

YOU'RE THE FLIGHT SURGEON

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It is a typical Monday morning in your flight medicine clinic when you receive a call from your squadron commander wanting to know the status of one of his pilots who was admitted to the hospital late Sunday night or early Monday morning. After getting the aviator's name, you let your commander know that you will call him back with an update as soon as you have the information. You ask the on-call flight surgeon if he/she knows anything about the case. The on-call flight surgeon reports that the 28-yr-old pilot called late Sunday night complaining of umbilical discomfort, which had localized to severe right lower quadrant pain associated with nausea, nonbloody emesis, and fever. The on-call doctor advised the pilot to go to the local emergency room for evaluation. You contact the hospital and are connected to the aviator's room. The aviator reports he is doing well postoperatively after having a laparoscopic appendectomy. He states that he should be discharged on Tuesday. The pilot does report a concern, as he had a severe, potentially life-threatening reaction to the intravenous (IV) contrast dye given during the computed tomography (CT) scan of the abdomen done in the emergency department to confirm the diagnosis of appendicitis.

1. What is the upper range of incidence of adverse reaction to conventional radiographic contrast media (RCM)?

- A. 0.04%.
- B. 12.66%.
- C. 8%.
- D. 3.1%.

ANSWER/DISCUSSION

1. A. Over 10 million radiographic exams are done annually in the United States that need radiographic contrast media (6). These RCM agents are known allergens and can cause a variety of adverse effects. Put in another context, 50–70% of all CTs performed include use of IV-administered contrast agent (11). These RCM agents are chemically inert substances given intravenously over a short period of time and generally are relatively safe (2). RCMs are highly concentrated solutions of tri-iodinated benzene derivative further classified into ionic or nonionic forms (1). Additionally, the ionic ones tend to be higher in osmolality than the nonionic forms (1). Many physicians are not familiar with the adverse effects of RCMs, which patients are prone to have reactions, and the ways to minimize the occurrence of a reaction according to a review of the literature (3). Conventional contrast agents are higher in osmolality than the newer lower osmolar ones, which are much more expensive (1). Conventional agents cause an adverse reaction 2.1–12.66% of the time administered (6,13). Conventional agents cause a moderate reaction defined as itching or urticaria 1–2% of the time, with newer agents causing a moderate reaction 0.2–0.4% of the time (3). Severe reactions defined as stridor, bronchospasm, or hypotension occur 0.2% of the time for conventional agents and 0.04% for the newer agents (2,3). Fatal reactions are reported to occur 1 out of every 168,000 administrations for the newer, low-osmolar agents (13). In summary, research has shown that conventional agents, although they result in severe reactions < 1% of the time and save in cost, are 10 times more likely to be associated with an adverse reaction than the newer agents.

You call the commander and update him on the status of the pilot. You inform the commander that the pilot tolerated the surgery well and is expected to be discharged home tomorrow. You inform the commander that you plan to visit the patient later that day. When you arrive at the hospital room, you happen to meet the patient's attending surgeon. The surgeon reports that the pilot is recovering well. Upon questioning, you determine that the pilot was given a conventional, high-osmolar RCM agent injection bolus during his CT scan of the abdomen. Within 10 min of the injection, the hospital records show that the pilot developed severe itching, airway swelling, and difficulty breathing, which the pilot described as trying to breathe through a

straw. The nursing notes in the chart show the pilot to have been tachycardiac and hypotensive during the episode. He was initially treated with IV saline fluid bolus, intramuscular epinephrine, IV steroids, and IV antihistamine. He responded well to the treatments, thus avoiding emergent intubation to protect his airway or IV epinephrine to counteract more severe cardiovascular collapse. The pilot states he had no prior history of allergies and had never had RCM prior to his exam last evening.

2. How would you classify the adverse reaction described by the medical record and history?

- A. Anaphylaxis.
- B. Vasovagal.
- C. Acute anxiety attack.
- D. Anaphylactoid.
- E. Hypoglycemia.

ANSWER/DISCUSSION

2. D. Large boluses of RCM agents can cause the full spectrum of allergic manifestations. The least severe reactions would be urticaria and/or itching. Allergic reactions can remain isolated to these manifestations or progress to include multisystem derangements. These more severe multisystem manifestations include laryngeal edema, bronchospasm, or presyncopal symptoms. A vasovagal reaction would not have urticaria or bronchospasm and would more likely have bradycardia associated with the episode (9). An anaphylactic or anaphylactoid reaction would most likely have tachycardia associated with the reaction, although bradycardia is possible in addition to the traditional histamine-mediated effects of itching, urticaria, bronchospasm, and cardiovascular collapse (9). Per the literature, RCM reactions would be classified as anaphylactoid instead of anaphylactic in nature (6). Anaphylactoid reactions mimic anaphylaxis to such a degree that they are clinically identical (9,10). Because of the difference in pathophysiologic pathways, anaphylactic and anaphylactoid reactions can be distinguished. Anaphylactic reactions are IgE mediated; thus, prior sensitization is required and reactions do not occur on the first exposure (6). Once sensitized, very little exposure is needed to elicit a subsequent response. Anaphylactic reactions can also be predicted by allergy skin testing. In contrast, since anaphylactoid reactions are independent of IgE-mediated pathways, they can occur on first exposure (9,10). Anaphylactoid reactions are similar to anaphylaxis except that they cause pathophysiologic effects by an undetermined immune reaction, which causes a histamine release (1,4). Anaphylactoid reactions are not dependent on IgE-mediated antibody mast cell or basophil degranulation like anaphylaxis (6). Anaphylactoid reactions can be classified as mild to moderate, which would include urticarial and/or angioedema or severe reactions such as stridor, bronchospasm, or hypotension (7). Differentiating anaphylaxis and anaphylactoid reactions relies on good clinical history. This distinction in the type of reaction is generally not clinically relevant, as in the acute phase both are managed in the same way (10,14). The distinction does become important in the aeromedical decision-making process. For this particular pilot, based on his clinical history, he experienced an anaphylactoid reaction.

When the pilot stops by the office on Tuesday after being discharged from the hospital to fill his discharge medications and sign Air Force Form 1042 to place him on duties not to include flying, he inquires as to whether the reaction he experienced was preventable.

3. What are the predictors of who will more likely have an RCM reaction?

- A. Previous reaction to RCM.
- B. Cardiovascular disease.
- C. History of atopy and/or asthma.
- D. Beta-blocker use.
- E. All of the above.

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ANSWER/DISCUSSION

3. E. Review of the literature shows that a previous anaphylactoid reaction to RCM has a 17–60% increased risk of a repeat reaction during a subsequent exposure (6). Other conditions also carry an increased risk of developing a reaction. Specifically, cardiovascular disease is associated with a twofold to fivefold increased risk, history of atopy a threefold increase, and presence of asthma a fivefold increase (6,9). Beta blocker use as a risk factor has had mixed results in terms of its predictive value as a risk factor for having an RCM reaction. For those patients on beta blockers who have an anaphylactoid reaction, a more severe reaction is often seen; however, not all studies consistently show an increased odds ratio (6). Additionally, those on beta blockers are harder to treat with epinephrine (7). In terms of demographics, patients 20 to 50 yr of age have the highest rates of reaction (13). Children and elderly patients have less frequent reactions but tend to have more severe ones (13). The overall rates of adverse reactions can be lowered by either pretreatment protocols or use of the newer, low-osmolality RCM agents (13). In the case of this pilot who had no predictors of increased likelihood of developing a reaction and who had never received an RCM agent prior, the reaction was not a preventable event.

The pilot reports he was advised by the surgeon's physician assistant not to eat seafood despite having no prior history of a seafood allergy, since he had a reaction to the RCM because of concerns of cross-sensitivity. Nonetheless, he asks you, his flight surgeon, the following question:

4. How well does a history of seafood allergy predict the likelihood of an adverse reaction when given an RCM agent?

- A. Not predictive.
- B. Mixed results.
- C. Predictive.

ANSWER/DISCUSSION

4. B. The literature is mixed in regard to the answer to this question. Several studies done in the 1970s showed that a history of shellfish allergy increased the risk of having a reaction when iodinated contrast media was given (8). However, more recent research has shown no evidence that a seafood allergy relates to increased adverse events in patients receiving RCM (3,9). In addition, no relationship has been found between the dose of iodine administered and the incidence of adverse events (11). However, studies have linked the osmolality of the agent to increased adverse reactions (3). Current consensus is to abandon the idea that a seafood allergy relates to adverse events.

Based on the available literature, you counsel the pilot that he has no need to avoid seafood. The pilot finishes his visit by asking when he should come back to the clinic so that he can return to flying status. He states that he was about to start upgrade training to instructor status and would like to return to flying as soon as possible so that he can proceed with the training.

Because the pilot had an anaphylactoid reaction to an RCM agent, he meets retention standards per Air Force Instruction 48-123, which requires a medical board for anaphylaxis secondary to stinging insects, foods, spices, or food additives (15). Urticaria, angioedema, and anaphylaxis are disqualifying for all flying classes in the U.S. Air Force per regulations (15). Urticaria and angioedema from known cause require routine treatment and grounding until the condition resolves; no further waiver or evaluation is required by U.S. Air Force policy (17). However, since this aviator had a multisystem involvement during his reaction, grounding and a thorough evaluation prior to consideration of a waiver are needed. To be considered for a waiver, the condition must not pose a risk of sudden incapacitation. In this case, the pilot will not be receiving IV contrast for CT examination during flight duties, so this requirement is met. Additionally, the condition does not pose a potential for subtle performance decrement based on the pathophysiology of an anaphylactoid reaction as described earlier. His acute reaction has completely resolved. Although the possibility of recurrence exists, it would require administration of an RCM agent, which is easily detectable and would not pose a risk to the safety of flight as the exposure would not occur during flying duties. He requires no exotic tests or invasive procedures. Finally, since his acute reaction has resolved and is dependent on a completely avoidable provocative agent, he has no contraindications to sustained flying operations from his condition. This pilot's anaphylactoid reaction to an RCM agent meets all the required criteria for consideration of a waiver (17).

Per the Navy waiver guide, any history of systemic or anaphylactic reaction is considered a disqualifying condition for all duties including flying (12). Decisions for waiver are made on a case-by-case basis. However, the rest of the entry focuses on reactions to insect bites or stings and does not specifically address anaphylactoid reactions to RCM.

According to the Army regulation, a history of anaphylaxis is a disqualifying condition for all classes (1/2/2F/3/4) of flying duties. Final determinations of medical unfitness for flying duty are made by the U.S. Army Aeromedical Activity (16). For civil aviators, severe allergic reactions are disqualifying per the Code of Federal Regulations Title 14, Part 67.401, and will require a special issuance. The Federal Aviation Administration would make a determination after submission of all pertinent medical information and current status for all classes of medical certificates (5).

The pilot had an uneventful recovery from his laparoscopic appendectomy and was granted an indefinite waiver for his anaphylactoid reaction by his major command authority after Aeromedical Consultation Service review and chart evaluation. The pilot was briefed on the need to request a newer, low-osmolality nonionic contrast agent and pretreatment protocol regimen prior to any further CT scans requiring radiographic contrast media administration.

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You are the flight surgeon at a small Air Force base. You are seeing a typical day of clinic when a 49-yr-old master navigator presents to your clinic for evaluation. He has been an avid runner for the last several years and has always been in excellent physical condition. He presents today with a concern about his exercise tolerance. He states that over the past several years he has run 20 to 50 mi/wk and he even ran a full marathon approximately 1 yr ago. However, over the past few months he has been unable to run as long or as far as he previously could. He finally decided to seek medical attention because he is concerned about potentially failing his upcoming physical fitness test. On further questioning, he reports that his primary concern is shortness of breath, stating that he cannot run even half a mile without becoming winded and needing to stop. The only time he typically develops any shortness of breath is with significant exertion. He denies any chest pain or tightness and has no aching pain in his jaw or arm with exertion or at rest.

1. What should you do?
 - A. Advise the patient that he is deconditioned and that he needs to intensify his exercise regimen.
 - B. Send the patient for an emergent cardiac evaluation at the local emergency department.
 - C. Take a more detailed history and physical.

ANSWER/DISCUSSION

1. C. Dyspnea is the most common atypical presentation for acute coronary syndrome (2), and in a 49-yr-old man complaining of dyspnea, acute coronary syndrome should be in the differential diagnosis. Immediate emergency evaluation is not indicated at this point since your flyer's chronic exertional dyspnea is more consistent with stable angina (if it is cardiac in etiology). Stable angina is a condition characterized by cardiac chest discomfort that is reliably elicited by stress or exertion and relieved with rest or nitroglycerin. Stable angina is reproducible with a similar amount of exertion or stress every time and does not occur at rest. In addition, the evaluation of stable angina is accomplished as an outpatient. This patient does not have classic angina, but his shortness of breath may represent an angina equivalent. If his dyspnea is cardiac in origin, his case would be classified as stable angina rather than acute coronary syndrome, so you proceed with the work-up in the outpatient setting.

On further questioning, the flyer denies lightheadedness, palpitations, and lower extremity edema. He also denies any new requirement for more pillows at night (orthopnea) and has had no episodes of awakening at night gasping for air (paroxysmal nocturnal dyspnea). The patient states that he has had no wheezing or cough and has no history of asthma. He has had no infectious symptoms, such as fever, chills, nausea, vomiting, or diarrhea. He states that his bowel patterns have been unchanged over many years, typically having one to two normal bowel movements per day. He denies hematochezia or melena.

Your flyer's social history is nonrevealing. He drinks beer occasionally, has never used tobacco or illicit drugs, and has been married for many years. He also has no family history of coronary disease, lung disease, or other significant medical conditions. He has two children, both of whom are completely healthy. He also denies any known environmental exposures other than the typical exposures experienced by all aircrew members.

On physical exam this patient appears his stated age and is in no distress. His vital signs are as follows: heart rate 98, blood pressure

125/75, respiratory rate 10, oxygen saturation 99% on room air, body mass index 23. His heart exam demonstrates a normal S1 and S2 with no obvious S3 or S4, with normal rate and rhythm. His lung exam is normal with good air movement throughout all lung fields and no wheezes, rales, or rhonchi. He has no lower extremity edema, no hepatosplenomegaly, and no jugular venous distention. The rest of his physical exam shows no obvious abnormalities.

2. What is your next step?
 - A. Obtain an electrocardiogram.
 - B. Obtain a chest X-ray.
 - C. Order basic labs, including a complete blood count (CBC).
 - D. All of the above.

ANSWER/DISCUSSION

2. D. In the case of chronic dyspnea, the most likely diagnoses are asthma, chronic obstructive pulmonary disease, interstitial lung disease, myocardial dysfunction, and obesity/deconditioning (7). Anemia should also be included in the differential.

The patient's electrocardiogram is performed in the clinic and reveals normal sinus rhythm with a normal axis, normal intervals, and no ST segment changes or T wave inversions. The chest X-ray is unremarkable with normal lung fields and no hyperinflation (indicative of chronic obstructive pulmonary disease) or prominent vascularity (indicative of congestive heart failure). His CBC returns with the following results: white blood count $3.5 \text{ K} \cdot \mu\text{l}^{-1}$, hemoglobin $9 \text{ g} \cdot \text{dl}^{-1}$, hematocrit 27%, platelets $275 \text{ K} \cdot \mu\text{l}^{-1}$, mean corpuscular volume 76 fl.

3. What should you do now?
 - A. Send this patient to a hematologist for evaluation.
 - B. Start the patient on iron supplementation.
 - C. Order labs to further define his anemia.

ANSWER/DISCUSSION

3. C. Iron deficiency is not the only cause of a microcytic anemia and the diagnosis should be confirmed with iron studies. Most anemias do not require evaluation by a hematologist.

Once the initial labs return, you follow up with iron studies. His iron level is $35 \mu\text{g} \cdot \text{dl}^{-1}$ with a transferrin saturation of 12%, and his ferritin level is $16 \text{ ng} \cdot \text{ml}^{-1}$, providing a clear diagnosis of iron deficiency anemia.

4. What is your next step?
 - A. Start the patient on oral iron supplementation.
 - B. Consult gastroenterology for upper and lower endoscopy.
 - C. Consult hematology for evaluation of anemia.
 - D. A and B.

ANSWER/DISCUSSION

4. D. Iron supplementation should be started in the setting of iron deficiency anemia. In addition, with the exception of young, menstruating women, patients with iron deficiency anemia should be evaluated for occult blood loss, typically in the gastrointestinal tract (5).

You bring the patient back to your office to let him know that he has iron deficiency anemia. As before, his history is completely unrevealing for an etiology of bleeding. You write him a prescription for iron sulfate 325 mg three times a day while awaiting results of the gastrointestinal evaluation. His colonoscopy and esophagogastroduodenoscopy (EGD) are grossly unremarkable, with no malignancy, ulcers, or arteriovenous malformations noted. However, the small bowel biopsies