50 years and older). These guidelines are shown in Table 4.

Bisphosphonates are considered the first-line drugs for osteoporosis treatment and work by inhibiting osteoclasts.\textsuperscript{14} Oral bisphosphonates have proven efficacy, manageable cost and have data available on long-term safety. There are multiple formulations and delivery routes available and there should be patient input as to which route they’d prefer. Table 5 shows the various bisphosphonates and their delivery route. The most common adverse effects are gastrointestinal including reflux, esophagitis and esophageal ulcers which can be mitigated by complete adherence to the oral regimen. This regimen for oral bisphosphonates includes drinking at least 8 ounces of water and staying upright for 30 minutes following taking the pills. With IV administration of bisphosphonates, flu-like symptoms of fever, myalgias, and arthralgias are not unusual in the first 24 to 72 hours after infusion.\textsuperscript{35} Hypocalcemia, musculoskeletal pain, renal impairment, ocular side effects and osteonecrosis of the jaw are other reported side effects. Clinically significant hypocalcemia does not occur unless the patient has concurrent hypoparathyroidism. Musculoskeletal pain, ocular side effects (pain, blurred vision, conjunctivitis, uveitis, and scleritis) and osteonecrosis of jaw are all rare.\textsuperscript{36}

Selective estrogen receptor modulators (SERM) have

---

**Table 4. NOF Guidelines for Beginning Pharmacologic Treatment of Osteoporosis**

<table>
<thead>
<tr>
<th>History of hip/vertebral fracture</th>
<th>T-score ≤ -2.5 (femoral neck or spine) with secondary causes excluded</th>
<th>T-score -1 to -2.5 + 10-year probability of hip fracture ≥ 3% or 10 year probability of any major osteoporosis-related fracture ≥ 20% (using FRAX calculator)</th>
</tr>
</thead>
</table>

**Table 5. Available Bisphosphonates and Delivery Routes**

<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>Delivery Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actonel (risedronate)</td>
<td>Weekly or monthly pill</td>
</tr>
<tr>
<td>Boniva (ibandronate)</td>
<td>Monthly pill or injection every 3 months</td>
</tr>
<tr>
<td>Fosamax (alendronate)</td>
<td>Weekly pill</td>
</tr>
<tr>
<td>Atelvia (risedronate sodium)</td>
<td>Delayed release Actonel, given weekly</td>
</tr>
<tr>
<td>Reclast (zoledronate)</td>
<td>IV infusion once a year</td>
</tr>
</tbody>
</table>
Estrogen agonist activity on bones and estrogen antagonist activity on breasts/uterus. These effects cause decreased bone resorption, a reduction in vertebral fractures, and reduce the risk for breast cancer. Adverse effects include hot flashes, leg cramps, peripheral edema, an increase in venous thromboembolic events and a decrease in low density lipoprotein (LDL). 37,38

Recombinant parathyroid hormone activates osteoblasts to stimulate bone formation greater than resorption which has been shown to decrease fractures. 39,40 Hypercalcemia and hypercalcuria can be seen in the short-term. In the long-term, improved back pain was seen though the mechanism is uncertain between decreased fractures or an analgesic effect.

The RANKL protein activates osteoclasts causing bone loss. Human monoclonal antibodies can be used to block RANKL leading to a reduction in osteoclastogenesis. Human monoclonal antibodies to RANKL have been shown to improve BMD in both postmenopausal women and men.41 Adverse effects include musculoskeletal pain, hypercholesterolemia and cystitis.42 Eczema, cellulitis and flatulence have also been reported with the incidence of eczema and cellulitis likely related to the suppression of RANKL within the immune system.43 Table 6 summarizes some of the drugs available in these classes and their usual delivery routes.

### Prevention

Prevention of osteoporosis and its related fractures involves managing several areas which include lifestyle and dietary changes. Table 7 summarizes the various aspects of osteoporosis prevention which can be addressed with every patient.

In 2013, the U.S. Preventive Task Force came out with a report assessing the utility of calcium and vitamin D supplementation for the prevention of fractures. In postmenopausal women they were unable to determine whether doses of vitamin D and calcium beyond normal daily intake had any effect on the rate of fracture.46

Screening for osteoporosis is also a part of prevention. The recommended populations who should be screened include: post-menopausal females aged 65 and older, men aged 70 and older, younger post-menopausal women/women in menopausal transition/men aged 50 to 69 who have clinical risks for fracture, adults with fracture after age 50 and adults with conditions or taking medications associated with low bone mass/bone loss.21 Individuals outside this population should be screened as their risk factors for osteoporosis warrant.47
Fall prevention for patients with and without osteoporosis (but especially with) is key. However, many people have significant risk factors for falling, Table 8, which need to be addressed and managed if possible.

**Conclusion**

Fractures related to osteoporosis can be associated with chronic pain, deformity, depression, disability and even death. Patients will face hospitalizations, surgeries and nursing home placement for rehabilitation or permanently and likely loss of independence. When looking at these consequences alongside the cost of acute and chronic medical care for osteoporosis related fractures, it is clear why this silent disease needs to be actively defended against. Today, there are multiple options for treating osteoporosis once it has been found which allow the physician to contribute to the patient’s fracture risk reduction.

### Table 8. Risk Factors for Falling

<table>
<thead>
<tr>
<th>Environmental</th>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of assistive devices in bathrooms</td>
<td>Age</td>
</tr>
<tr>
<td>Low level lighting</td>
<td>Anxiety/agitation</td>
</tr>
<tr>
<td></td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Environmental</td>
<td>Arrhythmias</td>
</tr>
<tr>
<td>Obstacles in walking path</td>
<td>Poor vision/use of bifocals</td>
</tr>
<tr>
<td>Medical</td>
<td>Dehydration</td>
</tr>
<tr>
<td></td>
<td>Previous fall</td>
</tr>
<tr>
<td>Age</td>
<td>Depression</td>
</tr>
<tr>
<td>Over-sedating medications (narcotic analgesics, anticonvulsants, psychotropics, sleep aids)</td>
<td>Diminished cognitive skills</td>
</tr>
<tr>
<td>Anxiety/agitation</td>
<td>Female gender</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>Urgent urinary incontinence</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Impaired transfer and mobility</td>
</tr>
<tr>
<td>Poor vision/use of bifocals</td>
<td>Vitamin D insufficiency</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>Previous fall</td>
<td>Other</td>
</tr>
<tr>
<td>Depression</td>
<td>Fear of falling</td>
</tr>
<tr>
<td>Diminished cognitive skills</td>
<td></td>
</tr>
</tbody>
</table>

### 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.*
Sacubitril/Valsartan (Entresto): The Next Blockbuster Medication?

By Chance D. Wachholtz; and William J. Hayes, PharmD, BCACP

Sacubitril/valsartan (Entresto) became the newest drug for patients with chronic New York Heart Association (NYHA) functional class II to IV heart failure with reduced ejection fraction (HFrEF) after its Food & Drug Administration (FDA) approval in July 2015.

Sacubitril/valsartan, an angiotensin receptor neprilysin inhibitor (ARNI), is the first of its kind, claimed as a “once-in-a-decade kind of breakthrough.” This article will review the mechanism of action, dosing, contraindications, adverse effects and the evidence for use of sacubitril/valsartan.

Sacubitril is an oral prodrug that converts to LBQ657 in the body. LBQ657 blocks the effects of neprilysin, causing increased levels of natriuretic peptides. Valsartan antagonizes the angiotensin II receptors directly. The bioavailability is over 60 percent and can be taken with or without food. It is 97 percent protein bound. Almost equally excreted between the urine and feces, sacubitril/valsartan requires dose reductions in the event of renal or hepatic impairment. The elimination half-life is roughly 12 hours for LBQ657 and 10 hours for valsartan.

Sacubitril/valsartan is available in three different dosage forms: 50 mg ( sacubitril 24 mg/valsartan 26 mg), 100 mg ( sacubitril 49 mg/valsartan 51 mg), and 200 mg ( sacubitril 97mg/valsartan 103mg) oral tablets. The recommended initial dosing is 100 mg twice daily (BID). The dose may be doubled as tolerated after two to four weeks, to target a maintenance dose of 200 mg BID. There is a recommended 36-hour washout period when switching from an angiotensin-converting enzyme inhibitor (ACE-I). Both patients previously taking a low dose ACE-I or an angiotensin-converting enzyme (ARB), and patients not currently taking an ACEI/ARB should be initiated at a lower dose of 50 mg BID. In patients with severe renal impairment, creatinine clearance of 30 mL/min or less, or moderate hepatic impairment, a Child-Pugh class B, a dose of 50 mg BID is recommended. Sacubitril/valsartan is not recommended for use in patients with severe hepatic impairment, Child-Pugh class C. Contraindications to sacubitril/valsartan include a history of angioedema related to previous ACE-I or ARB therapy, hypersensitivity to sacubitril, valsartan, or any component of the formulation, concomitant use or use within 36 hours of ACE-I, and concomitant use with Aliskiren in patients with diabetes. Some common adverse effects include hypotension (18 percent), hyperkalemia (12 percent), impaired renal function (1 to 16 percent), and angioedema (black patients: 2 percent; others: less than 1 percent).

The PARADIGM-HF trial is a randomized, double-blind, multicenter, multinational, parallel group, active controlled study between sacubitril/valsartan and enalapril in patients with HFrEF. The study examined 8,442 patients with a left ventricular ejection fraction (LVEF) of less than 40 percent and NYHA functional class II, III, or IV heart failure (HF) for time to first occurrence of either cardiovascular death or heart failure hospitalization. Authors estimated they would need approximately 8,000 patients for 34 months, with 1,229 deaths from cardiovascular causes, to provide the study with a power of 80 percent to detect a relative reduction of 15 percent in the risk of death from cardiovascular causes in the treatment group. Patients were screened and received enalapril 10 mg BID, for a two-week active run-in period followed by an active run-in of sacubitril/valsartan 100 mg BID for one to two weeks, with titration to 200 mg BID for a further two to four weeks. Patients were then randomized into a double-blind treatment of enalapril 10 mg BID or sacubitril/valsartan 200 mg BID. Patients with a NYHA class of II to IV and an LVEF of less than 35 percent (an amendment to the protocol mid-study) were included in this study. Patients had to have a B-type natriuretic peptide (BNP) level of at least 150 pg/mL, or had been hospitalized in the previous 12 months. Patients taking any dose of ACE-I or ARB were considered for
participation, but were required to take a stable dose for at least four weeks before screening. Excluded patients included those with symptomatic hypotension, estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m², a decrease in eGFR of more than 35 percent between screening and randomization, a potassium level greater than 5.2 mmol/L at screening or greater than 5.4 mmol/L at randomization, or a history of angioedema or unacceptable side effects from ACE-I or ARBs. The mean age of patients was 64, with over two-thirds having NYHA class II HF. The groups were balanced with respect to baseline characteristics.

The results from the trial show sacubitril/valsartan 200 mg BID had benefit when compared with enalapril 10 mg BID, with death from cardiovascular causes or first hospitalization for worsening heart failure lower at 21.8 versus 26.5 percent (HR=0.8 CI=0.73-0.87, P<0.001). These results yield a number needed to treat (NNT) of 22 patients. Patients in the sacubitril/valsartan group had significantly more symptomatic hypotension compared to enalapril (14 versus 9.2 percent) but fewer patients stopped their study medication because of an adverse event, 10.7 versus 12.3 percent P=0.03. The median follow up was 27 months.

The PARADIGM-HF trial results indicate sacubitril/valsartan was superior to enalapril 10 mg BID in reducing hospitalizations for heart failure or risk of death from cardiovascular causes. Authors state the trial findings are clinically significant, particularly since the dose of enalapril used, 10 mg BID, has been shown to reduce mortality. Despite these claims, the mean dose of enalapril in the study was 18.9 mg per day, which indicates many patients were not titrated to the full 10 mg BID. Moreover, the HFrEF target dose for enalapril is 10 to 20 mg BID according to guidelines. It is unclear how restricting the dosage of enalapril to exclude the upper end of the target dosage for HFrEF would have on the study’s results. Other limitations of the study include the usage of an active run-in period. This raises the question if patients will be able to tolerate the side effects from sacubitril/valsartan, as patients who could not, were not included in the trial. The twice-daily medication usage may be disadvantageous for patients with poor compliance. Also, the estimated cost is $12.50 per day or about $4,500 per year, which is more than many cheaper alternatives that also have mortality benefit. Patients who are on maximal HF therapy and still having symptoms may be candidates for sacubitril/valsartan, but its place in therapy is not yet certain. Sacubitril/valsartan touted mortality benefit over ACE inhibitors alone is its primary advantage, but the aforementioned flaws and whether the PARADIGM-HF trial merely illustrated two HF medications are better than one moderately dosed monotherapy is yet to be determined.

REFERENCES

About the Authors:
Chance D. Wachholtz, PharmD Student, South Dakota State University.
William J. Hayes, PharmD, BCACP, Rapid City.
What safe sleep looks like.

Find out why the new safe sleep guidelines are so important for your baby’s health.

Share these guidelines with family, day care providers, and anyone who takes care of your baby.

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Healthier moms + Healthier babies
My father was a World War II Veteran and I know the experience of being in that war left a huge mark on him. Many of the disciplinary methods he used on my sister and me were a direct result of his U.S. Army training, such as his, "No excuse, sir," type of stuff. I know he felt a great bond with any other veteran of any war, even when meeting them for the first time.

But his service was not without some bad consequences. I remember how he turned serious and silent when I asked him the awful question all kids wonder about their warrior fathers, "Did you ever kill anybody, Dad?" I never got an answer, and years later I’ve realized the question caused significant anguish. I know many people put in harm’s way, having to fight to survive, share this kind of struggle. I believe it represents at least one level of what is now called posttraumatic stress disorder (PTSD).

Personally, I struggle sending our young adults to fight against other young adults who were also sent to fight for some political reason. That debate must be left for another time and for better minds than I.

But I do not struggle with our government doing its level best to medically help those who are harmed by armed conflict, and I believe we do just that with our U.S. Department of Veterans Affairs (VA). In recent years, battlefield medical units have been so much more effective in bringing those injured through the acute trauma of war, that many more severely injured soldiers now survive when they would not have in times past. This is a remarkable accomplishment, and yet such survival has resulted in many more veterans who are severely disabled from physical and mental trauma.

Now these wounded soldiers are back home doing their best to cope and function in our society. To help these injured return to function has indeed been the evolving direction of the modern VA. For example, the VA has been on the cutting edge for research and development of prosthetic limbs. This work will also benefit others needing prosthesis, no matter what the cause. Of equal importance is the VA’s evolving work for those suffering from other severe injuries, to include PTSD.

We have no excuse, sir. Our responsibility as a government and a society should be for veterans: to care for them, understand them, hire them. Thank you to all who have served our country, and thank you VA.
Studies show 1 in 14 doctors face a malpractice suit every year - resulting in almost every physician dealing with more than one lawsuit during their career. The SDSMA Center for Physician Resources brings you the following 5 webinars with expertise on risk protection:

- **September 8, 2015 – 7 p.m. CT**
  Tips, Tricks and Steps to Take to Avoid a Malpractice Lawsuit

- **December 8, 2015 – 7 p.m. CT**
  Underwriting Considerations in Medical Malpractice Insurance

- **March 8, 2016 – 7 p.m. CT**
  Apology and Communication in Medicine

- **June 14, 2016 – 7 p.m. CT**
  Anatomy of a Medical Malpractice Lawsuit

- **September 13, 2016 – 7 p.m. CT**
  Physician Resiliency – Healing the Healer

The USDSSOM designates this live activity for a maximum of 1 AMA PRA Category 1 Credit(s). Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This series will also provide key advice on the litigation process and how to get through a malpractice claim both personally and financially.

Register at [www.sdsma.org](http://www.sdsma.org) or 605.336.1965

Brought to you in partnership with MMIC
Great Plains Quality Innovation Network (QIN) has been awarded a Special Innovation Project by the Centers for Medicare and Medicaid Services (CMS) to improve colorectal cancer (CRC) screening rates within the Great Plains QIN region – South Dakota, Kansas, Nebraska, and North Dakota. This project covers the period of Sept. 18, 2015 through Sept. 17, 2017. We plan to implement the intervention that supports the primary determinant of individuals having a colorectal cancer screening test – a physician recommendation – and the implementation of a systematic process that ensures recommendation and follow up for all patients.

According to the American Cancer Society (ACS) and the National Colorectal Cancer Roundtable, a practitioner’s recommendation is the single most influential factor in persuading individuals to be screened for cancer, and only a systematic approach that is designed to provide this recommendation to every eligible patient will make it possible to achieve the targeted screening rates.

Approximately 5 percent, or one in 20, Americans will be diagnosed with cancer of the colon or rectum in their lifetime. Prevention and early detection of colorectal cancer improves health, saves lives and reduces health care costs. Although the incidence of colon cancer has declined significantly over the past 10 years largely due to improvement in screening and early detection, rates of colorectal cancer remain highest in the Midwest. The four Midwestern states served by the Great Plains QIN continue to have colorectal cancer incidence rates that are higher than the national average, and colorectal cancer screening rates that are far below the national average.

Great Plains QIN utilized a CRC analytic file from CMS to review how our screening rates appear utilizing Medicare claims. Low rates of CRC screening mean that a greater proportion of CRC is diagnosed at a more advanced stage, resulting in greater treatment costs and higher mortality. As demonstrated in the following table, there is room for improvement in CRC screening in all four of the Great Plains QIN states.

According to the American Cancer Society Colorectal Cancer Facts and Figures 2011-2013, only 39 percent of colon cancers are found at the localized stage, which have a 90 percent five-year survival rate. If we can identify CRC in the early stages through regular screening, we not only improve survival rates for the patients, but also avoid the need for expensive treatment. Five-year survival rates for patients diagnosed at the regional stage fall to 70 percent, and those diagnosed at distant stage only have a 12 percent survival rate.

Great Plains QIN’s intervention with this project will include a three-part strategy consisting of: 1) A regional Learning and Action Network; 2) Direct technical assistance to recruited clinics; and 3) Coordination of public education and awareness with the “80% by 2018” campaign partners. Great Plains QIN is partnering with the ACS, ACS local affiliates, Centers for Disease Control and Prevention (CDC) grantees (Departments of Health), and the Health Information Exchanges in the four states. We will also partner with the Great Plains Tribal Chairman’s Health Board and with local public health units working on or near the tribal areas within our respective states.

This special innovation project provides Great Plains QIN with a great opportunity to integrate the efforts of this project into our existing work with providers under the 11th Statement of Work (e.g., cardiac health, diabetes, utilizing health information technology to improve outcomes, and adult immunizations).

For more information, please contact Great Plains QIN/ South Dakota Foundation for Medical Care at 605.336.3505 or email me at stephan.schroeder@area-a.hcqis.org.

### Baseline Colorectal Cancer Screen Rates

<table>
<thead>
<tr>
<th>State</th>
<th>Screening Rate Per Medicare Claims (Q3 2014 CRC Analytic File from CMS)</th>
<th>Screening Rate Per 2012 BRFSS Survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>North Dakota</td>
<td>46.4% (21,318 / 45,927)</td>
<td>59.8%</td>
</tr>
<tr>
<td>South Dakota</td>
<td>46.7% (29,187 / 62,531)</td>
<td>63.8%</td>
</tr>
<tr>
<td>Nebraska</td>
<td>44.7% (57,043 / 127,526)</td>
<td>62.1%</td>
</tr>
<tr>
<td>Kansas</td>
<td>45.2% (90,572 / 200,296)</td>
<td>65.7%</td>
</tr>
</tbody>
</table>
Thank You!

for adding quality to the ‘CARE’ in DAKOTACARE

In 1986, the physicians of our state created DAKOTACARE because they believed a health care plan should be locally owned and directed. Today, DAKOTACARE continues to improve on making healthcare coverage and services provided by South Dakota physicians a seamless process.

Your involvement is critical to making DAKOTACARE a success. Many South Dakota physicians are currently participating through various committees, work groups or in other capacities, helping to guide the business decisions of our organization. DAKOTACARE’s Medical Management Department, staffed with knowledgeable physicians, pharmacists and nurses work with you to provide quality health care to your patients.

Your ownership and insight puts the “care” into DAKOTACARE.

Paul Amundson, MD Chief Medical Officer
Mike Pekas, MD Associate Medical Director
James Engelbrecht, MD Associate Medical Director

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As you have certainly heard, on Oct. 1, 2015 the ICD-10 code set became effective. This is a major change for the physician office coding and reimbursement process, as well as for insurance payers. We did several years of planning, implementation, and testing for ICD-10 and we felt confident that our processes were in place. If you and your staff have experienced any issues with the ICD changes, please let us know.

The DAKOTACARE Fee Schedule Committee annually reviews the methodology and structure of the DAKOTACARE physician fee schedule. They also regularly do an analysis of DAKOTACARE HMO and DAS allowable fee levels based on claims and premium trends; and as a percentage relative to benchmarks such as South Dakota Medicare levels and the South Dakota payer market. As a result of the most recent analysis, the DAKOTACARE Board of Directors approved an update to the fee schedule effective with claims with dates of service July 1, 2015 and after. Some code allowables were increased, and some were lowered, with the 2015 fee schedule changes having a total effect of increasing net annual payments to DAKOTACARE physicians. Also, on Sept. 1, 2015 the State Employee Health Plan Physician Fee Schedule was updated with an overall increase.

The Fee Schedule Committee continues to meet annually to review issues regarding the DAKOTACARE physician fee schedule and physician reimbursement. If you have questions about the fee schedule or physician reimbursement, please contact Provider Relations at 605.334.4000.

As changes occur during the year in our medical and administrative policies, we use several different methods to communicate with physicians and their staff. We will send a general letter to all participating physicians for important changes affecting the entire physician network, and may target specific letters to physicians in certain specialties affected by a particular change or policy. We also publish periodic newsletters with information of interest to all providers. These items are also posted on our provider portal at www.DAKOTACARE.com, and we encourage you to explore it.

We are the health plan of the South Dakota Medical Association. We thank you for your support and welcome your questions, comments and input. Call us at 605.334.4000 or email scott.jamison@dakotacare.com

“DAKOTACARE Update” is a monthly feature sponsored by DAKOTACARE, the health care plan of the South Dakota State Medical Association.
For more information about DAKOTACARE, visit www.dakotacare.com
South Dakota Board of Medical and Osteopathic Examiners

- Protects the health and welfare of the state’s citizens by ensuring that qualified medical health care professionals are licensed to practice in South Dakota.

- Licenses and regulates over 9,000 licenses within fourteen different medical categories.

- Co-regulates medical professions with the Board of Nursing.

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Sign up to be Doctor of the Day!

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

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

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

South Dakota’s 2016 Legislative Session opens on Jan. 12. To see a listing of available dates, visit www.sdsma.org. If you are interested in volunteering, please contact Mark East at 605.336.1965 or meast@sdsma.org.

Source: SDSMA staff

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SDSMA Center for Physician Resources Practice Support Series on Risk Mitigation

The SDSMA Center for Physician Resources brings you its Practice Support Series on Risk Mitigation at 7 p.m. CT Tuesday, Dec. 8 with the webinar “Underwriting Considerations in Medical Malpractice Insurance,” the second of five webinars in the series. To register for the webinar, find a link at www.sdsma.org. The remaining programs in this series include the following:

- 7 p.m. CT Dec. 8, 2015 – Underwriting Considerations in Medical Malpractice Insurance
- 7 p.m. CT March 8, 2016 – Apology and Communication in Medicine
- 7 p.m. CT June 14, 2016 – Anatomy of a Medical Malpractice Lawsuit
- 7 p.m. CT Sept. 13, 2016 – Physician Resiliency: Healing the Healer

This series will also provide key advice on the litigation process and how to get through a malpractice claim both personally and financially.

The USDSOM designates this activity for a maximum of 1 AMA PRA Category 1 Credit(s). Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Source: SDSMA staff
Two major regulations pertaining to the electronic health record (EHR) meaningful use program were announced by the Department of Health and Human Services (HHS) on Oct. 6:

1) The “Medicare and Medicaid Programs Electronic Health Record Incentive Program – Stage 3 and Modifications to Meaningful Use in 2015 through 2017” final rule includes changes in current reporting requirements, as well as setting forth requirements for meaningful use stage 3, which is planned for implementation in 2018.


The first rule eases some of the previous meaningful use requirements, although its late publication raises questions about whether and how physicians who postponed reporting in 2015 can qualify for a hardship exemption. That rule also finalizes new requirements for meaningful use stage 3, despite calls from the SDSMA and American Medical Association to postpone issuing more requirements until the overall framework is developed for the new Merit-Based Incentive Payment System. HHS has, however, noted that it will continue to receive comments on stage 3.

Sen. John Thune sent a letter urging regulators to delay finalizing the meaningful use stage 3 regulations. The SDSMA and AMA will urge the administration to use the 60-day comment period and the upcoming MIPS rulemaking process to evaluate the meaningful use program.

Source: AMA

“The Issue Is” is the SDSMA’s monthly update on key policy issues of importance to physicians.

Legal Brief Highlight: Dispensing Controlled Substances and Drug Packaging Requirements

South Dakota’s Prescription Drug Monitoring law requires, with few exceptions, any person who delivers a controlled substance to the user to submit particular patient, prescriber, and prescription related information to a central data repository at least once each week to the South Dakota Board of Pharmacy. However, the following categories of dispensers are exempt from said requirement: a licensed hospital pharmacy that provides a controlled substance for the purpose of inpatient hospital care; a licensed health care provider or other authorized individual in those instances when the practitioner administers a controlled substance to a patient; or a licensed veterinarian.

Additionally, the Federal Poison Prevention Packaging Act of 1970 requires special packaging of a wide range of hazardous household products including oral prescription drugs and other substances related to medical treatment. If accidental poisoning occurs, a physician may be liable for failure to provide child-proof packaging of drugs dispensed in the physician’s office.

For more information, download the SDSMA legal brief Dispensing Controlled Substances and Drug Packaging Requirements at www.sdsma.org. Through the SDSMA Center for Physician Resources, the SDSMA has developed more than 40 legal briefs that are available to members. In addition, the Center develops and delivers and programs for members in the area of practice management, leadership and health and wellness.

Source: SDSMA staff
New Revisions to Articles & Bylaws Will Streamline Governance

At the SDSMA Council of Physicians on Sept. 18 in Mitchell, the Governance Task Force proposed a number of revisions to the SDSMA’s articles and bylaws to streamline governance to better meet the needs of members and to engage more members in policy development. The Council of Physicians will be renamed the Policy Council and will have a more purposeful role in policy work. Its role will be to set policy by adopting position and policy statements, and will retain the sole power to amend the articles and bylaws. The Executive Committee will be renamed the Board of Directors, and will be the governing body of the association.

Going forward, issue-specific committees on health care topics of the day will replace standing committees. These ad hoc committees will be shorter-term or time-limited and will provide more opportunity for involvement of members on a variety of topics to address timely issues.

Beginning in 2016, the Policy Council will transition to two meetings per year – a Policy Council meeting to coincide with the SDSMA Annual Meeting, and a November meeting. Terms of Councilors taking office at the close of the 2015 and 2016 annual meetings will end at the close of the 2017 Annual Meeting. The Council approved the task force's recommendations.

Source: SDSMA staff

Medicare Payments for Chronic-Care Management Services

Medicare this year began paying an average of $42 per patient per month for non-face-to-face chronic-care management services, such as consulting with other doctors caring for the same patient who might be dealing with dementia, heart disease or arthritis, according to Modern Healthcare. The Centers for Medicare and Medicaid Services (CMS) estimates 70 percent of Medicare beneficiaries — roughly 35 million — would be eligible, but CMS has only received reimbursement requests for 100,000 beneficiaries.

CMS says it is working to raise awareness and interest among providers and Medicare recipients. The American Medical Association is educating medical practices on chronic-care management services to help physicians get reimbursed for services they already provide.

Source: Modern Healthcare

SDSMA 2016 Membership Dues Renewal Now Available

Annually, SDSMA members must renew their membership to continue receiving the many great membership benefits. The renewal process will take place between Oct. 1 and Dec. 31 on the SDSMA website.

To ensure a smooth renewal process for 2016, complete the following today:

1. Log into your member profile on the SDSMA website at www.sdsm.org and verify your username and password is working. If assistance is needed with logging in, contact the SDSMA office at 605.336.1965 or membership@sdsm.org.
2. Do not create a new account. All members have an account at www.sdsm.org.
3. Once you have logged into your account, proceed to the Pay My Dues link at the top of the page. Payment by electronic check and credit card are both accepted through your account. A receipt will be emailed to you upon completion of the payment.

Step-by-step instructions on how to complete the renewal process is available at www.sdsm.org.

Information about joining SDSMA PAC, contributing to the SDSMA Foundation and becoming a member of the American Medical Association is also available online.

If you have any questions as you prepare for or complete the dues renewal process, please contact Laura Olson at 605.336.1965 or membership@sdsm.org.

Thank you for your membership in the SDSMA!

Source: SDSMA staff
### CME Events

**November 2015**

- **November 4**
  - Internal Medicine Grand Rounds – Current Approaches to Pulmonary Hypertension: Clinical Cases Across Categories
  - AMA PRA Category 1 Credit(s)™ available
  - Register online: usdssom.learningexpressce.com

- **November 4**
  - VA Tumor Conference
  - AMA PRA Category 1 Credit(s)™ available
  - Register online: usdssom.learningexpressce.com

- **November 5**
  - Pediatric Grand Rounds – Covenant, Kindness and Patient Care
  - AMA PRA Category 1 Credit(s)™ available
  - Register online: usdssom.learningexpressce.com

- **November 11**
  - Dermatopathology Conference
  - AMA PRA Category 1 Credit(s)™ available
  - Register online: usdssom.learningexpressce.com

- **November 17**
  - Humphreys’ Forum for Infectious Disease
  - AMA PRA Category 1 Credit(s)™ available
  - Register online: usdssom.learningexpressce.com

- **November 17**
  - VA ACLS
  - AMA PRA Category 1 Credit(s)™ available
  - Register online: usdssom.learningexpressce.com

- **November 18**
  - Surgery Grand Rounds – Surgical Treatment of Ectopic Pregnancies in Unusual Locations
  - AMA PRA Category 1 Credit(s)™ available
  - Register online: usdssom.learningexpressce.com

- **November 18**
  - VA Tumor Conference
  - AMA PRA Category 1 Credit(s)™ available
  - Register online: usdssom.learningexpressce.com

- **November 19**
  - Pediatric Grand Rounds
  - AMA PRA Category 1 Credit(s)™ available
  - Register online: usdssom.learningexpressce.com

- **November 20**
  - VA Medical Center CME Activity – Pharmacy Clinical Pearls II
  - AMA PRA Category 1 Credit(s)™ available
  - Register online: usdssom.learningexpressce.com

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**DO YOU HAVE A CME EVENT COMING UP? WOULD YOU LIKE TO HAVE IT LISTED HERE?**

Contact: Elizabeth Reiss, South Dakota Medicine, 2600 W. 49th Street, Suite 200, Sioux Falls, SD 57105
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MedPlus Disability Evaluations

Physicians needed for Saturday physicals in Sioux Falls, SD. Payment is $1,000 per day. All dates are scheduled a month in advance and can vary month to month depending on the physician’s schedule. We provide an office, staff, forms, brief training, electronic medical record or transcription service and malpractice coverage. If interested or would like more information contact Dr. Fox at 443-838-1168 or CEFox@medplusdisability.com

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ENT
Yankton Medical Clinic, P.C., Yankton, South Dakota is seeking a BE/BC in ENT to join an established practice. Call one week per month. Competitive salary and outstanding benefits.

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Yankton Medical Clinic, P.C. is a 42 Physician independently owned, multi-specialty clinic. Located in the southeast corner of South Dakota along the Missouri River, Yankton is a community of 13,700 people, with excellent schools, low crime rate, and an all season recreation.

For additional information please email
Ann Rynke at aryken@yanktonmedicalclinic.com.

Apply online at:
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Black Hills Urgent Care, LLC seeks an outstanding physician to serve a well-established and growing patient base in Rapid City, SD and the Black Hills Region. Ideal candidates should possess strong clinical knowledge and skills; excellent patient communication skills; and high levels of commitment to efficiency; service; and maintaining and increasing patient volumes. Family Medicine or Internal Medicine physicians who have board certification are desired. Key features of this opportunity include:

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- Benefits include competitive compensation consisting of base pay, incentive pay based on production, and comprehensive benefit package.

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