

Team Management of the Female Athlete Triad

Part 1: What to Look for, What to Ask

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In brief

The female athlete triad of disordered eating, amenorrhea, and osteoporosis affects many active women and girls, especially those in sports that emphasize appearance or leanness. Because of the athlete's psychological defense mechanisms and the stigma surrounding disordered eating, physicians may need to ask targeted questions about nutrition habits when assessing a patient who has a stress fracture or amenorrhea, or during preparticipation exams. Carefully worded questions can help. Physical signs and symptoms include unexplained recurrent or stress fracture, dry hair, low body temperature, lanugo, and fatigue. Targeted lab tests to assess nutritional and hormonal status are essential in making a diagnosis that will steer treatment, as are optimal radiologic tests like dual-energy x-ray absorptiometry for assessing bone density.

Today's female gymnast weighs almost 20 lb less than her counterpart of 20 years ago. Examples such as this of a heightened focus on thinness have been cited as a factor in disordered eating among female athletes, especially those participating in sports that emphasize appearance or leanness, or those that involve weight classifications. In addition, eating disorders are often accompanied by amenorrhea and osteoporosis; these three conditions are known collectively as the female athlete triad.

Because of their unique role in patient care, primary physicians especially need to be aware of what to look for and what

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For CME credit, see page 135

This is the first of two roundtable articles on the female athlete triad. The second, on treatment and prevention, will appear in a subsequent issue.

Moderator:



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Participants:



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Joseph Martire, MD, is the director of nuclear medicine at the Union Memorial Hospital and Sports Medicine Center and an assistant professor of radiology at Johns Hopkins University School of Medicine, both in Baltimore. He is also a member of the editorial board of *THE PHYSICIAN AND SPORTSMEDICINE* and a fellow of the ACSM and the American College of Radiology.



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questions to ask in diagnosing this often insidious syndrome. They also need to work with other members of the healthcare team as they make a diagnosis that will lead to appropriate treatment of all underlying problems.

Prevalence of the Triad

Joy: What is the general prevalence of disordered eating and menstrual dysfunction in female athletes?

Nattiv: Prevalence data on disordered eating in athletes are limited to a few studies.¹⁻⁵ Most studies have used self-reporting from surveys that have differed significantly in the types of questions asked and in the screening tools used. The athletic population investigated also varies, making it difficult to draw conclusions about the true prevalence. In the United States, studies suggest, based on limited data, a prevalence in female athletes between 15% and 62%.¹⁻³ However, because there is no true consensus on the definition of disordered eating and no validated screening tool in athletes that best detects individuals at risk, the true prevalence is not known.

The reported prevalence of athletic amenorrhea also depends on the definitions used. Most studies define amenorrhea as cessation of menses for at least 3 to 6 months, or fewer than three cycles per year (in women who have already been menstruating).

Most data show a prevalence of amenorrhea between 3.4% and 66%.⁶⁻⁹ In elite athletes, the prevalence is probably on the higher end, especially in sports in which poor nutrition habits are practiced and a lean physique is emphasized.

What appears to be a critical factor with regard to bone health is the cumulative estrogen exposure that a woman experiences in a given time period. As Drinkwater and colleagues have illustrated,^{10,11} the severity of menstrual dysfunction, based on menstrual history and current status, appears to be linearly associated with a decrease in bone mineral density.

Joy: Of female athletes who sustain stress fractures, what percentage also have disordered eating and/or menstrual irregularity?

Ireland: I can't cite percentages, but I am most

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concerned about high school athletes. Our region has a lot of thin cheerleaders and gymnasts, in whom we see a lot of spondylolysis and fibular and tibial stress fractures. Disordered eating is significantly underdiagnosed in these patients. Physicians should ask specifically about diet, past injury, and menstrual history.

Typical Characteristics

Joy: What are some of the typical characteristics of those who have the triad?

Nattiv: Typically, the young woman is a perfectionist with high goals—athletically, as well as in other areas of her life (table 1). Being very critical of herself and having very high expectations and fairly low self-esteem is a recurrent pattern. An emphasis on maintenance of an “ideal body weight” or optimal body fat is also common.

Varechok: Most of these patients are dedicated athletes. They are very motivated, are achievement oriented, avoid taking shortcuts, and have a strong work ethic. They are not complacent about success. They tend to ignore or minimize minor injuries. Coaches tend to admire these traits, so affected athletes often elude detection.

Physicians need to be prepared for athletes who may deny or rationalize symptoms and minimize problems. Because an eating disorder is, in a lot of ways, a coping strategy, these athletes often hold on to their eating disorders tenaciously. If you get to know the athlete well enough—which can be difficult—you may see some fear of gaining weight, some obsession with calories. You may see mood swings, irritability, and depressive symptoms such as poor concentration, memory, and attention span.

The patient and her teammates will likely have a preoccupation with their bodies and dietary habits. These characteristics, however, are probably not going to be found in the physician’s office, so communication with the athletic support staff and parents of younger athletes can provide good leads.

Joy: My experience as a primary care physician is that athletes first present with the triad in several ways. One is, they come in because they’ve had a dramatic weight loss, causing

Table 1. Common Characteristics of Patients Who Have the Female Athlete Triad

Perfectionist personality; high expectations for self
Competitive athlete
Self-critical behavior
Low self-esteem
Depressive symptoms
Achieving or maintaining low body weight and lean physique
Stress fracture without significant change in training
Multiple or recurrent stress fractures
Young age (adolescent, young adult)

Table 2. Common Signs and Symptoms of Anorexia

Amenorrhea	Lanugo, particularly on trunk
Fat and muscle loss	Lightheadedness
Dry hair and skin	Decreased ability to concentrate
Cold, discolored hands and feet	Bradycardia
Decreased body temperature	

Table 3. Common Signs and Symptoms of Bulimia

Swollen parotid glands	Face and extremity edema
Chest pain	Diarrhea or constipation
Sore throat	Menstrual irregularities
Fatigue	Knuckle scars
Abdominal pain	Bloodshot eyes
Erosion of tooth enamel	

someone to suspect disordered eating (tables 2 and 3). Or they have a stress fracture or suspected stress fracture.

Key Questions in the History

Joy: What questions should primary care physicians ask regarding eating behaviors?

Ireland: I ask about menstrual cycle and nutrition history whenever I see a youngster with a stress fracture. I will usually refer the patient for an in-depth nutrition assessment and to a physician who has expertise in treating hormonal disorders in young female patients.

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Clark: Some good questions to ask would be, "How *much* of an issue is weight for you?" (weight is an issue for most women, but the intensity varies) and "How do you rate your diet?"

If the patient says, "I try to eat very healthfully" or "My diet is very good," you should be cautious. What a patient sees as a wonderful diet could be nothing but fruits and vegetables. Or they could say "My diet is pretty bad," in which case they could be asking for help. I always ask about their protein intake, because protein in food tends to be coupled with fat and is therefore often severely restricted.

When getting background medical information I ask, "Do you currently have regular menstrual periods, and have you always?" If the client is amenorrheic, I will mention how amenorrheic female runners tend to have a 4.5 times higher risk of stress fracture than the average woman and talk about how food affects health. Another good question is, "How often do you take a day off from training?"

Addressing past rather than present behavior can help a patient admit to practices of disordered eating—even if she is still doing them.

Aurelia Nattiv, MD

Joy: I'll ask "What's the most you've weighed in the last year,

what's the least you've weighed in the last year, and what do you think your ideal weight is?" Because we typically have their current weight, I have found these questions to be very helpful.

Nattiv: Also, asking the athlete if she has certain "forbidden" foods (eg, chocolate, other desserts, nuts) that she will not allow herself to eat, can provide a tip-off. Another important question is, "Have you ever used laxatives or diet pills or made yourself vomit *in the past*?" If you address her past, it is less threatening, and I have found that patients are much more likely to admit to such practices even if they are still doing them.

Other questions I find helpful include asking if the athlete has ever used excessive exercise to control her weight in the past and if she is satisfied with her present weight or physique. If she is not satisfied, I ask her what she feels her ideal weight or percent body fat should be.

Varechok: Athletes who have disordered eating will tend to avoid straightforward questions about symptoms for fear of being identified. Sometimes physicians can word questions to be less threatening by using a nonauthoritative, open-ended approach to get the patient talking.

Joy: What questions do you ask in screening for menstrual dysfunction?

Nattiv: I usually start with the dietary questions because poor nutritional habits often coincide with menstrual dysfunction. A history of low body weight or an abrupt change in body weight may contribute to menstrual dysfunction. I also ask pointed questions about their menstrual history, because menstrual history, along with current menstrual status, is one of the best predictors of bone density. I ask when they started their period, and then have them detail how frequently they get their period. It's also helpful to ask if they have signs or symptoms of ovulation, such as changes in cervical mucous midcycle or midcycle cramps. Many athletes with menstrual dysfunction do not experience these.

Ireland: Some athletes are not aware that amenorrhea is a problem. A basketball player might say, "I menstruate in the summer months, but when I'm competitive I don't menstruate." When a patient says her periods are the same as always, the examiner needs to ask further. "The same as always" could mean 9 months of amenorrhea each year.

Other Historical Clues

Joy: Besides a history of stress fractures, are there other historical points that identify those at higher risk for osteoporosis? Are patients more likely to have acute injuries?

Ireland: Other than stress fractures, I have not seen any trend of serious acute injuries in young athletes who have the triad. Neither have I seen a stress fracture progress into a displaced, unstable fracture. These individuals may have recurrent stress fractures, but they will usually heal with reduction of axial loading and appropriate nutritional and hormonal assessment and treatment.

Bone health is a living homeostatic process, so we probably miss a lot of stress reactions

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when youngsters change activities or sit for a while. There probably are relatively painless bone reactions that we don't even see.

In addition, some athletes who have the triad seem to be repeat customers for soft-tissue injuries.

Clark: One of my patients with an eating disorder had been healthy for 2 years but got one injury, and then another and another. She described her body as a car whose wheels started falling off. It's amazing how long some of these athletes who have eating disorders can be healthy, but when they do get injuries, the injuries linger and, often, more come.

Ireland: Overuse injuries can result in stress fractures, but also sprains and strains. The effect of estrogen on muscle, ligament, meniscal, articular surface, and collagen tissues is not completely understood and probably underestimated. In particular, I see cheerleaders and gymnasts who have many recurrent lumbar strains and ankle sprains. Is this related to the sport, or are there multiple risk factors, including hormonal balance and nutrition?

Clark: The cause of injury can be multifactorial, with nutrition being one factor. If athletes have overuse injuries, the questions arise: Why are they overexercising? Is an eating disorder involved? For example, I counseled a woman who would eat a baked potato for 100 calories but would then have to run 10 miles afterward to burn them off. She got injured in that process, and poor nutrition was a part of her injury and lack of healing, but it was not the sole problem.

Emphasis on Calcium

Joy: Is low dietary calcium intake an independent risk factor for osteopenia in the adolescent and young adult female?

Nattiv: Myburgh et al¹² in 1990 showed that athletes who had a higher incidence of stress fractures also had lower calcium intakes as well as less use of birth control pills.

Clark: Weight-conscious teenage girls commonly drink a lot of diet soda but too little milk. They think milk is fattening, but they should have four servings a day of calcium-rich foods.

Ireland: If we think about calcium as a deposit in a bank, every healthcare provider should have major concerns if there's not enough calcium in the bank during the developmental years. If patients don't have the calcium stores then, they're going to run out of calcium early and then sustain a hip fracture at age 30 instead of at 70.

Clark: There's even a step before hip fractures. I know of one woman who was an amenorrheic runner in high school and college, and at age 29 has osteoporosis and doesn't know if her bones can support a pregnancy.

Joy: This is a real public health issue. We need to encourage young female adolescents to continue drinking milk.

Nattiv: At least in the postmenopausal population, studies show that 800 IU of vitamin D can prevent hip fractures. I recommend doses of 400 to 800 IU in younger athletic patients. Vitamin D can help with calcium absorption and may have additional beneficial effects on bone formation.

Physical Exam Findings

Joy: Let's talk about the classic physical exam findings. People with the restricting type of disordered eating like anorexia classically have physical signs of starvation (table 2). They often appear cachectic, or at least very thin, and have low body weight for height and low body fat. They can have bradycardia and hypotension. They have lanugo on the face and body, which is usually quite striking—patients are often referred to as "furry." They can have yellowish skin that may in part be due to increased beta-carotene intake.

Bulimia is harder to identify because these patients tend to be normal weight, but some have characteristic signs (table 3).

Nattiv: I agree that the bulimic population is tougher to identify. There's also a lot more denial in that group, often because of shame and feelings of guilt. With the self-induced vomiting you might see the "chipmunk cheeks" facial edema and peripheral edema. Individu-

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When a patient says her periods are normal or the same as always, the examiner needs to inquire further. She is often oligomenorrheic.

Mary Lloyd Ireland, MD

als with bulimia are often normal weight or overweight. If the individual is very thin, she may be participating in both restrictive eating and bulimic behaviors, as they often coexist. But usually in the athletic population, you don't see these classic features of bulimia—patients look normal. In anorexia, orthostatic hypotension and the low pulse rate that you mentioned are very important, as well as hypothermia and cold intolerance.

Joy: I recently saw a 45-year-old runner who has chronic bulimia. She had some interesting physical exam findings, like abdominal striae from changes in weight. She would have rapid weight gains, then she would lose the weight with restricting-type behavior like extensive use of laxatives and self-induced vomiting.

Because of her chronic laxative use, she developed chronic megacolon and had abdominal distention and a tympanic abdomen and all the symptomatology of megacolon. She would get petechiae in her sclera because of forceful vomiting. Those are things I've read about but don't see very often.

Primarily in the athletic population, you are going to see a younger patient whose disease hasn't been going on for quite as long, and she doesn't have some of the signs of chronicity of an older patient. But if a patient has abdominal complaints, the family physician must ask questions about disordered eating.

Clark: Patients very often have a grayish, unhealthy look and poor complexion. Their muscles are wasted. Many women express concern about their hair falling out.

Ireland: As an orthopedic surgeon who is aware of the underdiagnosis of disordered eating, I'm still not sure when I'm seeing it. We may identify the extreme cases, but the ones that are on the fence can be difficult. Young women who have a stress fracture may have some component of disordered eating.

I encourage caregivers of these young female athletes to think about being blunt and persistent. Ask the patient by herself and later with family, peers, and coaches about the possibility of her having disordered eating. Be up front if you are thinking about an eating disorder. It's

probably there. A quote to remember is, "You may not have seen it, but it has seen you."

Nattiv: I think that with every stress fracture, orthopedists and primary care physicians need to ask about eating disorders and menstrual function. That should be a knee-jerk reaction and should be taught during residency training.

Joy: Should all amenorrheic athletes receive a pelvic exam?

Nattiv: It depends on age and other factors. I do not always do a pelvic exam in girls under 18 who have not been sexually active unless they have a history of primary amenorrhea. First, a medical work-up is indicated. Athletic amenorrhea is a diagnosis of exclusion and cannot be assumed in an athlete with menstrual dysfunction. If I start oral contraceptives, however, I do recommend a pelvic exam and Pap smear.

Laboratory Work-Up

Joy: What laboratory tests do you consider essential in the workup of secondary amenorrhea? (The scope of this conversation is too limited to discuss primary amenorrhea.)

Nattiv: My basic workup for athletes includes tests for follicle-stimulating hormone (FSH), prolactin, and thyroid-stimulating hormone (TSH); a pregnancy test; and, usually, a complete blood cell count and chemistry panel because of the nutritional issues. If the patient is hirsute, has acne, or polycystic ovarian syndrome is suspected, I will often obtain a free testosterone and dehydroepiandrosterone sulfate (DHEA-S), and luteinizing hormone (LH) in addition.

A progesterone challenge test (with medroxyprogesterone acetate 10 mg/day for 7 to 10 days) can be helpful as an indirect assessment of estrogen status. Uterine bleeding after progesterone administration indicates that estrogen levels are usually not markedly decreased.

Joy: I sometimes get a serum estradiol test as well. If the FSH value is borderline and the estradiol level is less than 20 pg/mL, I'll usually prescribe oral contraceptives. In part, estradiol can

Low serum estradiol levels can be a motivator. Having the level of a postmenopausal woman convinces some patients to change behavior.

Elizabeth Joy, MD

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be a motivator for taking birth control pills. Most patients understand estrogen and progesterone, so if their estrogen level is less than 20, you can show them the laboratory reference value that says "postmenopausal: less than 20," and say, "You have the estrogen level of a postmenopausal (or prepubertal) woman."

Radiology Tests

Joy: How extensive should bone scans be when a stress fracture is suspected?

Martire: The most common site of stress fractures is the leg; therefore, I do triple-phase technique of both legs from hip to ankle. This is not very time-consuming with a large-field-of-view camera, and I can look at a large area, which is important because pain is often referred. For low-back pain, I scan the entire thoracic to sacral spine, as well as the pelvis and hips. If I suspect osteoporosis, I ask the team physician for permission to do a dual-energy x-ray absorptiometry (DEXA) study to see if the athlete's bone density is below the female adult standard.

Triple-phase bone scans are the most common diagnostic imaging tests used to evaluate overuse injuries. Studies have shown that low bone-mineral density is a definite factor for the development of stress fractures in athletes.¹² Obviously, when we do a bone scan we do not know whether a female patient is osteoporotic. Therefore, some of the things we might look for include multiple stress fracture, often in different stages of healing (eg, a new stress fracture in the tibia and an older, healing stress fracture in the tarsal navicular or os trigonum). Gymnasts and ballet dancers can have stress fractures in uncommon locations—such as the anterior tibia, proximal fibula, or medial malleolus—that may be difficult to heal. Finally, continuous or repetitive occurrence of stress fractures would be another tip-off of the female athlete triad.

Magnetic resonance imaging (MRI) can also be useful. It can detect early changes in bone and help differentiate stress fracture from other pathologic conditions.

Joy: When do you order a bone density study?

Nattiv: There are no guidelines in this age-group as yet, but I will offer it if the athlete has

experienced a recurrent history of oligomenorrhea, or has more than 6 to 12 months of amenorrhea. It's more important to order a bone density study if you think it's going to change treatment. The information that the athlete receives from her assessment will often—especially if significant bone loss is revealed—personalize the problem enough to lead to better compliance.

Joy: I've heard of using other radiologic tests to evaluate people for osteoporosis, like ultrasound to look at bone microarchitecture. But I would say that most of us use DEXA. Is there any reason to order another test for bone density?

Martire: Most experts agree that DEXA is still the test of choice for bone densitometry. Other modalities—like MRI, quantitative computed tomography (QCT), and ultrasound—have their claims and backers, but nothing beats DEXA for availability, safety (radiation exposure), cost, ease of use, speed, accuracy, and reproducibility.

The DEXA test takes 20 to 30 minutes maximum with the patient supine and has a radiation dose of 3 to 10 millirems—a fraction of that from a single-view chest film and 1% of the dose of a QCT. DEXA is cheaper than QCT or MRI and has an error range of 1% to 3%, which matches the accuracy of any other test. The cost ranges from about \$100 to \$200 per study but will vary by region. The results are compared with standards in young female adults and assigned a plus or minus standard deviation.

In addition to its diagnostic value, abnormal DEXA can give a baseline for measuring efficacy of follow-up treatment. It can also provide a powerful quantitative stimulus to show the young female athlete how harmful her condition is.

Nattiv: Because patients sometimes think they are invincible, having the evidence from bone densitometry that shows they are two standard deviations below the mean can influence their health patterns. They are much more likely to follow the treatment program, such as taking birth control pills and ingesting more calcium.

Clark: But if you find that they're two standard deviations below the mean, do they sometimes have the opposite reaction: "It's hopeless, I'm doomed, I'm already way below the average"?

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INDICATIONS AND USAGE: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below.

Lower Respiratory Tract Infections caused by β -lactamase-producing strains of *Haemophilus influenzae* and *Moraxella* (*Branhamella*) *catarrhalis*. **Otitis Media** caused by β -lactamase-producing strains of *Haemophilus influenzae* and *Moraxella* (*Branhamella*) *catarrhalis*. **Sinusitis** caused by β -lactamase-producing strains of *Haemophilus influenzae* and *Moraxella* (*Branhamella*) *catarrhalis*. **Skin and Skin Structure Infections** caused by β -lactamase-producing strains of *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella* spp. **Urinary Tract Infections** caused by β -lactamase-producing strains of *E. coli*, *Klebsiella* spp., and *Enterobacter* spp. While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β -lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic. Because amoxicillin has greater *in vitro* activity against *Streptococcus pneumoniae* than does ampicillin or penicillin, the majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin and *Augmentin*. (See Microbiology subsection.)

Bacteriological studies to determine the causative organisms and their susceptibility to *Augmentin* should be performed together with any indicated surgical procedures. Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β -lactamase-producing organisms listed above. Once results are known, adjust therapy, if appropriate.

CONTRAINDICATIONS: Patients with a history of allergic reactions to any penicillin, or patients with a history of *Augmentin*-associated cholestatic jaundice/hepatic dysfunction.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH *AUGMENTIN*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED IMMEDIATELY. APPROPRIATE THERAPY, INCLUDING SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS FLUIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED. Pseudomonas colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis." After the diagnosis of pseudomonas colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomonas colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis. Use *Augmentin* cautiously in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with *Augmentin* use is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)

PRECAUTIONS: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin class antibiotics should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin. Co-administration of probenecid cannot be recommended. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rash is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

Drug/Laboratory Test Interactions: Oral administration of *Augmentin* will result in high urine concentrations of amoxicillin. High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinistix®, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin and therefore *Augmentin*, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Tes-Tape®) be used.

Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated estrone, estrone, estradiol, and estradiol has been noted. This effect may also occur with amoxicillin and therefore *Augmentin*.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. **Mutagenesis:** The mutagenic potential of *Augmentin* was investigated *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and *in vivo* with mouse micronucleus test and a dominant lethal test. All were negative apart from the *in vitro* mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations.

Impairment of Fertility: *Augmentin* at oral doses of up to 1200 mg/kg/day (5.7 times the maximum human dose, 1480 mg/m²/day, based on body surface area) was found to have no effect on fertility and reproductive performance in rats dosed with a 2:1 ratio formulation of amoxicillin/clavulanate.

Teratogenic effects: Pregnancy (Category B): Reproduction studies performed in pregnant rats and mice given *Augmentin* at oral dosages up to 1200 mg/kg/day, equivalent to 7200 and 4080 mg/m²/day, respectively (4.5 and 2.8 times the maximum human oral dose based on body surface area), revealed no evidence of harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, length of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forces delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

ADVERSE REACTIONS: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were mild and transient; <3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis, mucocutaneous candidiasis and pseudomonas colitis. Onset of pseudomonas colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.) Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia and systemic fever), erythema multiforme (rarely Stevens-Johnson Syndrome) and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis). These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin. (See WARNINGS.) A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. Interstitial nephritis and hematuria have been reported rarely. Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*. Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

DOSEAGE AND ADMINISTRATION

Since both the *Augmentin* 250 mg and 500 mg tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), 2 *Augmentin* 250 mg tablets are not equivalent to 1 *Augmentin* 500 mg tablet. Therefore, 2 *Augmentin* 250 mg tablets should not be substituted for 1 *Augmentin* 500 mg tablet.

Dosage:

Adults: The usual adult dose is 1 *Augmentin* 500 mg tablet every 12 hours or 1 *Augmentin* 250 mg tablet every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be 1 *Augmentin* 875 mg tablet every 12 hours or 1 *Augmentin* 500 mg tablet every 8 hours.

Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of <30 mL/minute should not receive the 875 mg tablet. Patients with a glomerular filtration rate of 10 to 30 mL/minute should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 mL/minute glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection. Hemodialysis patients should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis. Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals. (See WARNINGS.)

Pediatric Patients: Pediatric patients weighing 40 kg or more should be dosed according to the adult recommendations.

Due to the different amoxicillin to clavulanic acid ratios in the *Augmentin* 250 mg tablet (250/125) versus the *Augmentin* 250 mg chewable tablet (250/62.5), the *Augmentin* 250 mg tablet should not be used until the pediatric patient weighs at least 40 kg or more.

Administration: *Augmentin* may be taken without regard to meals; however, absorption of clavulanate potassium is enhanced when *Augmentin* is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, *Augmentin* should be taken at the start of a meal.

BRS-AG-ALZ

female athlete triad continued

Nattiv: That's an important question. There can be negative repercussions. But this population may not have reached their peak bone density yet, so this can help motivate them to realize that there is still a small window of time to improve their bone health.

Joy: Another down side is, for example, in a young gymnast who hasn't had a period in 4 months and is eating 800 calories a day, but whose spine and femur are 120% of normal for her age. The test indicates that everything is fine, but she's setting herself up for serious bone-mineral loss down the road. The test result may lull her into a dangerous complacency.

Ireland: The bottom line is that physicians should have a specific reason for ordering any tests. They should ask themselves, "Will it change my treatment of this individual?" **FSM**

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