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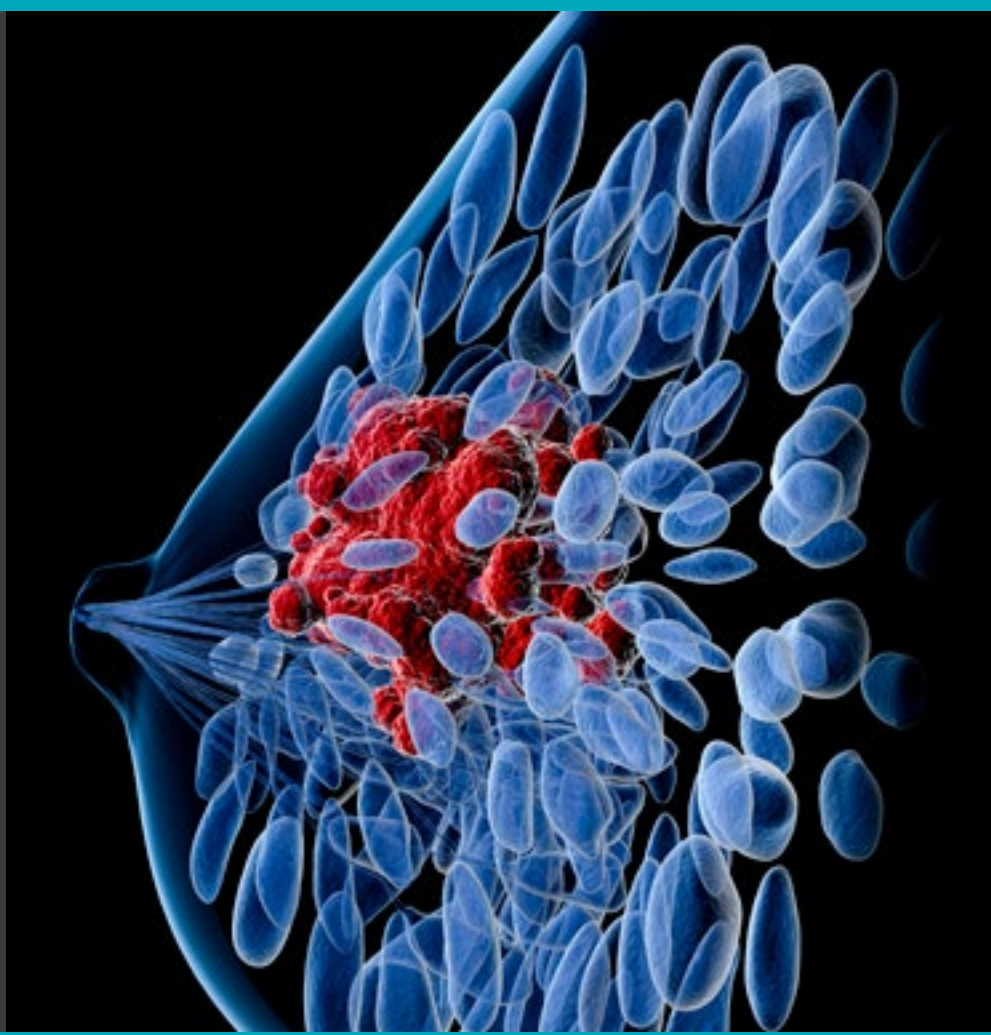

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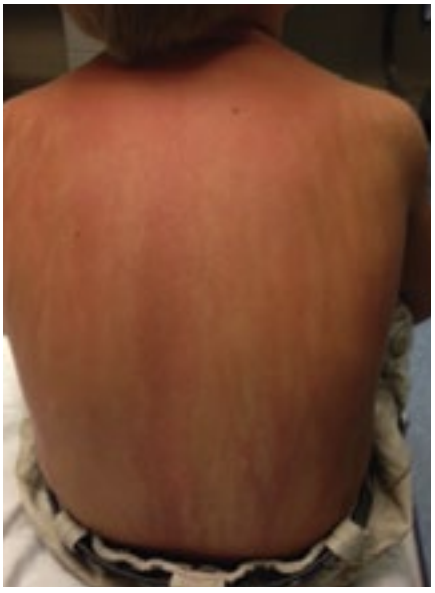

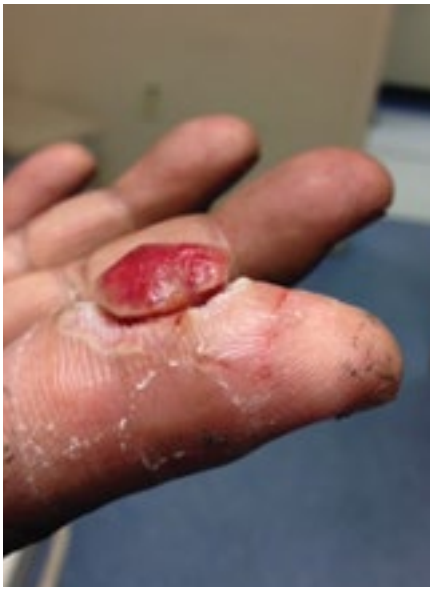

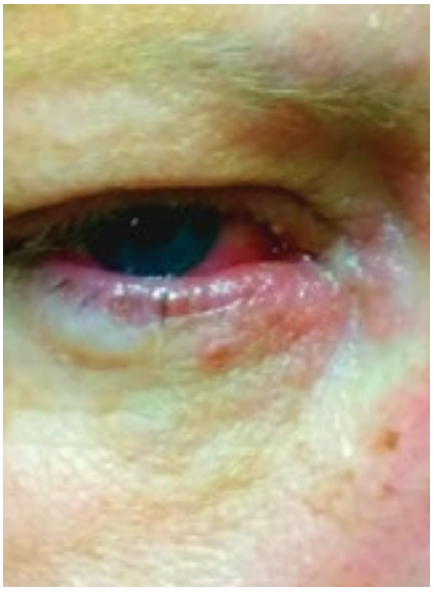

Osteopathic Family Physician

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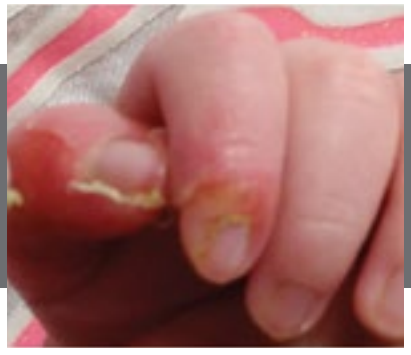

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CONTENTS

OSTEOPATHIC FAMILY PHYSICIAN SPECIALTY PEER REVIEWERS

2016 STUDENT PEER REVIEW INTERNS

INSTRUCTIONS FOR AUTHORS:

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EDITOR'S MESSAGE

Breast Mass Evaluation

Amy J. Keenum, DO, PharmD, Editor, Osteopathic Family Physician

The lead topic of my personal life this calendar year has been the female breast mass. My closest friends, (friends of twenty years variety) have been diagnosed with breast cancer as well as some of my dearest patients. They all had one thing in common, caring physicians who immediately ordered the correct diagnostic testing with timely biopsy. One smart doctor sent my friend back for another biopsy fearing the negative initial result was due to the biopsy of the wrong area of the breast and he was unfortunately correct. This careful attention to detail likely saved her life.

The lead article this issue is the evaluation of a breast mass. After a mass is discovered by the patient or by the physician the process is a diagnostic process and not a screening process. Screening mammograms have no place in the evaluation of a breast mass. The article mentions that 90% of breast masses are benign. I sometimes mention this fact when my discovery of a mass on a more routine exam is causing great anxiety. At the same time, it is that worry that may be pushing the patient to get all the needed imaging, biopsies and treatment. This is a scary ordeal.

The article mentions the use of ultrasound in young women. No adverse effects have ever been attributed to ultrasound. There is no radiation, no contrast- but it can be uncomfortable from the pressure applied by the operator. In patients with palpable dense breast tissue I send the ultrasound order with the diagnostic mammogram order. It makes the referral to the breast center go more smoothly.

Some breast cancers are only visualized with magnetic resonance imaging (MRI) and are not seen with other imaging modalities. MRI may also reveal more tumors that are not palpated. A breast cancer risk calculator at www.cancer.gov can aide in the determining the risk of breast cancer. If the patient is high risk the insurance company should more likely approve MRI imaging.

The patient who is lactating is not mentioned in the article. (Oh yes, I had a pregnant friend diagnosed with breast cancer this year too.) While clogged milk ducts and mastitis can cause masses in nursing patients, malignancy can also be present. Some common sense is needed in this scenario. Breastfeeding may reveal a mass that is not palpated at the end of pregnancy when the breasts are dense and enlarged. Diagnosis of breast cancer during pregnancy is challenging and mammography is not very useful as the images are all white, (there is calcium everywhere.) In cases of breast mass in a lactating patient ultrasound and/or MRI should be ordered. As many women delay pregnancy to complete their education, more women of advanced maternal age find themselves in this scenario.

Men do get breast cancer. The rate is thought to be 1 in 100 cases of breast cancer. The diagnosis algorithm is the same as in women. They get the pink ribbon too.

I hate cancer.

FROM THE PRESIDENT'S DESK

Payment Readine$$

Larry W. Anderson, DO, FACOFP *dist*.
2016 - 2017 ACOFP President

Everyone wants to know how they are going to get paid now and in the future. ACOFP understands that payment requirements are going to change on January 1, 2017. These changes will have impact on what you are paid, either for the positive (incentives) or negative (penalty).

While "confusion" seems to describe the state of payment today, ACOFP wants you to know that we will provide you the most updated information on CMS and payor reform in a manner that you can apply to your practice. No CMS-speak, just relevant and actionable information. We want our members to survive and thrive in this changing payment environment. But first, you need to understand it.

The Four Pillars of Payment

CMS is requesting all doctors who see Medicare patients to comply with these four "pillars of payment." Each pillar, or category, represents part of a total score that is called your "Composite Performance Score" or CPS.

The CPS is then translated into the "Payment Modifier" that is used to calculate payment on each Medicare claim you make. It can be a positive modifier, like +4 percent, or a negative modifier, - 3 percent. This will be the modifier on all of your Medicare claims for the year. In the coming years, the payment modifier may go as high as +9% or -9%.[1,2]

If we look at each category in Table 1, you will likely have heard of three of them. The difference is that they are now combined into one score that will be used to determine your payment. Quality Reporting is the most heavily weighted component of the CPS, accounting for 50 percent of the total.[3]

ACOFP has been diligently speaking to members about ACOFP Quality Markers 7.0™. For a low ACOFP Member Service rate, physicians can insure that Quality Reporting is completed annually and avoid the non-reporting penalties. Contact Debbie Sarason, Manager of Practice Enhancement and Quality Reporting at 847-952-5523 or debbies@acofp.org.

CMS has continued to include "Resource Use" and "Meaningful Use," (now called Advancing Care Information) as categories in assessing a physician's payment modifier. CMS has added a new category called "Clinical Practice Improvement Activities" (CPIA). This measurement is worth 15 percent of your total score. Each CPIA is rated either "High," worth 20 points, or "Medium," worth 10 points.[5]

The total points you can earn from CPIA's is 60 points. There is a list of 90 CPIAs to select from. (For a copy of the activities, e-mail Debbie Sarason at ACOFP at debbies@acofp.org).

CPIAs are segmented into sub-categories. These include:

- Population Management
- Expanded Practice Access
- Care Coordination
- Integrated Behavioral and Mental Health[6]

CMS will require documentation of the activities performed (this might include copies of patient charts, care plans, minutes of staff meetings, etc.) as well as signed attestations.

TABLE 1:

Four Clinical Measurements Comprise the CMS Composite Performance Score (CPS) for 2017.[4]

Measurements	% of CMS Composite Performance Score (2017)
Quality Reporting	50%
Resource Use	10%
Advancing Care Information *(Previously Meaningful Use)*	25%
Clinical Practice Improvement Activities	15%

From the American College of Osteopathic Family Physicians.

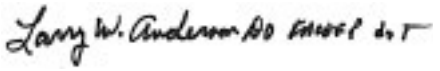
A few of the actual activities include:

- Collection of patient experience/satisfaction data on access to care and development of an improvement plan, such as outlining steps for improved communication with patients to help understanding of urgent needs. Medium Level – 10 points
- Participation in Million Hearts Campaign, or other Center for Medicare and Medicaid Innovation model (CMMI). Medium Level – 10 points
- Seeing new and follow-up Medicaid patients in a timely manner including individual dually eligible for Medicaid and Medicare. High Level – 20 points

It only takes a few of them to add up to 60 points. CMS is allowing physicians to select those that are most relevant to their practice. In completing these activities, physicians will have a positive impact on outcomes, patient satisfaction, and patient engagement. Some of these activities are easily completed and documented by using ACOFP Quality Markers 7.0 ™.

I hope this has given you greater confidence in meeting one of the four pillars of CMS's Composite Performance Score. Please check the "Payment and CMS Policy" at www.acofp.org for updates on CMS policies, and ways to meet CMS payment requirements. We will also have other featured articles on the "Pillars of Payment" for your review in the coming months.

Sincerely,



Larry W. Anderson, DO, FACOFP *dist.*
ACOFP President

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REVIEW ARTICLE

Evaluating Breast Masses in Adults

David Wood, DO[1] & David J. Park, DO, FAAFP, FACOFP[2]

[1] Family Physician with Golden Valley Memorial Healthcare
[2] Vice Dean and Southern Utah Campus Dean, Rocky Vista University College of Osteopathic Medicine

Keywords:
Breast
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According to the CDC, the second leading cause of death in females is cancer, with breast cancer being the most common type of female cancer and the second deadliest. It is predicted that there will be over 200,000 diagnoses of breast cancer made this year in the United States, with nearly 40,000 deaths attributed to breast cancer.[1] It is important to be able to identify a breast mass to assess whether it is benign or cancerous. One of the most frequent medico-legal claims in the United States is the missed diagnosis of breast cancer, with the majority of malpractice claims being awarded to women whose breast cancer diagnoses were delayed due to the physician not performing a mammogram and/or a clinical breast exam.[2] Nearly 10% of breast mass work-ups actually end up being breast cancer.[3] Therefore, it is imperative to be able to adeptly assess a breast mass to accurately determine its pathology. Screening and diagnostic modalities can easily be ordered by any physician and a discovered breast mass can be worked up effectively by using simple guidelines, which this paper will discuss.

INTRODUCTION

Breast mass complaints are common in the clinical setting and physicians should be comfortable performing breast mass evaluations. One study found that 40% of breast complaints in women aged 40-69 were for breast lumps or masses.[4] The discovery of a breast lump can cause significant anxiety and distress to the patient. Fortunately, approximately 90% of masses are benign in women in there 20's to early 50's, with fibroadenomas and cysts being the most common benign masses.[4,5] See Table 1 for types of breast masses.

The overall incidence of breast cancer has decreased by 0.9% and mortality decreased by 2.1% from 2000-2009. According to the CDC, the incidence of breast cancer still remains the most common cancer diagnosed in women.[6] It is important to work-up any breast mass in a thorough and concise process to prevent missed diagnoses and also to ensure an early diagnosis. Being diagnosed with a breast mass can be quite frightening to a patient and efficient management could greatly help alleviate worry and stress for the patient.

EVALUATION

The evaluation of a patient with a breast lump requires a thorough medical history of the lump, including when and how the patient discovered the lump, progression of size, and any associated symptoms.[8] It is also important to identify and assess any risk factors for breast cancer, including age, race, family history, smoking and various others *(See Table 2)*. In 2009, the United States Preventive Services Task Force (USPSTF) recommended against routine self-breast examinations (category D). However, the January 2016 USPSTF breast cancer screening guidelines removed self-breast examination recommendations as it now supports patients being aware of changes in their bodies and discussing these changes with their clinicians.[9]

PHYSICAL EXAM

A thorough clinical breast exam (CBE) is imperative in assessing a breast mass. The physician should start the CBE by looking at both breasts and noting any abnormalities or asymmetry. The visual inspection typically starts with the patient in the sitting position. The patient should be asked to place her arms above her head, as this may cause dimpling from a fixed mass. A mirror is sometimes helpful to look at the inferior portions of the breast. The breasts should then be checked for skin color changes, texture changes, skin thickening, dryness, and temperature changes.[11,12] The nipples should be checked for inversion and the areola should be checked for relative symmetry as these may be signs of an underlying mass. Only after a thorough visual exam should the physician then palpate the breasts. The visual exam portion may give important clues to surface area differences and help the clinician be more specific and attentive to a certain area during palpation. The palpation portion of the CBE should be performed while the patient is in the supine position. Palpation of breasts should be performed in a systematic fashion by following a linear or circular pattern. It is considered good practice to overlap palpations so as not to miss any areas. Axillary, supraclavicular, and infraclavicular lymph nodes should also be palpated in this systematic process. Finally, the nipples should be expressed to check for any nipple discharge or bleeding.

CORRESPONDENCE:
David J. Park, DO, FAAFP, FACOFP | dpark@rvu.edu

TABLE 1:

Common Breast Masses [7]

Benign	Cancerous
Fibroadenoma	Infiltrating Ductal 76%
Cyst	Invasive Lobular 8%
Traumatic Fat Necrosis	Ductal Carcinoma In Situ 7%
Fibrocystic Changes	Lobular Carcinoma In Situ
Intraductal Papillomas	Mucinous 2.4%
Lipoma	Medullary 1.5%
Abscess	Tubular 1.2%
Adenomas	Papillary 1%
Galactocele	
Diabetic Mastopathy	
Hamartomas	
Sarcoidosis	
Idiopathic Granulomatous Mastitis	
Pseudoangiomatous Stromal Hyperplasia	
Radial Scars	
Epithelia Related Calcifications	

TABLE 2:

Common Risk Factors for Breast Cancer [10]

- Gender (females 100 times more likely to be affected)
- White Race
- Higher Socioeconomic Class
- Northeastern United States
- BMI >33, 27% increased Risk
- Increase in Age
- Family History (BRACA-1 and BRACA-2 gene positive)
- Environmental Exposure to Radiation
- Benign Breast Conditions
- Smoking
- More than one alcoholic drink a day
- Late pregnancy
- Early first Menses
- Nulliparity
- Late Menopause
- DES Exposure in Utero
- Estrogen Supplementation
- Increased Breast Density
- Prior Biopsies

IMAGING

Mammography

Plain x-ray mammography is the most common imaging modality used for both screening and diagnostic purposes. The latest 2016 breast cancer screening guidelines by the USPSTF recommends a screening mammography every two years for women aged 50 to 74 years (Grade B). For women under 50, the decision to start screening mammography should be an individual one (Grade C).[9] If a mass is found on screening mammography or on the CBE, a diagnostic mammogram should be ordered as the first line testing for women over the age of 30.[7,10] If a breast mass is identified in a woman under 30, mammography is not the first line choice for diagnostic purposes due to the generally increased density of breast tissue in this group.

Mammograms can pick up two types of lesions: soft tissue masses and clustered micro calcification masses. Radiologists use the Breast Imaging-Reporting and Data System (BI-RADS) criteria to assess whether a mass is benign or potentially malignant.[12] The BI-RADS system was developed by the American College of Radiology to describe mammographic findings *(See Table 3)*.

Mammograms may also be useful to the surgeon in determining the location and size of the mass. Further, preoperative mammograms can aid in the follow-up assessment of the postoperative course.[7]

Some clinicians may tend to perform the CBE quickly due to the sensitive and potentially embarrassing nature of the exam. However, it should be noted that more extensive exams tend to be more thorough and allow more masses to be identified.[13] The CBE alone detects up to 10% of breast cancers while more than 90% of breast cancers are found through mammograms.[14] It is important to be reminded that discovering a mass on the CBE does not mean other masses do not exist. Therefore, it is important to order a mammogram in conjunction with the CBE at all times. It is also important to note that imaging does not always detect all masses. In fact, 10-15% of breast masses are not seen on mammography.[15] Therefore, both CBE and mammograms are recommended in conjunction for any breast mass evaluation.

TABLE 3:

BI-RADS Assessment Categories

0: Incomplete

1: Negative

2: Benign finding(s)

3: Probably benign

4: Suspicious abnormality

5: Highly suggestive of malignancy

6: Known biopsy – proven malignancy

From The American College of Radiology (ACR) Breast Imaging Reporting & Data System Atlas (BI-RADS Atlas). Reston, Va: © American College of Radiology; 2003

Ultrasound

Any female under the age of 30 should have masses evaluated by ultrasound due to the dense nature of breasts in young females.[16] Ultrasonography can help determine whether a mass is solid or fluid filled (cystic) and has been shown to be remarkably accurate. In one study, breast ultrasonography demonstrated a sensitivity of 98.4% for correctly classifying a breast mass as malignant or indeterminate.[17] If found indeterminate, a mammogram should be performed next.

MRI

MRI with gadolinium enhances most invasive breast cancers.[7,18-21] MRIs are probably the best radiologic method to assess the size and location of a breast mass, which would give beneficial information to the surgeon, especially if other modalities fall short.[22] One study found the sensitivity of MRI for malignant breast masses to be 100%.[15] However, the specificity of MRI is relatively low; around 70%.[23-25] Since all suspicious breast masses should be biopsied, the addition of an MRI is not critically necessary or cost effective in the evaluation of breast masses.[23]

MRI does play a role for patients with silicone breast implants whose mammographic images are fully or partially obscured. MRI gives the highest spatial resolution and contrast between implants and soft tissues of the breast.

Biopsy

Fine Needle Aspiration (FNA) biopsy is commonly used as a technique for breast mass biopsy because any trained clinician can perform it in the office setting. The procedure is not difficult to perform and is easily done in the family physician's office. Most often, FNA is performed with skilled palpation, but may also be performed under ultrasound guidance. Good FNA technique has 98% sensitivity and 97% specificity when performed by skilled operators.[26] The procedure is usually done with a 10-20 ml syringe with a 23-27 gauge needle. The fine needle is systematically advanced in and out of the mass multiple times, collecting tissue specimens. If aspirated fluid is clear and not bloody, the fluid does not need to be sent for cytology and can be discarded. Bloody or blood-tinged contents should be collected in a CytoLyte solution and sent for a pathologic analysis.[27]

Core needle biopsy is similar to the FNA biopsy but a larger needle is used, usually a 14-18 gauge cutting needle. This technique is more advantageous due to the collection of larger tissue samples. However, core needle biopsies require larger volumes of local anesthesia and have an increased risk of bleeding compared to FNA biopsies, due to larger needle sizes. Ultrasound imaging is usually used for better accuracy and therefore, core needle biopsies are usually done by a surgeon or an interventional radiologist.

An excisional biopsy is usually performed when FNA biopsy, core needle biopsy, or imaging provides insufficient results.[7,12,28] It is the most definitive method for histological analysis of a breast mass. An incisional biopsy can be done when the mass is very large and the patient is concerned about cosmetic effects. However, most patients opt for the excisional biopsy because they feel more comfortable having the mass completely removed. Cysts or microcysts are not indications for an excision due to possible interference with future mammograms.[7,10,29] However, excision is indicated whenever cysts reoccur, grow large, are complex, or if needle aspirations show malignancies.

CONCLUSION:

Although most breast masses are benign, a physician should evaluate all breast masses swiftly and properly. The incidence of breast cancer may be declining, but it still remains the second most common form of female cancer.[1] The controversy of recommending for or against self-breast examinations has largely been resolved as both the United States Preventive Services Task Force (USPSTF) and the American College of Obstetricians and Gynecologists (ACOG) have recently taken more neutral positions that self-identified breast masses should be discussed with a clinician and may help in detecting breast cancer. Therefore, the authors do not recommend teaching and instructing patients to perform routine self-breast examinations. The Triple Test (clinical breast exam, imaging, and tissue samples) should be used for diagnosing breast masses and to alleviate any anxiety and doubt for a patient.[12] Biopsy and tissue sample analysis remain the gold standard for making a definitive diagnosis and can be easily performed in the outpatient setting. The evaluation of a breast mass should not be delayed. A specialist referral is not a requirement in the early stages. Any primary care physician can initiate the work-up, and with proper training perform the biopsy in the office setting. Unsuccessful biopsies or lesions suspicious for malignancy upon work-up warrant an immediate referral to a breast surgeon. See Figure 1 for evaluation algorithm.

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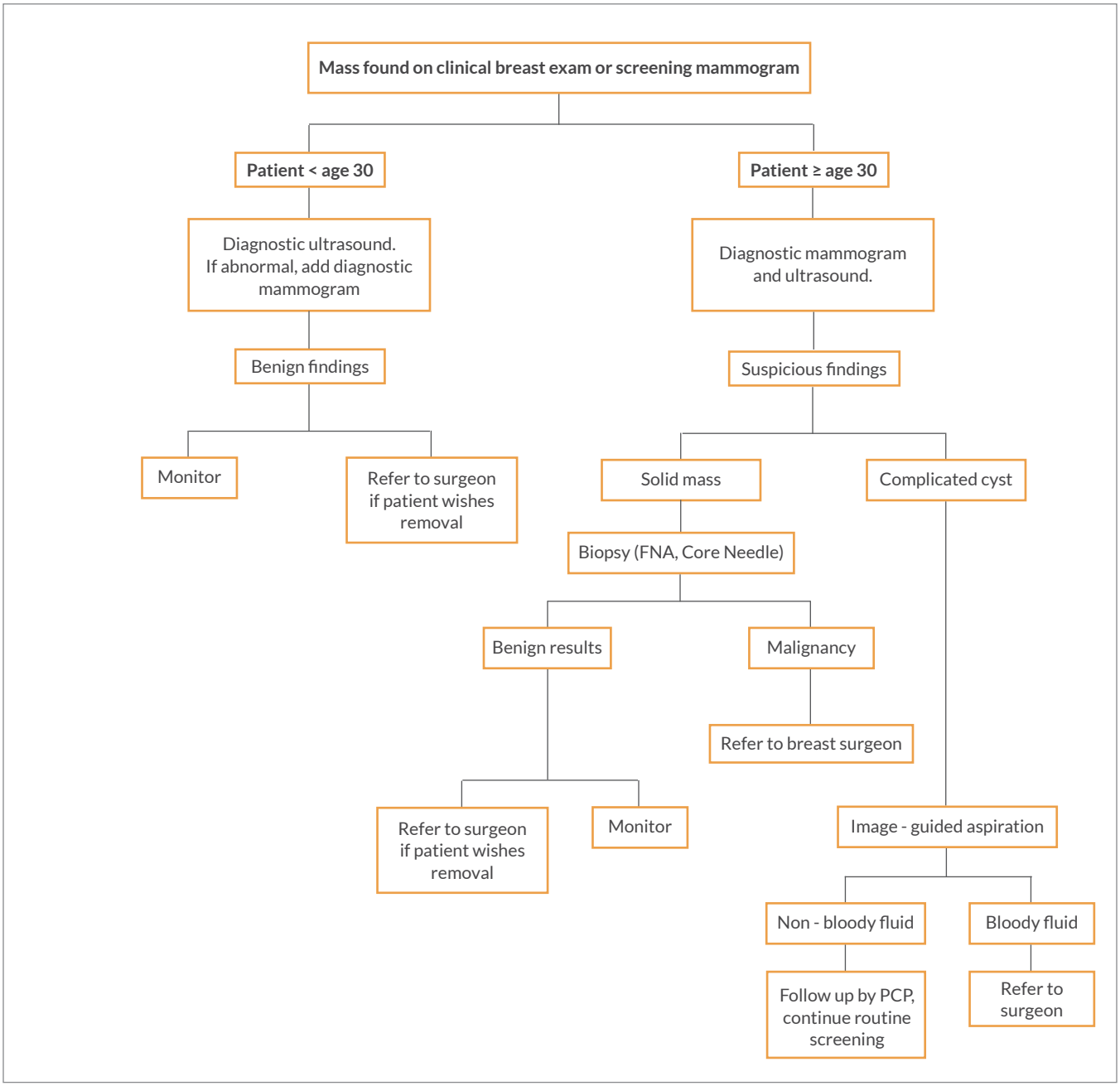
FIGURE 1:

Decision pathway for work-up of a breast mass



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REVIEW ARTICLE

Fibromyalgia Management

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Fibromyalgia can be a debilitating syndrome that can frustrate patients and physicians alike. Understanding the etiology and methods for diagnosis can allow for improved patient interactions and better introduction of an overall care plan for the patient. Management of the the patient with fibromyalgia requires an osteopathicapproach, integrating a multidisciplinary approach with a patient-centered focus. The Osteopathic Primary Care physician plays a valuable role in incorporating both pharmacological and non-pharmacological methods of treatment. Goals for treatment should be improvement in health related quality of life and improved patient function. Using a collaborative approach to treatment will produce increased patient satisfaction with care with reduced medical utilization and better long-term clinical outcomes.

INTRODUCTION

Fibromyalgia (FM) is a syndrome primarily consisting of widespread chronic pain, transient cognitive difficulties, non-restorative sleep, and fatigue. Other symptoms such as headaches, vertigo, tinnitus, Raynaud's phenomena, pelvic pain, palpitations and paresthesias have also been reported. The disorder is relatively common with a prevalence in the general population of about 3%. Fibromyalgia most commonly presents between the ages of 30-50 years old, however the incidence increases with age. The female to male ratio of diagnosed patients is approximately 9:1.

Historically, FM was a diagnosis of exclusion. The wide variety of presentations and lack of definitive serological or imaging tests has led to confusion on the pathophysiology of the syndrome and skepticism of its validity as a diagnosis. Concomitant diagnosis with DSM Axis I disorders such as generalized anxiety or major depression have further confounded the accurate diagnosis of FM. Multiple hypotheses on pathophysiology exist, but the prevailing theory is that FM is at least in part a neurosensory disorder of central sensitization.

ETIOLOGY & PATHOPHYSIOLOGY

Evidence for Central Sensitization

Multiple factors are thought to contribute to the development and perpetuation of FM. The current prevailing hypothesis is that it is a disorder of central sensitization and aberrant pain signaling.[1] Compared to healthy controls and even other chronic pain patients, FM patients report increased pain perception to noxious stimulus in healthy tissue. Referred pain patterns also tend to be more widespread and distressing to the FM patient. Increased nociceptive response to stimulus compared to other chronic pain populations suggests a failure of endogenous pain inhibition and the descending pain pathways.[2] On PET scan, FM patients show decreased mu-opioid receptor binding potentials compared to healthy controls. The degree of decreased binding potential in the cingulate and striatum is inversely proportional to perception of pain.[3]

Sleep dysfunction is also exceptionally common in FM. Poorer sleep quality and duration is associated with increased physical debility and psychological distress.[4] There is conflicting evidence as to whether this association is bidirectional, or whether sleep dysfunction is merely a result of other FM symptoms.

Musculoskeletal differences

Even when accounting for the historic "tender points" in the 1990 ACR guidelines for diagnosis, a higher number of myofascial trigger points have been found in FM patients.[5] Manipulation of these trigger points reproduces the spontaneous pain patterns encountered in FM. Further research has shown that FM tender points have a high correlation to discrete myofascial tender points, which may be part of the etiology of peripheral pain.

Patients with FM show a dysfunctional response to exercise, one of the mainstay lifestyle changes suggested to patients with chronic pain. Compared to controls, FM patients have decreased blood flow to muscles in response to aerobic demand.[6] There is also a decreased anti-inflammatory response during recovery after exhaustive exercise.[7] These physiological differences may explain why many patients with FM have difficulty tolerating exercise regimens. Given the other positive benefits of exercise on quality of life such as increased stamina and physical function, awareness of its effects on muscle tissue can help providers educate patients and counsel on exercise regimens that are tolerable.

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DIAGNOSIS

The American College of Rheumatology (ACR) in 1990 presented the first standardization of FM diagnosis with research led by Frederick Wolfe, MD. The diagnostic criteria included physical examination as well as a test of 18 bilateral tender points. A presence of tenderness to 4-kilogram pressure applied in 11 of the 18 tender points was considered a positive result.[8] The criteria was revised in 2010 to eliminate the tender point test and introduce two measures of both physician assessment and patient self-reporting. The Widespread Pain Index (WPI) measured the extent of pain across the body and Symptom Severity Scale (SSS) measured symptoms related to sleep, fatigue, and cognition. The reasoning behind the revision includes difficulty in standardization of tender point measurement and the temptation to use tender points as a definitive diagnostic tool. More important measures in diagnosing FM include sleep, fatigue, pain, and general impact on patient quality of life.[9]

The 2010 criteria were further revised in 2011 to focus entirely on patient self-reported symptoms. The FM Survey Questionnaire (FSQ) is a 31 item-screening tool based on these criteria and developed by Hauser that requires no objective exam or symptom evaluation by the clinician. This allows it to be used in any practice setting without special training. The FSQ has been shown to have similar sensitivity and specificity to both the 1990 ACR Criteria as well as the 2010 ACR revised criteria.[10] A Spanish-language version of the FSQ has been shown to be as reliable as the original FSQ, which provides useful cross-cultural relevancy to the survey.[11]

FM is diagnosed primarily through the history and physical exam, and there are no laboratory tests that can definitely diagnose fibromyalgia. While blood testing is not required for the diagnosis of fibromyalgia, many practitioners will order lab work to exclude other primary diagnoses. However, fibromyalgia can be comorbid with other rheumatologic diseases, so a positive diagnosis of another disease does not automatically exclude fibromyalgia. Commonly ordered tests include complete blood count (CBC), vitamin D, calcium/phosphate levels, thyroid-stimulating hormone (TSH), and C-reactive protein. Ruling out and correcting anemias, thyroid pathology, inflammatory processes, and vitamin deficiencies can help reduce the complicated clinical presentation of FM syndrome. At this time, there are no laboratory tests that are specifically suggested by any organization.

There is some correlation to genetic markers HLA-B27, HLA-B51 and FMF but there is insufficient evidence to use them for exclusion.[12] Current recommendations by the ACR do not advise routine screening for FM in asymptomatic patients.

MANAGEMENT IN THE PRIMARY CARE SETTING

As of publication, there is no 'gold standard' management for fibromyalgia syndrome. Different modalities have variable levels of success, and improvement in pain and health-related quality of life (HRQOL) from pharmacological agents alone is minimal.[13] Adjuvant non-pharmacological treatments are critical for effective management of symptoms and pain and debility-related psychosocial correlates. Providers must be straightforward with patients to communicate realistic expectations of continual symptom management, as full remission is rare.

Clinical trials of FM medications have historically excluded patients with long-standing injuries or other rheumatological disorders. We now know that FM often presents concomitantly with chronic pain conditions, so these study populations may not be representative of patients who will present to the primary care office.

MEDICATION MANAGEMENT

Centrally Acting Drugs

Currently, there are three FDA-approved drugs for the treatment of FM on the market. The first approved was pregabalin (Lyrica) in 2007, followed by duloxetine (Cymbalta) in 2008, and finally milnacipran (Savella) in 2009. Drug monotherapy with one of the FDA-approved agents along with patient lifestyle modification is considered first line treatment. Amitriptyline is also widely used for FM treatment, although it is not FDA-approved for this indication.

Duloxetine is one of the commonly used SSRIs used in the treatment of FM. It has been shown to reduce pain and stiffness, but the majority of benefit comes from decreased fatigue and anti-depressive and anxiolytic effects.[14] Many patients find benefit at lower than recommended dose (30 mg vs 60 mg). Patients prescribed duloxetine also show greater compliance and reduced inpatient and outpatient service utilization.[15]

Milnacipran is an SNRI with similar effects on pain and functioning as compared to duloxetine. The benefit milnacipran has over duloxetine is the longer time to diminished therapeutic response: approximately three years. However, it has been associated with more adverse events and one meta-analysis has called into question whether the number of patients who benefit from milnacipran: (40% in the test groups vs 30% in the placebo groups) is worth the adverse effect profile.[16]

Lyrica (pregabalin) provides distinct benefit in pain and sleep quality, as well as significant anxiolytic effects with a low risk of dependence. Compared to other drugs used to treat FM, pregabalin has been shown to have a longer time to diminished therapeutic response in the domains of sleep and fatigue,[17] allowing patients to maintain significant relief without constant medication changes. With pregabalin also being used for the treatment of nerve pain disorders like diabetic neuropathy and post-herpetic neuralgia, this treatment may provide relief in patients whose predominant pain pattern is neuropathic or characterized as "burning" or "electric". Side effects include weight gain, dizziness, and edema. Once-daily dosing before bedtime can minimize somnolence associated with pregabalin treatment.

Amitriptyline is another centrally acting drug, and is the most commonly prescribed tricyclic antidepressant in the treatment of FM. The mechanism of action in pain improvement is thought to be activation of the descending inhibitory pain pathways. Patients report a modest decrease in tenderness and stiffness, with increased duration and quality of sleep. Amitriptyline also has significant effects on depression and mood symptoms. Many patients who discontinue this medication do so because of the prevalent side effects of weight gain and exacerbated fatigue. The best response is found with low doses administered at bedtime, as this reduces daytime fatigue. Although the use of the FDA- approved drugs duloxetine, pregabalin, and milnacipran have increased, they show no increased benefit in fatigue or functioning over amitriptyline.[18]

The patient's predominant symptoms and concerns about functioning and adverse effects should guide treatment choices. Patients whose primary concern is pain may benefit more from pregabalin, while those who struggle more with cognitive symptoms and poor sleep often do better on duloxetine. Given the higher drug costs and significant side effect profile, providers must carefully weigh the benefits of each drug's use based on individual patient presentation and treatment goals.

Analgesics

Treatment of FM with analgesics is not considered first line, as symptoms are thought to be due to excess pain sensitivity rather than increased rate of pain signal transmission. Research on the treatment of peripheral pain in FM is sparse and many of the studies available have limitations from prior treatment or medical comorbidity exclusion criteria.

The only analgesic that has shown positive effects in the treatment of FM is tramadol, particularly when prescribed with acetaminophen.[19] Opioid analgesics such as hydrocodone and oxycodone are often used in the treatment of other chronic pain conditions; however, there is currently no evidence to suggest that opioid analgesics improve HRQOL in FM. While gross pain may decrease, the patient-oriented measures of pain-related disability and distress show little benefit. Given the side effects and dependence risk, there is no place for them in the routine treatment of FM.[20]

Non-steroidal anti-inflammatory medications such as ibuprofen and naproxen show no increased efficacy over placebo in the treatment of FM-specific pain, and given the gastrointestinal and cardiovascular risk factors of long-term maintenance therapy, they should be avoided unless used for the treatment of comorbid osteoarthritis.

Muscle Relaxants

While not FDA-approved for the indication, low dose cyclobenzaprine given daily at bedtime has been shown to improve quality and duration of sleep, a significant contributor to FM symptoms.[21] Effects on pain are not as significant, with decreased pain peaking early in treatment and eventual habituation approaching baseline levels. With an estimated number needed to treat (NNT) of 4.8, many patients will find significant relief with this drug alone.[22] Side effects are generally mild and include somnolence and dizziness. Physicians should be aware of the slightly increased risk of serotonin syndrome when prescribing cyclobenzaprine with SSRI/SNRIs, and educate patients on the signs and symptoms of serotonin toxicity.

There have been few studies on other muscle relaxant agents in the treatment of FM, and their improvement measures have been based on the old ACR 1990 criteria focusing on tender point pain. A small-scale study on carisoprodol-acetaminophen-caffeine showed moderate reduction in tender point pain in FM, although there was no HRQOL improvement.[23] There is little data on the role of other muscle relaxants on the treatment of FM.

Complementary Medicine & Alternative Therapies

As a relatively common syndrome of unknown etiology, FM has become a ripe target for alternative medicines, special diets, and treatment programs based in little scientific evidence. Providers must be cautious when discussing alternative treatments with patients, as many of these are difficult to monitor and control. At this time, there is no strong evidence to suggest that complementary or alternative therapies such as homeopathy, reiki, supplements, or mindfulness-based meditation provide any measurable benefit.[24] Acupuncture shows no benefit over placebo.[25] Routine supplementation of iron in FM patients without clinical anemia is also not recommended.[26] There is no correlation between FM severity and serum levels of vitamin A, C, E, or magnesium.[27]

While not specific to FM syndrome, hypovitaminosis D has been correlated to diffuse and persistent musculoskeletal pain without any other identifiable cause.[28] With a negligible side effect profile and affordable treatment, close monitoring of vitamin D levels and necessary supplementation should be considered for any patient presenting with nonspecific fatigue and musculoskeletal pain.

Whole-body warmth therapy has shown significant benefit in pain and symptom relief in multiple studies, and was reported as the first most effective treatment intervention in the German Fibromyalgia consumer reports.[29] Variations of warmth therapy such as warm baths were also reported as effective. Patients can be advised to take warm showers or baths for symptom relief, or utilize devices such as electric blankets or heating pads. Patients using contact heat therapy should be counseled on the risks of developing erythema ab igne secondary to prolonged exposure, particularly given the dysfunctional pain processing inherent in FM.

Equally effective to whole-body warmth therapy is transcutaneous electric nerve stimulation (TENS).[30] The advantage of using TENS therapy is the portability of TENS devices and the temporary restoration of central pain inhibition.[31] Benefits of treatment last as long as the stimulator is active, and patients are able to control the intensity and duration of the treatments. Perceived pain-related self-efficacy and locus of control in treatment reduce anxiety and increase response to intervention in other chronic pain conditions.

Gentle exercise is also a common suggestion, from both a general health and a pain reduction perspective. Yoga specifically has been shown to reduce the impact of fibromyalgia pain on a patient's quality of life, and decrease pain perception over time.[32] Beyond the physical benefit, formalized yoga programs that focus on mindfulness and stress reduction have also been shown to improve maladaptive pain-related behaviors such as catastrophizing and pain-related anxiety.[33]

NEW, EXPERIMENTAL TREATMENT

With the vast array of contributing factors and new research into mechanisms of FM symptoms, there have been many targets of new pharmacologic therapy. The hypothesis that mu-opioid receptor dysfunction leads to some FM symptoms has led to trials of naltrexone, an opioid-receptor antagonist, in an effort to increase pain inhibition.[34] While pilot studies show an improvement in symptoms, the paucity of research and small sample sizes of existing studies make it impossible to generalize these results to the greater population at this time.

Cannabinoids such as nabilone and medical cannabis show some preliminary positive benefit on sleep quality and duration with modest effects on pain; however, there have not been any studies on FM patients specifically.[35] Furthermore, this option is not legally available in most areas and there have been few studies on the

long term effects of cannabinoids. Legal clarification of the medical validity of cannabinoids and THC derivatives is necessary before recommending them as a treatment option.

OMT & MANUAL THERAPY

There is limited research on the role of osteopathic manipulation in the interdisciplinary treatment of FM, perhaps in part because there is no standard presentation and therefore no clear target for treatment interventions. Empiric treatment of specific dysfunctions may be warranted in individual cases; however, FM patients have a lower threshold for pressure than other chronic pain patients. This mechanical hyperalgesia may warrant the use of gentler and more indirect techniques. In one German consumer report, osteopathy was listed as the ninth most effective intervention in the treatment of fibromyalgia.[29] However; the lack of a true clinical trial makes it difficult to recommend specific treatments.

Massage is often sought by patients seeking relief of FM pain, however, targeted myofascial release shows significant benefit over Swedish massage in treatment of neck and back pain in FM.[36] Connective tissue massage has shown some temporary benefit in FM symptomology, although benefits are short-lived and treatments must be repeated every 3-6 months.[37] In the general population, manual therapies including spinal manipulation and spinal mobilization have measurable effects on the areas of the brain responsible for sensory integration and modulation of the pain experience.[38] Further research would be necessary to determine if this effect extends to the FM population, as patients have aberrant integration and processing of pain.

There is evidence that FM has some features of dysautonomia and sympathetic dysfunction.[39] Osteopathic treatments used to normalize sympathetic activity such as rib-raising could have positive benefits on symptom severity or duration. If future research were conclusive, this would be an area where Osteopathic physicians are uniquely suited to manage this aspect of the FM patient's care. There have been some studies showing OMT as an effective adjunct to medical management of FM,[40] and with new diagnostic criteria and an evolving understanding of the nature of FM, more research is necessary to develop effective treatments for pain control.

MENTAL HEALTH

Mental health is a primary concern with FM. Even patients with no initial presentation of psychiatric symptoms can develop anxiety and depression related to long-term uncontrolled pain and loss of independence. Withdrawal from favored activities and support networks can compound this issue. Providers should encourage patients to maintain community engagement as much as possible, and address mental health concerns as they arise. Control of depression and anxiety is associated with better health-related quality of life (HRQOL) outcomes and decreased duration and impact of pain.[41]

Psychological counseling services may also be beneficial, as poor coping skills can increase perception of pain and functional debility related to symptoms. Catastrophizing, pain anticipation, overgeneralization, and avoidance of situations that might exacerbate pain are all factors in lower HRQOL.[42]

CONCLUSION

It is the opinion of this author that the goal of FM treatment should focus not on a cure, but rather patient education and a collaborative approach to symptom management. A patient-centered approach improves pain-related anxiety and pain intensity,[43] both of which are significant contributors to debility and lower HRQOL. Evidence suggests that an intensive interdisciplinary approach to FM management leads to better quality of life.[44] However, we must consider the burden placed upon the patient using such an approach. If the goal is to improve independence and minimize the effects of FM, it may be a disservice to the patient to shuttle them from specialist to specialist or place them in an intensive program. Symptom relief may occur, but the patient's overall quality of life may suffer.

By providing care with a holistic approach to treatment and applying the Osteopathic tenets, primary care providers can provide integrated care in biological, psychological, and social dimensions of care. Physical therapy, occupational therapy, and specialized psychological services are only valuable pieces of the plan when they are properly integrated into the overall care for the patient.

Further research into the effects of specific manual treatments is necessary to characterize presentations of FM and identify treatment targets. With a broader clinical picture, Osteopathic physicians will be able to manage medication and manual treatment within a single visit, therefore increasing patient access to interventions and leading to better long-term clinical outcomes.

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REVIEW ARTICLE

Probiotic Clinical Considerations: Where do they fit?

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Interest in probiotic use for certain clinical conditions has substantially increased over the past few years. There is much research regarding probiotics as preventive, adjuvant, and primary therapeutic agents. While many studies have shown that probiotics have some efficacy, there is difficulty in determining a specific, evidence-based prescription. Studies have been limited by design due to limited sample sizes, high attrition rates, heterogeneous selection of probiotic type, and differing treatment lengths. It is not entirely clear which probiotic species is the best, but the evidence is promising for several clinical conditions. This article will answer some common questions concerning four broad clinical areas of suggested probiotic use: adult and pediatric diarrheal illness, genitourinary infections, atopic dermatitis, and upper respiratory tract infections. Probiotic safety and quality will also be discussed. In the age of increasing antibiotic resistance and the emerging role of the gut microbiome in health, further research is encouraged in the development of probiotics going forward.

INTRODUCTION

There is a growing interest in probiotic use for health benefits and disease treatment strategies. Probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host."[1] The term probiotic comes from the Greek word "for life" and has been identified as bacteria or yeast in certain dietary supplements and foods. The most common probiotics available include bacteria *Lactobacillus* and *Bifidobacterium*, and yeast *Saccharomyces boulardii*. Probiotics as single species or combinations of multiple species are found in products over the counter including yogurt, dairy drinks, capsules, tablets, packets, and sachet powders. Each probiotic has unique qualities but there is little evidence supporting various species combinations when advertised for synergy.[2] There is no known class effect regarding species and health benefits.[2, 3] Table 1 *(page 22)* lists the types of probiotics found in many available products.

Probiotic Mechanisms of Action

Several characteristics of probiotics have been reported to play a role in health. These include the ability to 1) transit through and survive in the gastrointestinal (GI) tract, 2) colonize and reproduce in the gut by adherence, 3) modulate the host immune system and block pathogens, and 4) balance homeostasis of the gut flora. Other important characteristics include quality manufacturing practices that ensure shelf life stability and the development of probiotics that are not pathogens.[2, 4]

Probiotic Safety

Probiotic safety and research is limited. Adverse effects reported have been minimal and are primarily GI in nature. Didari et al. conducted a systematic review in 2014 of clinical studies using common probiotic species that included *Bifidobacterium*, *Lactobacillus*, *Saccharomyces boulardii*, *Streptococci*, *Enterococcus*, *Propionibacterium*, and *Escherichia coli species Nissle 1917*. Their observations determined that "overwhelming existing evidence suggests that probiotics are safe;" however, there were some studies that reported adverse risks including fungemia, sepsis, and GI ischemia.[5] This review highlighted an important connection between serious illnesses and certain high risk patient groups including those who were hospitalized, immunocompromised, post-operative, in the intensive care unit, and critically sick infants. For example, several cases of fungemia caused by S. boulardii were identified in critically ill patients who had central venous catheters.[5] The National Institutes of Health (NIH) acknowledges many studies demonstrate probiotic safety with certain species, but advises caution about applying this to all probiotics.[2,4]

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TABLE 1:

Microorganisms Considered Probiotics[2]

Bacteria		Other	Yeast
Lactobacillus species (LAB)	*Bifidobacterium species*	*Bacillus cereus*	*Saccharomyces boulardii (S. boulardii)*
L. acidophilus	*B. adolescentis*	*Enterococcus faecalis*	
L. bulgaricus	*B. animalis*	*(considered pathogenic)*	
L. casei	*B. bifidum*	*Enterococcus faecium*	
L. cripatus	*B. breve*	*(considered pathogenic)*	
L. fermentum	*B. infantis*	*Escherichia coli Nissle (E.coli)*	
L. gasseri	*B. lactis*	*Streptococcus thermophiles*	
L. johnsonii	*B. longum*		
L. lactis			
L. pantarum			
L. reuteri (LR)			
L. rhamnosus GG (LGG)			

TABLE 2:

Yale / Harvard 2015 Workshop Probiotic Expert Recommendations[6]

A	Based on strong, positive, well-conducted, controlled studies in the primary literature, not abstract form
B	Based on positive, controlled studies but the presence of some negative studies
C	Based on some positive studies but clearly an inadequate amount of work to establish the certainty of "A" or "B"

Probiotic Quality

The majority of probiotic products are sold as dietary supplements which are not subject to Food and Drug Administration (FDA) approval before marketing. In order for a specific probiotic to be marketed as a drug for clinical treatment, more stringent studies must be performed to meet the FDA requirements. Many probiotic advertisements make online statements regarding safety and health promotion, but they cannot make disease prevention claims without FDA regulation.[2,4]

Finding high quality commercial probiotics can be challenging. First, manufacturing processes may damage viable microorganisms.[3] Second, clinical studies have raised concern regarding the species composition in current products along with the lack of universal quality assurance programs. The label or manufacturing process may state "generally recognized as safe" (GRAS), but this applies to food supplements and is not supported by FDA quality or safety standards as indicative of therapeutic benefit.[2,4] Finally, many products available online need to be stored in a cool environment which makes receiving probiotics in the mail subject to quality concern.[2,5]

This article will focus on answering common questions regarding four broad clinical areas of suggested probiotic use: adult and pediatric diarrheal illness, genitourinary infections, atopic dermatitis, and upper respiratory tract infections. Each section will include a discussion of recent evidence from meta-analyses and systematic reviews. Additionally, recommended evidence ratings from the Yale/Harvard 2015 Workshop of probiotic experts will be included *(Table 2)*.[6]

SHOULD PROBIOTICS BE RECOMMENDED FOR USE FOR GASTROINTESTINAL CONDITIONS, SUCH AS DIARRHEA, INFLAMMATORY BOWEL DISEASE, OR IRRITABLE BOWEL SYNDROME?

The administration of probiotics improves gut colonization with enteric flora. Theoretical benefits include restored gut barrier function, improved mucosal immunity, reduced inflammation, and improved bile acid metabolism.[7] A variety of probiotic formulations have been studied for gastrointestinal conditions, but each report has a high degree of variability in species, dosing, and research endpoints.

Diarrhea - Recommended for Acute Infectious Diarrhea & Antibiotic Associated Diarrhea

Acute infectious diarrhea (AID) can be viral, bacterial, or parasitic in nature. These types of infections are most commonly treated with rehydration and anti-diarrheal agents. As adjunctive therapy, probiotics modify gut pH, compete with the infectious agent for nutrients, and may improve the immune response. The use of probiotics for the treatment of AID was evaluated in a 2010 Cochrane systematic review of 63 randomized controlled trials (RCTs). Most trials evaluated *LGG* and *S. boulardii* and included AID of any

infectious origin. In addition, 18 trials specifically reported data from rotavirus infection in children. Overall, probiotics reduced the duration of diarrhea by a mean of 24.8 hours (95% CI, 15.9 to 33.6) and reduced the risk of diarrhea lasting 4 days or longer (RR 0.41, 95% CI 0.32 to 0.53).[8]

Broader studies of probiotics as adjuvant to rehydration for acute gastroenteritis in children have been found to decrease the duration of symptoms. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) supports with strong recommendation the use of *LGG* and *S. boulardii* for 5 to 7 days in otherwise healthy children. However, these recommendations are based upon low quality evidence, unclear randomization protocols and study blinding, and varying definitions of clinical endpoints.[9] The Yale/Harvard 2015 Workshop expert panel also supports the use of *LGG*, *S. boulardii*, and *L. reuteri* with an "A" recommendation. The use of *L. reuteri* is given a weaker but also positive recommendation from ESPGHAN.[6,9] Notably, ESPGHAN published a strong recommendation against the use of *E. faecium* SF 68 due to safety concerns with vancomycin resistance.[9]

Antibiotic-associated diarrhea (AAD) results from disruption of the normal gut microflora. Because discontinuation of antibiotics for a clinical condition is not usually recommended, prevention of AAD is a preferred strategy. Several recent meta-analyses evaluated the use of probiotics for prevention of AAD. Videlock et al. evaluated 34 placebo-controlled studies of probiotics and found a reduced risk of AAD (RR 0.53; 95% CI 0.44 to 0.63).[10] Hempel et al. reviewed 63 studies and found a similar risk reduction (RR 0.58; 95% CI 0.50 to 0.68).[11] Goldenberg et al. evaluated 23 trials of the use of probiotics to prevent AAD in patients up to 18 years of age, also demonstrating a lower risk of AAD (RR 0.46; 95% CI 0.35 to 0.61).[12] All authors identified significant heterogeneity between studies. Participants in the Yale/Harvard 2015 Workshop support the use of *S. boulardii*, *LGG*, and a combination of *Lactobacillus/Streptococcus thermophilus* species for AAD with an "A" recommendation.[6]

Data are more variable on the use of probiotics for the prevention of *C. difficile*-related diarrhea.[6] The American College of Gastroenterology (ACG) does not support the use of probiotics for treatment or prevention of *C. difficile* diarrhea. They further caution against probiotic use among immunocompromised patients.[13]

Irritable Bowel Syndrome (IBS) - Weakly Supported

Irritable bowel syndrome (IBS) is defined by the ACG as "abdominal discomfort associated with altered bowel habits.[14] The Rome III criteria is often applied in the research setting. This criteria specifies IBS as the recurrence of abdominal pain or discomfort for at least 3 days per month over 3 months, and the presence of at least 2 of the following findings: onset of symptoms associated with a change in either stool frequency and/or appearance and improvement of symptoms with defecation. Patients can be further categorized into four subtypes based upon bowel patterns: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed type (IBS-M), and unclassified (IBS-U).[14]

The pathophysiology of IBS is complex and not fully defined. A disruption in the gut-brain connection leading to visceral hypersensitivity has been hypothesized as an underlying cause. Additional theories have implicated serotonergic, immunologic, genetic, and psychosocial contributors. Alterations in the gut microbiome and the function of the gut barrier have been the focus of recent investigations.[7]

Therapeutic options for IBS range from dietary changes that increase fiber intake and restrict gluten or FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) to pharmacologic treatments. Traditional use of antispasmodics and antidepressants has expanded to several symptom-specific options for IBS-D (alosetron, eluxadoline) and IBS-C (linaclotide, lubiprostone).[14, 15, 16] The possible contribution of an altered gut microbiome has prompted the investigation of antimicrobial agents (e.g., rifaximin, metronidazole) and probiotics as potential therapeutic options.[14, 15]

The ACG supports a "weak" recommendation for the use of probiotics for IBS.[14] A similar grade is noted by the Yale/Harvard 2015 Workshop expert panel with a "B" recommendation for *B. infantis* and VSL #3.[6] The ACG guideline cites literature that identifies a positive impact of probiotics on "global symptoms" including abdominal pain, flatulence, and bloating.[14] The guideline does not support any recommendation for a particular probiotic over another due to variable data. A 2014 meta-analysis found probiotics were associated with a lower risk of IBS symptoms persisting after treatment when compared with placebo (RR 0.79; 95% CI 0.70 to 0.89).[17] The probiotics most commonly included *Lactobacillus*, *Bifidobacterium*, *Escherichia*, and *Streptococcus* species, but products varied widely in formulation and dosing. These probiotics appeared to be well tolerated; however, further evidence suggested a higher risk for adverse events including abdominal pain and bloating, versus placebo (RR 1.21; 95% CI 1.02 to 1.44).[17]

Many unanswered questions about the clinical role of probiotics for IBS remain. A trial of probiotics seems to be a reasonable option, particularly for patients complaining of abdominal pain, flatulence, and bloating. However, the optimal probiotic formulation and dose have not been determined, requiring further studies for clarification.

Inflammatory Bowel Disease (IBD) - Recommended for Ulcerative Colitis

Inflammatory bowel disease, including ulcerative colitis (UC) and Crohn's disease (CD), is often characterized by features of abdominal pain and diarrhea. Conventional therapeutic interventions focus on acute management of symptoms followed by maintenance of remission utilizing various anti-inflammatory and immune modulating agents.[18,19] Although pathophysiology of the two conditions is not well understood, a recent interest in the gut microflora immune and inflammatory response has stimulated investigations into the role of probiotics.

Studies of probiotics in UC have focused primarily on the use of VSL#3 and *E. coli* Nissle species. Their use has been targeted for induction and maintenance of remission. In a meta-analysis, Fujiya et al. found that probiotics appeared as effective as mesalazine for prevention of remission (RR 1.00; 95% CI 0.79 to 1.26).[20] The Yale/Harvard 2015 Workshop expert panel assigned a "B" recommendation for the induction of remission and an "A" recommendation for maintenance of remission.[6]

The prevention of pouchitis, an inflammatory condition occurring after an ileal pouch-anal anastomosis procedure for UC appears to be another promising therapeutic use. A recent systematic review showed that probiotic formulation VSL#3 (containing several *Lactobacilli* and *Bifidobacterium* species plus *S. thermophilus*) prevented pouchitis and maintained remission at higher rates than placebo.[21] Participants in the Yale/Harvard 2015 Workshop support the use of VSL #3 with an "A" recommendation.[6]

The evidence regarding the use of probiotics in CD is limited. Studies of probiotics for CD have yielded conflicting data, offering a "C" recommendation from the expert panel at the Yale/Harvard 2015 Workshop.[6] The ACG recommends that further investigation of probiotics is necessary before supporting use in CD.[18]

SHOULD PROBIOTICS BE RECOMMENDED IN FEMALE GENITOURINARY TRACT INFECTIONS: BACTERIAL VAGINOSIS, VULVOVAGINAL CANDIDIASIS, & RECURRENT URINARY TRACT INFECTIONS?

The female genitourinary tract is predominantly colonized by *Lactobacilli* (LAB) species. Changes in the vaginal microbiota can lead to genitourinary tract infections including bacterial vaginosis (BV), vulvovaginal candidiasis (VVC), and recurrent urinary tract infections (UTIs). This disruption or "vaginal dysbiosis" can be caused by the use of broad spectrum oral antibiotics, changes in sexual partners, menopause, diabetes, obesity, poor hygiene, and elevated vaginal pH. This most likely occurs through intestinal colonization by pathogenic bacteria which enter the vagina from the rectum.[2,22] The mechanisms of action (correction of dysbiosis) proposed for the predominant LAB species found in the genitourinary tract involves 1) lowering the pH by producing lactic acid and hydrogen peroxide, 2) producing bacteriocins toxic to pathogenic bacteria, and 3) blocking pathogenic bacteria adhesion to the genitourinary epithelium. Collectively, this decreases genitourinary colonization of pathogenic bacteria and maintains a healthy balance.[22, 23, 24]

Several studies using either oral or intravaginal probiotics for the treatment or prevention of genitourinary infections have been performed. Studies have used two approaches: primary therapy using probiotics alone (either single species or a combination of species) or additive therapy to conventional treatment. Interpretation of data from several well organized RCTs is challenging because variations were used in study design, probiotic species, treatment length, and patient follow-up.[23, 24, 25]

Bacterial Vaginosis - Probiotic Recommended as Adjuvant

BV is one of the most frequent vaginal infections in the world and results from the overgrowth of bacteria in the genitourinary tract, most commonly *Gardnerella*, *Atopobium*, and *Prevotella*. The overgrowth of these bacteria can raise the pH creating vaginal dysbiosis. Symptoms include pruritus, vaginal discharge, and dysuria. BV is typically treated with metronidazole or clindamycin, either orally or intravaginally. However, failure and recurrence rates are estimated at 30-40%.[2, 23]

One of the first reported meta-analyses of RCTs regarding the effects of probiotics for the treatment of BV was published in 2014 by Huang et al. This study included 1,304 individuals from 12 RCTs with a primary outcome specifically for BV cure rate. Authors concluded that "probiotics show a beneficial effect in patients who are suffering from BV" [RR 1.53; 95% CI 1.19 to 1.97]. They further examined a subgroup of the 9 highest quality studies and determined that probiotics either orally or intravaginally were effective either alone or in combination with conventional antibiotics for the treatment of BV [RR 1.60; 95% CI 1.16 to 2.22].[24] A literature review by Homayouni et al. in 2014 included several of these studies and reported similar conclusions.[25]

Many experts state the preferred probiotic delivery route should be intravaginal but online searches suggest this type of product is limited.[22, 24, 25] Several oral products are available, but the viability of probiotics to survive the gut and finally enter the GU tract was not thoroughly investigated in clinical trials. Timing of GU colonization after oral administration was not consistent and further studies are recommended.[24, 25]

Considerable heterogeneity was found among the type of probiotic used in the meta-analyses.[24] For example, Ya et al. randomized 117 Chinese women with BV to vaginal probiotic capsules (Probalac Vaginal: containing 108 CFU of *L. rhamnosus*, *L. acidophilus*, and *Streptococcus thermophilus*) versus placebo. Patients used probiotics for 7 days on and then omitted for 7 days, alternating this schedule for 30 days. Conversely in a different study, Bradshaw et al. randomized 268 women with BV to oral metronidazole 400 mg BID for 7 days followed by vaginal pessary use daily containing *L. acidophilus KS400* ≥ 107 CFU and 0.03 mg of estriol for 12 days, versus oral metronidazole 400 mg BID for 7 days followed by vaginal pessary placebo for 12 days. The women in this study were followed for 180 days.[24]

The Yale/Harvard 2015 Workshop expert panel offered a recommendation level "C" regarding probiotics for BV treatment.[6] However, given the general safety of probiotics, they should be considered as adjuvants either orally or intravaginally for women with BV.[3, 24, 25] In several studies, *L. rhamnosus* and GR-1 and *L. reuteri RC-14* were found effective for the treatment of BV when added to standard metronidazole therapy.[6,22,24,25] Similar probiotics may be found online and include UltraFlora (oral) by Metagenics, FemDophilius (vaginal) by Jarrow, and Terbiotics (oral) by Klaire Labs. *(See Table 3, page 26)* These products have not been approved by the FDA.

Vulvovaginal Candidiasis - Insufficient Evidence to Recommend

Vaginal dysbiosis may also lead to an overgrowth of *Candida* species with the most common type as *Candida albicans*.[22] VVC symptoms include vaginal discharge, dysuria, and pruritus. Many studies report the use of either oral or intravaginal *LGG*, *L. rhamnosus*, *L. reuteri*, and *L. acidophilus* for use in women with a history of recurrent VVC.[2,6,26] However, most studies to date have had small sample sizes, lacked statistical significance, or had high attrition rates.[26] Although probiotics are considered safe for use in most women, the use of probiotics for the primary treatment or added to conventional therapy has not been supported.[3,22] Furthermore, probiotics for VVC should not be used as primary treatment because LAB does not compete with *Candida* colonization. Only conventional anti-infectives will eliminate *Candida* thus allowing LAB to establish homeostasis.[22]

Recurrent Urinary Tract Infections - Weakly Supported

Urinary tract infections are common including infection of the kidney, ureter, urethra, or bladder. The most common pathologic bacteria is *E. coli*, a gram positive cocci.[27, 28] UTIs can be asymptomatic or symptomatic with cloudy urine, pyuria, urgency, frequency, and hematuria. Ascending infection may cause flank pain, fever, and chills. Mortality increases among the elderly and immunocompromised with UTIs.

Historically, probiotic research targeting UTIs increased in the 1980's. Authorities confirmed that vaginal dysbiosis, including the depletion of healthy LAB, leads to an increased rate of UTI recurrence in many patients. In the development of probiotics and in-vitro research studies, attempts to displace gram-positive cocci adhesion were made by adding *L. reuteri RC-14* to *L. rhamnosus GR-1*. Many studies showed promising results, but the quality and design of several clinical trials were questioned.[27]

In response, a 2010 Cochrane systematic review by Schwenger et. al evaluated probiotics (any formulation) versus placebo (no therapy) for prevention of UTIs in susceptible patients. They included 9 studies with 735 individuals and measured rates of UTI recurrence with probiotic or placebo. These studies were also challenged by high risk of bias, small sample sizes, and insufficient methodological detail. The authors reported that "a benefit could not be ruled out due to insufficient data" and more research in this area is needed. It has been further discussed that BV infection may increase the risk of recurrent UTIs.[29] Due to the promising use of probiotics for the treatment of BV, a plausible link between probiotics and prevention of both BV and UTIs may emerge in the near future.

SHOULD PROBIOTICS BE RECOMMENDED FOR THE PREVENTION OR TREATMENT OF ATOPIC DERMATITIS?

Recommended in Specific Clinical Situations

Atopic dermatitis (AD) is widely considered an inflammatory skin condition in all ages, but infants and children are more commonly affected. Clinical conditions vary in severity and frequent exacerbations are reported. Patients report itching, pain, and discomfort, which can significantly affect activities of daily living and sleep quality. AD standard therapy includes emollients and topical steroids.

The underlying pathophysiology of AD involves a complicated cellular immune response between the skin as a barrier and the bacteria that normally colonize the surface. Given the role of probiotics with respect to GI immune response and inflammation, and the general safety of probiotics, studies have demonstrated a possible role in AD.[30, 31, 32] Interestingly, it has also been reported that children who have slow development of both LAB and *Bifidobacterium* in the GI tract were found to be more susceptible to allergies.[32]

Specific use of probiotics LAB and *Bifobacterium* for the prevention of Pediatric Atopic Dermatitis (PAD) is recommended by the Yale/Harvard 2015 workshop experts.[6] Additionally, the World Allergy Organization (WAO) performed a systematic review in 2015 providing conditional recommendations for the prevention of PAD in high risk infants. Infants at risk were defined by having any biological parent or sibling with a history of allergic rhinitis, asthma, eczema, or food allergy.[33] The WAO further recommended for this risk group oral probiotic use by the mother during pregnancy and breastfeeding, and in infants who were not breastfed. The most significant risk reduction in PAD was reported when probiotics were used during pregnancy (RR 0.72, 95% CI 0.61 to 0.85) and when given to infants (RR 0.81, 95% CI 0.70 to 0.94).[33]

The American Academy of Dermatology published review by Baquerizo et al. reports several meta-analyses regarding the risk reduction of PAD with the use of prenatal and/or postnatal probiotics. In an analysis of 16 trials with probiotics (LAB and *Bifobacterium*) the risk of PAD was reduced by 20-24% (RR 0.79). This review recommends starting LAB orally for the mother during the last 2 weeks of pregnancy and continuing for the first three months post-delivery. The review did not state if the probiotics should be taken by the mother or the infant during post-delivery.[30] Other recommendations suggest *L. rhamnosus* orally for the mother during the last 4 weeks of pregnancy and for the first 6 months of breastfeeding with a transition to oral probiotics to the infant continuing until age 2.[34]

With respect to the treatment of AD, probiotic use has been supported by clinical trial evidence. The Yale/Harvard 2015 workshop experts support a level "A" recommendation for the use of LGG and *B. lactis* in the treatment of AD associated with cow's milk allergy.[6] In addition, a recent 2014 meta-analysis of 25 clinical trials (n=1,599) by Kim et al. assessed the treatment of all AD using probiotics. The endpoint of the study included any change in the Scoring of Atopic Dermatitis (SCORAD) symptoms scale. For all ages the SCORAD decreased by a mean of 4.51 points (95% CI -6.78 to -2.24). The most significant symptom reduction was found among patient ages 1-18 (-5.74, 95% CI -7.27 to 14.20) and was not found effective in infants <12 months. Considerable heterogeneity was found among all studies; however, probiotic species reported most beneficial included LAB or a combination of LAB with *Bifidobacterium*.[32]

SHOULD PROBIOTICS BE RECOMMENDED FOR THE PREVENTION OR TREATMENT OF UPPER RESPIRATORY TRACT INFECTIONS?

Weak support

Upper respiratory tract infections (URTIs) include viral and bacterial infections such as colds, sinusitis, and pharyngitis. Several systematic reviews have recently assessed probiotic effectiveness in prevention of or shortening duration of URTIs.[35, 36, 37] Probiotics may prevent URTIs by reducing the colonization of pathogenic bacteria in the GI tract, removing bacterial toxins, and enhancing humoral immune responses.[38, 39]

Probiotics may be more effective than placebo for prevention of URTIs in adults according to a Cochrane meta-analysis published in 2015 that included twelve RCTs (n=3,720).[35] Fewer patients in the probiotic group versus the placebo group were diagnosed with one episode of URTI (OR 0.53; 95% CI 0.37 to 0.76). The mean duration of the URTI was less in the probiotic patient group (mean difference -1.89 days; 95% CI -2.03 to -1.75). While probiotics in this review seemed to be more effective than placebo, the quality of evidence in these studies was low.[35]

Another meta-analysis reported similar results in 2014. In this review of 20 clinical trials (n= 3,350) the duration of URTI symptoms with probiotic use of *Lactobacillus* or *Bifidobacterium* versus placebo suggested shorter illness courses.[36] The duration of probiotic therapy use ranged from three weeks to seven months and patients in the probiotic intervention group had shorter illness by ½ - 1 day compared to placebo (weighted mean difference -0.77; 95% CI -1.5 to -0.04). The probiotic group had less work or school absenteeism (mean difference -0.17; 95% CI -0.31 to -0.03). Similar to the Cochrane meta-analysis, clinical trial design varied and although probiotics were more effective than placebo, the quality of evidence was low.[35, 36]

SUMMARY

Although there are many studies regarding the use of probiotics for a wide variety of conditions, there is no consensus on the most appropriate species, dose, and products to recommend. The Yale/Harvard 2015 workshop experts provide important guidance through their published evidence ratings for certain clinical conditions.[6] Some products are included in Table 3 for consideration. These products have not been fully evaluated by the FDA with quality and safety studies. In the age of increasing antibiotic resistance and the emerging role of the gut microbiome in health, further research is encouraged in the development of probiotics going forward.

TABLE 3:

Summary of Probiotic Recommendations[2, 6, 24]

Clinical Condition & Species (Harvard/Yale 2015 Workshop Rating*)	Product Examples & Species Type in Product**	Approximate Cost
Diarrhea Treatment of acute infectious diarrhea in children (A*) *L. rhamnosus (LGG)* *L. reuteri* *S. boulardii* Prevention of Antibiotic Associated Diarrhea (A*) *S. boulardii* *LGG* Combination of probiotics including: *L. bulgaricus, S. thermophiles, L. casei*	Danimals Yogurt *LGG* (amount not specified) (contains dairy) Culturelle (ConAgra Foods) *LGG* 10 Billion per tablet Florastor (Biocodex) Yeast: ***S. boulardii*** 250 mg/capsule or packet DanActive (Dannon, Canada) ***S. thermophilus, L. bulgaricus, & L. casei*** > 10 billion per 93 ml bottle - ***(Contains Milk)***	$5 for 12 pack (Walmart) www.danimals.com $21 for 30 tablets (Drugstore.com) www.culturelle.com $48 for 100 capsules (Costco) www.florastor.com $8 for a Pack of 8 bottles (Amazon) www.danone.ca/en/products/danactive
Inflammatory Bowel Disease Ulcerative Colitis (UC) Pouchitis Prevention & maintenance (A*) VSL#3 UC Maintenance of Remission (A*); Induction of Remission (B*) *E. coli Nissle or VSL#3*	VSL #3 (Sigma-Tau Pharmaceuticals) *L. casei, L. plantarum, **L. acidophilus, L. bulgarius, B. longum, B. breve, B. infantis & S. thermophilus*** 450 billion in a packet & 112.5 billion in a capsule Prescription strength (VSL#3-DS) 900 billion	$88 for 30 pack capsules or packet www.vsl3.com
Irritable bowel Syndrome (B*) *B. infantis 35624* or VSL #3	Align (Proctor and Gamble) - ***B. infantis 35624*** contains 1 billion CFU and (1 x 107 CFU) until at least the "best by" date. ***(contains milk)***	$30 for 28 capsules (Drugstore.com) www.metawellness.com
Vaginitis & Vaginosis (C*) *Lactobacillus rhamnosus GR-1* *Lactobacillus rhamnosus GR-1 & L. reuteri RC14* *L. acidophilus*	UltraFlora Women's (Metagenics) ***L. rhamnosus GR-1 and L. reuteri RC14*** 2 Billion (contains milk) Fem-Dophilus (Jarrow Formulas) ***L. rhamnosus GR-1 and L. reuteri RC14*** 5 Billion (contains dairy)	$31.95 for 30 capsules www.metagenics.com $13 for 30 capsules (Amazon) www.jarrow.com
Atopic eczema associated with cow's milk allergy Treatment & prevention (A*) *LGG* *B. lactis*	Culturelle (ConAgra Foods) *LGG* 10 Billion per tablet	$21 for 30 tablets (Drugstore.com) www.culturelle.com

**Yale/Harvard 2015 Workshop grade applies to the species type and clinical condition. It does not represent a rating for the product example listed. "A" recommendation is based on strong, positive, well-conducted, controlled studies in the primary literature, not abstract form. "B" recommendation is based on positive, controlled studies but the presence of some negative studies. "C" recommendation is based on some positive studies but clearly an inadequate amount of work to establish the certainty of "A" or "B".*

*** Product examples are commonly found in stores or online, but do not represent all available products on the market. These products have not been fully evaluated by the FDA and are not intended to diagnose, cure, treat, or prevent any disease.*

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REVIEW ARTICLE

Medical Management of Anemia in the Surgical Patient

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Keywords:

Anemia

Blood Transfusion

Surgical Patient

Iron Supplementation

Hemoglobin

Hematology

Anemia is defined as a medical condition in which the body does not have enough healthy red blood cells in order to provide oxygen to the body tissue. This article serves to review the clinical presentation, work-up and management of anemia, specifically anemia that is seen in pre/postoperative patients. Similar to hypertension, anemia can often go unnoticed if mild and if severe can cause irreversible damage, including death. An efficient, simple way to evaluate for anemia in a patient is to obtain a Complete Blood Count (CBC). There are endless etiologies that may cause anemia including but not limited to medications, chronic disease, cancers, pregnancy, malnutrition and trauma. In surgical patients, anemia has been linked to increased postoperative morbidity and mortality despite being a medical condition that can be treated. Primary care physicians can become a crucial component in the preoperative preparation and postoperative treatment of anemia in their surgical patients. In order to efficiently achieve maximum surgical success, patients must be educated about the common symptoms seen with anemia in addition to regular primary care physician visits. With the proper treatment of anemia, patients will have a decreased risk of postoperative complications including a decreased cost of care, infections and length of hospital stay.

INTRODUCTION

The major contributor to red blood cell production in the human body is the bone marrow. Healthy red blood cells last between 90 and 120 days.[1] When old red blood cells are removed from the body, a hormone called erythropoietin, which is made in your kidneys, signals your bone marrow to make more red blood cells.[1] When the body does not have the necessary building blocks to make more red blood cells, anemia ensues. It is estimated that one-third to one-half of surgical patients may be anemic preoperatively secondary to the conditions for which they require surgery. After surgery, anemia is even more common, found to affect nearly 90% of the patients.[2] Anemia should be viewed as a significant clinical condition, rather than simply an abnormal laboratory value.[3] Whether to transfuse the patient or administer iron supplementation with or without erythropoietin remains controversial to this day. Research on universal treatment guidelines for pre/postoperative patients has largely been ignored. A more efficient and agreeable approach to treating perioperative anemia has the potential to reduce medical costs and possible complications that anemic patients may experience.

METHODS

The National Center for Biotechnology Information PubMed database was used as the primary source of references used to complete this review. Keywords and phrases searched include pre/postoperative anemia, causes of anemia, anemia treatment, transfusion complications, iron supplementation, erythropoietin and anemia guidelines. Medscape and Google were also used to access reference information. Material published with an emphasis on pre/postoperative patients was included in the compilation of this review.

PATHOPHYSIOLOGY OF ANEMIA & RISK FACTORS

Inflammatory cytokines after surgery and trauma invoke a response characterized by, among other effects, decreased iron uptake from the gastrointestinal tract and iron sequestration in macrophages, along with a diminished erythroid response to erythropoietin.[4] Other contributory causes to postoperative anemia include pre-existing preoperative anemia and trauma/surgical blood loss. Added to these is an element of hemodilution occurring as a result of fluid replacement before, during, and after surgery.[4] Common causes of anemia not related to surgery that should be checked preoperatively include chronic diseases, cancers, malnutrition, thalassemia and certain medications. The body needs certain vitamins, minerals, and nutrients to make enough red blood cells. Iron, vitamin B12, and folic acid are three of the most important ones required for red blood cell production.[1] Several studies have shown that patients with preoperative anemia have a higher incidence of needing an allogeneic blood transfusion, compounding the problems from anemia which may include a longer hospital stay and an increased likelihood of death after surgery. Patients who are transfused after surgery as a result of anemia are more likely to develop postoperative infection, require longer periods of mechanical ventilation, and have a greater risk of mortality.[5]

CLINICAL PRESENTATION

Educating patients on the symptoms of anemia can help when obtaining the history of present illness and give a more definitive

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time of onset of symptoms. Depending on the severity of anemia, patients may either be asymptomatic or present with nonspecific complaints including feeling grumpy, generalized weakness, fatigue, headaches and problems concentrating initially.[1] It is important to take into consideration that feeling tired when recovering from surgery is very common as surgery puts an extreme stress on the body. If the anemia worsens, one could expect a patient to have pale skin, develop pica, dyspnea, develop brittle nails and complain of a sore tongue.[1] Some pertinent exam findings seen in an anemic patient include new onset heart murmur, low blood pressure (especially with standing), pallor and tachycardia.[1] If any of the above symptoms/findings are met and there is a clinical concern for anemia, baseline laboratory orders should include a CBC, vitamin B12/folate level and an iron/ferritin level.

RESULTS

When a CBC is drawn post operatively and the patient's hemoglobin is found to be low, there are generally two treatment options: a transfusion or iron supplementation. Many patients that are placed on iron supplementation only have a hemoglobin level checked and are not further evaluated to see if they are actually iron deficient. Several studies have been performed evaluating the effectiveness of administering oral iron supplementation versus not supplementing iron in postoperative patients. In a recent study published, focusing specifically on anemia in elderly patients who had undergone hip surgery, the population of patients was divided into an experimental group, receiving ferrous sulfate orally four times a day for the duration of their hospitalization and a control group, which did not receive any supplementation.[6] After analysis, there was no significant difference in mean hemoglobin levels between the treatment and control groups (95% confidence interval [CI]) and a conclusion was subsequently made that the administration of oral iron supplements to elderly, healthy orthopedic patients postoperatively did not hasten the recovery of hemoglobin levels, provided adequate tissue iron stores were present.[6]

Furthermore, there was an additional study published that was conducted to determine if early recovery from severe post-operative anemia is accelerated by intravenous (IV) iron therapy alone or in combination with recombinant erythropoietin (EPO).[7] In this double-blinded, placebo controlled randomized study, there was no clinical significant difference between the treatment and control groups and a conclusion was subsequently made that early postoperative treatment with IV iron alone or in combination with EPO does not appear to accelerate early recovery from postoperative anemia.[7] The majority of the literature searched showed similar conclusions on postoperative anemia treatment leading to the conclusion that the prescription of iron to all anemic patients immediately post-operatively should be avoided and only used if the patient is found to be truly iron deficient.[4]

MANAGEMENT

The overall prevalence of anemia in the general population increases with age, so that in the elderly (>65 yr old), the prevalence of anemia as defined by the World Health Organization (WHO) is 11% and 10.2% for men and women, respectively.[8] According to current guidelines from the American Society of Anesthesiologists, RBC transfusion is recommended if the hemoglobin concentration drops below 6–10 g/dl. Transfusions over 10 g/dl are rarely indicated, and transfusions are generally indicated if hemoglobin falls below 6 g/dl.[9] Allogeneic transfusion is a common treatment for perioperative blood loss resulting in low postoperative hemoglobin, but it has a number of well-recognized risks, complications *(Table 1, page 30)*, and costs.[9] Iron supplementation is another common treatment for anemia, however, this really only has an effect if the patient is truly iron deficient, which a large portion of postoperative patients are not.[4]

The most effective strategy to avoid postoperative anemia and transfusion therapy is to identify and correct preoperative anemia whenever possible.[4] While hemoglobin screening is included in standard pre-admission testing, it usually occurs only 3-7 days prior to surgery.[5] This does not provide enough time to effectively evaluate and manage a patient who is found to be anemic. Whenever clinically feasible, elective surgical patients should have their hemoglobin level tested a minimum of 30 days before the scheduled surgical procedure. This allows for adequate evaluation and treatment if a patient is found to be anemic preoperatively.[5]

When a patient is found to have unexplained anemia, a secondary cause should be evaluated because treatment of this problem may resolve the anemia. When a hemoglobin returns low, laboratory testing must be performed to further evaluate if the anemia is from nutritional deficiencies, chronic renal insufficiency, and/or chronic inflammatory disease.[10] If a screening CBC detects anemia, evaluation should begin with an assessment of iron status. The assessment of iron-restricted erythropoiesis needs to distinguish between absolute iron deficiency, iron sequestration due to inflammation, and/or functional iron deficiency due to erythropoietin stimulation.[11] The accurate differentiation of these is difficult using traditional biochemical markers of iron status, such as serum iron, percentage saturation of transferrin, and serum ferritin.[12] As ferritin is an acute-phase reactant, traditional laboratory thresholds of <12 µg/L (1 ug/L = 1 ng/ml) may be suitable for identifying absolute iron deficiency in normal individuals, but not in patients with any evidence of an inflammatory process.[13] For patients without chronic renal disease, ferritin levels >100 µg/L confirm the presence of stored iron.[10]

When absolute iron deficiency is detected, consideration to pursue a work-up to rule out a gastrointestinal malignancy as a source of chronic blood loss is indicated.[14] If laboratory evaluation or a diagnostic trial of iron therapy rules out absolute iron deficiency, measurement of serum creatinine and glomerular filtration rate (GFR) may indicate CKD with further management directed by the level of renal disease.[14] If ferritin, iron saturation values, and/or other markers of iron-restricted erythropoiesis are inconclusive, further evaluation to rule out iron deficiency or iron sequestration due to inflammation/chronic disease is necessary. A therapeutic trial of oral iron therapy would confirm absolute iron deficiency .[10] If there is no response to iron therapy, one cannot rule out absolute iron deficiency as this may possibly be caused by patient non-compliance[11] ongoing blood (iron) losses in excess of oral iron absorption[15] and/or diminished gastrointestinal absorption of iron due to inflammation.[12] Using the above mentioned recommendations preoperatively will significantly decrease the patient's postoperative morbidity and mortality risk. Furthermore, if preoperative anemia is treated, there is less of a chance that the patient will need a transfusion or iron supplementation (if found to be iron deficient) after surgery.

TABLE 1:

Incidences of potential risks associated with allogeneic blood transfusions

	Risks Associated	Incidence
Volume Overload	Hypertension, pulmonary edema	1:100 – 1:1,000
Mistransfusion	Acute hemolytic reaction Delayed hemolytic reaction	1:6,000 – 1:33,000 1:2,000 – 1:11,000
Bacterial Contamination	Sepsis	1:10,000 – 1:100,000
Viral Contamination	HIV Hepatitis C Hepatitis B Hepatitis A Cytomegalovirus Epstein–Barr virus West–Nile virus	1:2,300,000 1:1,800,000 1:350,000 1:1,000,000 1:10–1:30 1:200 1:3,000–1:5,000
Prion Contamination	Creutzfeldt–Jakob Disease	Unknown
Transfusion-related acute lung injury	Immune Nonimmune	1:625 1:2,800
Allergic transfusion reaction		1:100–1:2,000
Immunosuppression		1:1
Alloimmunization		1:16,000

CONCLUSION/DISCUSSION:

Anemia often presents with vague and nonspecific symptoms, however, if left untreated especially in preoperative patients, anemic patients are at an increased risk of mortality and morbidity. A proper history and physical is imperative in the management of anemia. Despite being a treatable medical condition, anemia is often just looked at as simply an abnormal laboratory value. One of the best ways to increase a patient's surgical success is to prevent the need for a transfusion and/or prescribing unnecessary iron/EPO supplements as both these medical treatments can cause unwanted complications. Primary care physicians can become a crucial component in the preoperative preparation and postoperative treatment surrounding their patient's surgery. As mentioned previously, the recommendations that a primary care physician can partake in preoperatively include: elective surgical patients having a hemoglobin level determination 28 days before the scheduled surgical procedure and the patient's target hemoglobin before elective surgery must be within the normal range. If anemic, further laboratory testing to evaluate if the anemia is caused from nutritional deficiencies, chronic renal insufficiency, and/or chronic inflammatory disease is necessary. Lastly, treat those deficiencies prior to surgery and provide supplementation if warranted.[13] A more efficient and agreeable approach to treating pre/postoperative anemia has the potential to reduce medical cost and possible complications that our patients may experience added on to the already stressful time in their life surrounding their operation.

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CLINICAL IMAGES

Erythema Ab Igne

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A 39-year-old female with a past medical history of chronic back pain, due to scoliosis and associated leg length discrepancy, presents to the emergency room with a rash on her diffuse lower back. Her pain had worsened over the past week due to a change in weather and was unrelieved by her normal prescription and over the counter pain control regimen. She had applied a heat pack to her lower back while she was sitting in a chair studying and accidentally fell asleep for an hour. When she woke up, she took a shower and noticed a stinging/burning sensation to her lower back, which she attributed to a burn from the heat pack. When she woke up the next morning, her husband noted the following rash on her back, which persisted for 1 week prior to presentation to physician (Figures 1 and 2).

She initially noted a few blisters which had resolved. She denies associated fevers, chills, myalgias, arthralgias, pruritis, insect bites or rash elsewhere on her body and denies previous episodes of the rash. The patient does admit to frequent heating pad usage for back pain.

QUESTIONS:

1. The most likely etiology of this patient's dermatologic presentation is:
   - A. Contact dermatitis
   - B. Exposure to thermal heat
   - C. Livedo Reticularis
   - D. Vasospasm after heat pad removal

2. What is the recommended treatment?
   - A. Removal of the offending heat source
   - B. Treat the underlying cause of pain
   - C. Monitor skin changes for hyperkeratotic changes
   - D. All of the above

FIGURE 1:

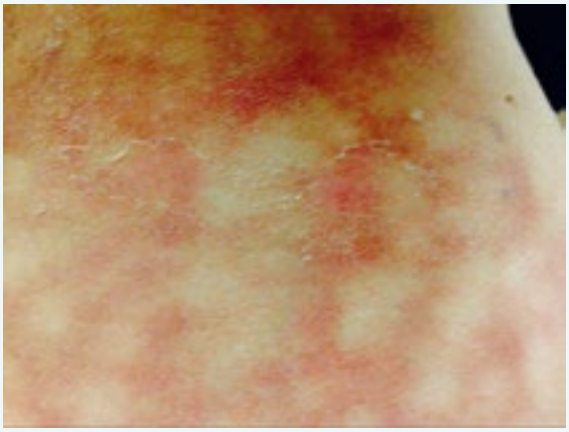
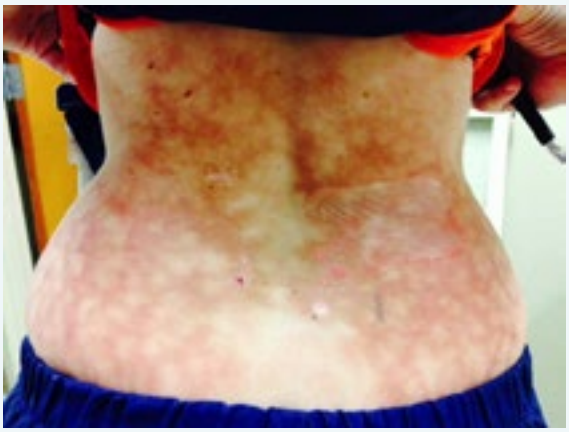


FIGURE 2::



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ANSWERS

1. The most likely etiology of this patient's dermatologic presentation is:

The correct Answer is:

B) Exposure to thermal heat

Thermal Heat. Erythema ab igne (EAI) presents as an erythematous, reticular, net-like dermatosis that develops due to chronic exposure to low level thermal heat.[1,2,3,4] While contact dermatitis can also occur after contact with a foreign substance, it develops an irritant or allergic reaction.[5] Manifestation includes erythema, scaling with well-demarcated borders and can affect any area of the body.[5] Livedo Reticularis (LR) is a disorder of skin vasculature caused by concomitant vasodilation and vasospasm, which presents as a erythematous/purple, mottled, reticulated vascular pattern similar to erythema ab igne, and can be secondary to cold exposure or underlying systemic disease.[4] Cutis marmorata, physiologic livedo reticularis and Raynaud's disease are due to vasospasm related to exposure to cooler temperatures.[4] Generally symptoms resolve after cold exposure is removed, however some forms of LR may persist.[4] Specific vascular causes can be secondary to autoimmune connective tissue diseases, vasculitis and blood disorders that slow blood flow or obstruct the vascular lumen.[4] In the above case, the history leads to thermal exposure as the suspected cause.

2. Which of the recommended treatment?

The correct Answer is:

D) All of the above

The rash will generally fade over weeks to months without treatment.[6] In this case, the underlying cause of back pain should be addressed so as to assist the patient in avoiding further thermal heat use. If a patch of EAI fails to fade, or if there are hyperkeratotic plaques present, it may be reasonable to consult a dermatologist.

DISCUSSION

Erythema ab igne (Latin, meaning "redness from fire"), also known as "toasted skin syndrome", presents as an erythematous, macular dermatosis that develops due to chronic exposure to low level thermal heat.[1,2,3,4] While known as being a historical disease, this skin condition has since seen a reemergence that reflects modernized technology. Formerly, the condition occurred on the shins of elderly people due to lengthy and close proximity to coal fires or stoves.[3] With the arrival of central heating, most cases now are due to the use of heating pads, heated car seats, laptop computers, and electric heaters.[4,7] Acutely, the skin changes associated with EAI manifest as coalescing red bands with erythema present diffusely. Only after repeated exposure will microscopic changes in the skin result in a more defined pigmentary variation.[3,8]

It is reported that the rash can appear with as little as two weeks of heat exposure, however the time course depends on the temperature of the heat source.[9] The acute presentation of this mottled rash may be viewed as benign, however, over time there is concern about the development of thermal keratosis and, rarely, squamous cell carcinoma (SCC), cutaneous marginal zone lymphoma, and Merkel cell carcinoma.[1,3,10]

German dermatologist Abraham Buschke first described erythema ab igne in the early 1900's.[11] As with many diseases, there are certain distinguishing cultural and geographical features that are associated with EAI. Most cases have been reported in countries with a cooler climate where people resorted to alternative ways of maintaining their body heat during the cold months.[12] One of these very characteristic cases were the Chinese kang cancers. A Chinese kang is a long, traditional platform made of clay or bricks that was heated by a cooking fire and used for general living and warmth during sleep, thus the greater trochanter was a common area for EAI and SCC to develop.[13]

The early appearance of EAI is that of a transient macular erythema that is distributed in a reticular, or net-like, pattern and is blanchable.[4] The lesions are characteristically painless, but the patient may complain of a diffuse minor burning sensation or pruritus that resolves as the rash fades.[4,6] The rash may exhibit multiple colors simultaneously, with areas differing from light pink, to a duskier rose and brown.[4] Over time, and with chronic exposure to the source of thermal heat, the dermatosis progresses into a dusky hyperpigmentation and no longer blanches.[4] If the source of heat persists, skin hyperpigmentation may be permanent. Scarring is probable if bullae have formed.[7] Livedo reticularis, a vasospastic vasculopathy, produces a rash similar to that seen in early EAI and thus should be included in the differential diagnosis.[3,10] Cutis marmorata and Poikiloderma should also be considered.[4]

Thermal heat damages the epithelium by several mechanisms. First, is direct injury to the cellular structure of the tissue, and second by the release of local mediators such as cytokines.[14] Heat provokes an inflammatory response within the tissue resulting in the release of toxic cytokines as well as free oxygen and nitrogen radicals which potentiate the injury by damaging essential proteins, lipids, and DNA. One of these cytokines is TNF, an acute phase reactant that plays a role in systemic inflammation and cell apoptosis.[15] Cell membranes are specifically prone to these oxidative stresses.[15] Mast cells recruited to burned tissue release histamine, resulting in local vasodilation and edema.[14] Histologically, there may be an abundance of inflammatory cells, connective tissue disintegration, and hemosiderin deposition.[14] The rash pattern parallels the dermal venous plexus, where hemosiderin deposition results in the net-like reticular appearance.[4,9]

Many patients do not associate their rash with the source of heat exposure. It may be up to the clinician to perceive the markings of EAI and then question the patient about a possible persistent exposure to a heat source. Specific questioning should focus on occupation and hobbies, as certain exposure patterns have been noted (EAI on the forearms of bakers, or the face and arms of glass blowers and foundry workers).[4,6] In other instances, patients may be using heat as a means of pain relief. EAI is often seen in patients with longstanding back and abdominal pain who find comfort with the application of heat.[3] EAI in the lumbosacral region suggests a musculoskeletal dysfunction.[4] It has also been seen in the setting of

malignancy or visceral disease, specifically pancreatitis, peptic ulcer disease, primary cancers, as well as metastatic neoplasms.[4,7,16] In these cases, EAI ensued after the chronic use of a heating source to mitigate pain associated with these underlying processes.[7]

Within a longstanding patch of EAI, a keratotic skin lesion called a thermal keratosis (TK) may emerge.[11] TKs will appear as hyperkeratotic papules and plaques. There has been reported evolvement of these lesions to invasive squamous cell carcinoma from TKs, however there is little information in the literature with reference to the percentage of progression of TK to invasive SCC or of the prognosis of thermal SCC.[1,7,10,13]

The diagnosis of EAI is a clinical diagnosis with labs and imaging offering little benefit. If there is uncertainty of the diagnosis, however, or if there are hyperkeratotic plaques or papules within the patch, a punch or shave biopsy is indicated.[1,3,13,17] If multiple lesions exist, the clinician should pick the largest, most representative lesion in the least cosmetically important area for biopsy.[18] When concerned regarding SCC, sample from the most central and thickened area of the lesion.[18] The most important step in treatment is to remove the offending heat source. In most cases, the rash will fade over weeks to months without treatment.[6] If there are cosmetic concerns due to hyperpigmentation, topical tretinoin may be used to improve the appearance of the rash.[6,17,19] Laser therapy and cryosurgery are also acceptable options if tretinoin is contraindicated. If a patch of EAI fails to fade, or if there are hyperkeratotic plaques present, it may be reasonable to consult a dermatologist. 5-fluorouracil cream has been used if the lesions exhibit pre-cancerous morphology on punch biopsy.[3,8]

Osteopathic manipulative therapy (OMT) may have proven helpful in this particular patient. The OSTEOPATHIC trial was a randomized double blind trial that demonstrated that OMT treatment did result in moderate to substantial improvement in low back pain symptoms when used to complement other co-treatments. OMT also decreased the need for prescription medications. Some of the techniques utilized in the study were high-velocity, low-amplitude thrusts, soft tissue stretching, kneading, and pressure, myofascial stretching and release, and positional treatment of myofascial tender points.[8]

In summary, EAI presents as a localized, erythematous, and reticulated rash that develops due to a low level of heat below the point for a thermal burn. Over time, if continued thermal damage occurs, squamous atypia may appear histologically, which can progress to a cutaneous malignancy, namely SCC. First and foremost, the physician should determine the underlying reason for the use of heat. Many patients who present with EAI are attempting to alleviate chronic pain, in rare cases hinting at an underlying malignancy.[8] EAI itself can be very easily identified and allow prevention of progression to more serious cutaneous disease. The ICD 10 code for EAI is L59.0.

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FIGURE LEGEND:

Figure 1 and 2: EAI

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[1]*A subset of Quality Markers measures qualify for PQRS and QCDR reporting.*

[2]*Provider is responsible to register with CMS as necessary and to have available the necessary data points for reporting requirements.*

CLINICAL IMAGES

Purple Urine: Cause for Concern?

John S. Bissett, DO[1] & Thomas F. Beaman, DO[2]

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The patient is an 85 year old, white female presenting with purple discoloration of her urine and collecting bag (Figure 1-2). This condition is found upon routine, monthly physical exam. She is a long term resident of the nursing home and has a chronic, in-dwelling urinary catheter. She has only limited ambulation with the help of nursing staff. She has no complaints at the time of exam and no changes have been made to her care regimen. Her medical and family histories are non-contributory and the remainder of the physical exam shows a frail, somewhat weak constitution but is otherwise unremarkable.

QUESTIONS:

1. What is the diagnosis?

A. Porphyria

B. Medication side effect

C. Purple urine bag syndrome

D. Alkaptonuria

FIGURE 1:

Purple urine with purple discoloration of collecting bag and tubing

FIGURE 2:

Purple urine with red and blue undertones inside Foley bag

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ANSWERS

1. What is the diagnosis?

The correct Answer is:

C) Purple urine bag syndrome

The descriptively named Purple Urine Bag Syndrome (PUBS) is a phenomenon often encountered in chronically catheterized, female nursing home residents. In this condition, red and blue pigments are thought to combine and give the urine and its collecting system a purplish hue[1] (Figure 1-2). Porphyria can sometimes lead to a red or reddish-brown discoloration of urine. There are several types of porphyria but they are all due to defects in the heme biosynthetic pathway. Because of lacking or defective enzymes, the upstream substrates of the heme pathway can accumulate. These excess porphyrins can spill into the urine and give it the classic "port-wine" color.[2] This patient did not have a history of any subtypes of porphyria nor was she exhibiting any symptoms thereof. Also, with porphyria one would expect a more reddish color to the urine as opposed to the striking purple of our patient's sample. Medication side effects should always be considered in the differential but this patient was not on any medications known to cause urine discoloration. Alkaptonuria is a rare, autosomal recessive genetic disease resulting from a defect in the tyrosine catabolism pathway. Upon standing, the urine of individuals with alkaptonuria becomes oxidized and takes on a black color. Alkatponuria is usually associated with other symptoms such as arthritis and ochronosis (deposits of black pigment in various tissues).[3]

DISCUSSION

Purple Urine Bag Syndrome (PUBS) is a rare, albeit strange entity whereby urine and its container take on a purple hue (Figure 1). This phenomenon was first described via the literature in 1978, but descriptions of bluish urine date back to King George III.[1,4] This is primarily a condition of elderly females who have been chronically catheterized. There is also an association with constipation.5 Being a rare and usually benign condition, the epidemiology on the subject is lacking but there does seem to be an increased occurrence amongst nursing home residents. The prevalence has been reported to be as high as 9.8 % in long term residents who are chronically catheterized.[1]

Although the exact mechanism of PUBS remains somewhat elusive, it is thought that bacterial enzymes break down urinary products into visible pigments. The cycle is believed to start with tryptophan, contained in dietary components. In the gut, tryptophan is broken down into indole, which is shunted into the portal circulation. Indole is then conjugated in the liver to indoxyl sulphate. The indoxyl sulphate is then excreted into the urine in high amounts.[6,7] If the enzymes indoxyl sulphatase or indoxyl phosphatase are present in the urine, they can then break down the indoxyl sulphate into indigo and indirubin, which appear blue and red respectively. The combination of these two pigments is thought to create the purple hue (Figure 2). Certain bacteria have been shown to contain the enzymatic machinery (indoxyl sulphatase and indoxyl phosphatase) capable of carrying out these reactions. These include Providencia, Proteus, and Klebsiella species.[5,8] The association with female gender is possibly due to female genitourinary anatomy, which predisposes to UTIs and bacterial colonization. Similarly, catheterization also predisposes to UTIs. High tryptophan content in the diet is thought to provide more substrate for enzymatic degradation into indoxyl sulphate. Constipation slows gastrointestinal transit time and is thought to provide more time for tryptophan degradation. It is also posited that increased urine alkalinity facilitates indoxyl oxidation.[1] At this time, more studies are needed to further elucidate the underlying mechanisms of PUBS.

Treatment of PUBS consists of assurance to the patient and family, who can become alarmed at the drastic and sudden change of urine color. Although usually benign, doctors should be aware that this syndrome can be associated with chronic UTIs and poor urinary hygiene. Medical intervention is aimed at evaluating and treating any underlying infections and correcting any poor Foley practices.[1]

The color of urine has been analyzed by healers since the dawn of medicine. Hippocrates is generally credited with being the father of urinalysis, or uroscopy, as it was called then. However, the study of urine is thought to be much older. As early as 4000 BC, ancient Sumerians and Babylonians studied urine and recorded their findings on clay tablets.[9] Tailabindu Pariksha, an ancient form of Ayurvedic urinalysis, focused on several aspects of the urine, including detailed descriptions of its color.[10] Around 600 years ago, Paracelsus and others started to look toward a biochemical model of urine diagnostics which eventually evolved into the "modern" approach used today.[11] As Western medicine advances and methods of urinalysis become increasingly complex, physicians cannot abandon the use of their own senses in physical diagnosis. In this case, timely recognition of PUBS saved the patient considerable stress and the financial burden of an expensive and unnecessary workup.

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JULY / AUGUST 2016 ANSWERS: 1. B 2. A 3. A 4. C 5. A 6. B 7. B 8. D 9. A 10. A

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BREAST CANCER SCREENING

Peter Zajac, DO, FACOFP, Author

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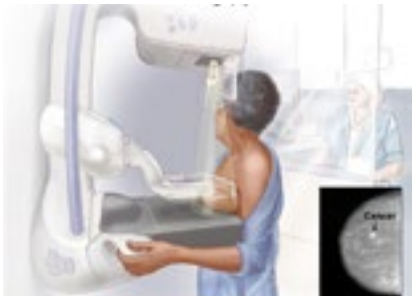

Early detection is still the most important defense available to patients in preventing the development of life-threatening, advanced-stage breast cancer. Breast cancer screening is when doctors examine the breasts for early signs of cancer in patients who have no symptoms. Factors associated with an increased risk in breast cancer include being female, increasing age, a personal and/or family history of breast cancer, inherited genes that increase the risk of cancer, obesity, drinking alcohol, beginning your period at a younger age, having your first child at an older age, having never been pregnant, beginning menopause at an older age, postmenopausal hormone therapy, and radiation exposure. The earlier breast cancer is found, the more easily and successfully it can be treated. The two most common methods used for early detection are a clinical breast exam and mammogram. Your doctor may use ultrasound if there are suspicious findings on mammography or physical examination. Your doctor also may use Magnetic resonance imaging (MRI) as a screening test if you have a high risk of breast cancer.

CURRENT BREAST CANCER SCREENING RECOMMENDATIONS:

FOR WOMEN AT AVERAGE RISK FOR BREAST CANCER:

The U.S. Preventive Services Task Force (USPSTF) 2016 guidelines recommend:

- A screening mammogram every 2 years for women between the ages of 50 to 74 years.
- For women aged 40 to 49 years, the balance of benefits and harms of screening is not as clear. The USPSTF states that the decision to start regular screening mammography every 2 years in women before the age of 50 years should be an individual one based on the woman's values regarding specific benefits and harms, her health history, and what she prefers. Your doctor can help you understand the balance of potential benefits and harms of screening in your specific case.

The American Cancer Society (2015 update) recommends:

- Women should start regular screening at the age of 45 years with a mammogram every year until the age of 54 years.
- Women at the age of 55 years and older, should transition to having a mammogram every 2 years. This can continue as long as their overall health is good and they are expected to live 10 or more years. The Society also states that women should have another option based on their values and preferences. This option is to begin annual screening mammography between the ages of 40 and 44 years and have the opportunity to continue screening annually at the age of 55 years and older.

The age at which screening no longer helps reduce death from breast cancer is not known. If you are the age of 75 years or older, talk to your family doctor about mammography as a regular part of your health care plan.

MEDICAL CARE & TREATMENT OPTIONS:

If you have any questions about breast cancer screening, please contact your Osteopathic Family Physician. With a thorough history and physical exam, along with assessing your risk for breast cancer, your family doctor will help you determine which current screening recommendations will be best for you. In case of any emergency, you should call your doctor or 911 right away.

SOURCE(S): American Cancer Society, Breast Cancer Screening. Gov, Medscape, and USPSTF.

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