Emergency Medicine Reports
Practical, Evidence-Based Reviews in Emergency Care

Volume 35, Number 15 / July 13, 2014 www.emreports.com

Authors:

Roselynn Gentles, MD, St. James Healthcare, Butte, MT.

Larry Mellick, MD, MS, FAAP, FACEP, Professor, Department of Emergency Medicine and Pediatrics, Georgia Regents University, Augusta, GA.

Peer Reviewer:

Steven M. Winograd, MD, FACEP, St. Barnabas Hospital, Clinical Assistant Professor, Emergency Medicine, New York College of Osteopathic Medicine, Old Westbury, NY.

Statement of Financial Disclosure

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Farel (CME question reviewer) owns stock in Johnson & Johnson. Dr. Schneider (editor) is a retained consultant for Logical Images. Dr. Stapczynski (editor) owns stock in Pfizer, Johnson & Johnson, Axogen, Walgreen Company, and Bristol Myers Squibb. Dr. Gentles (author), Dr. Mellick (author), Dr. Winograd (peer reviewer), Ms. Mark (executive editor), and Ms. Hamlin (managing editor) report no financial relationships with companies related to the field of study covered by this CME activity.

AHC Media

Disease Presentations of the Uvula

I work in a county hospital ED, and as you already know by that statement, we see an interesting and sometimes unusual patient population. We are also close to the Phoenix airport and main bus station, so we commonly have travelers from all over coming by with their problems and issues, some mundane and other fantastical. We have patients complete a registration form with the name, birthdate, and statement, in their own words, why they are coming today to the ED. We get all sorts of responses, some just a few words, others a long tale of woe. It is sometimes a challenge to figure out why, and why now, even after talking with the patient.

For non-critical patients, those who do not need urgent assessment and treatment, my role as an attending is to discuss the patient with the residents after they have performed the history and physical examination. Now it is my turn to try and make sense of these sometimes confusing complaints. It's my time to cut through the clutter and impart definition to the patient's problem. And sometimes I'm stumped. If there is a complaint localized to a usual body part or an issue claimed by the patient that I have never heard of (a potential range that shirks the older I get — I may not know the specific details of the latest insights, but at least I have heard of it before), I have a stalling response to give me time to marshall my thoughts; I respond to the resident that I must have been absent that day in medical school where this was discussed.

After that admittedly lame attempt at humor, the resident and I can then work through the patient's problem together.

So it once was when patients came in complaining of pain or swelling of that thing that hangs in the back of the throat. I have seen a few cases of uvulitis over the years and read the individual case reports. The authors of this issue have written an excellent review of this unusual problem. After reading this issue, you can say with confidence, I know about this problem.

— J. Stephan Stapczynski, MD, FACEP

Introduction

The uvula, or as our patients describe it, "the little thing that hangs down the back of the throat," is one of the most commonly ignored parts of the body. However, like all organs of the body, even the diminutive uvula can have its own unique problems and disease presentations. The purpose of this article is to review different disease presentations and conditions of the uvula. (*See Table 1.*)

Angioedema: Quincke's Disease or Isolated Angioedema

An isolated form of angioedema called Quincke's disease can involve the uvula. Quincke's disease is induced by several factors, including foods, drugs, and inhalants. It is most commonly attributed to a type 1 hypersensitivity reaction, but may also be due to medication reactions, inhalation reactions, trauma (usually from intubation or endoscopy), hereditary angioedema, or infections.[5-9] It should be differentiated from uvulitis, which is primarily considered to be an

Executive Summary

- Most infections of the uvula are viral.
- Bacterial infections are the most common cause of isolated uvulitis.
- Group A Streptococcus is the most common organism causing bacterial uvulitis.
- In cases of isolated uvular edema, think of the possibility of hereditary angioedema.
- Because thermal or chemical burns of the uvula are often associated with illegal activity, patients may not be forthcoming with this history.

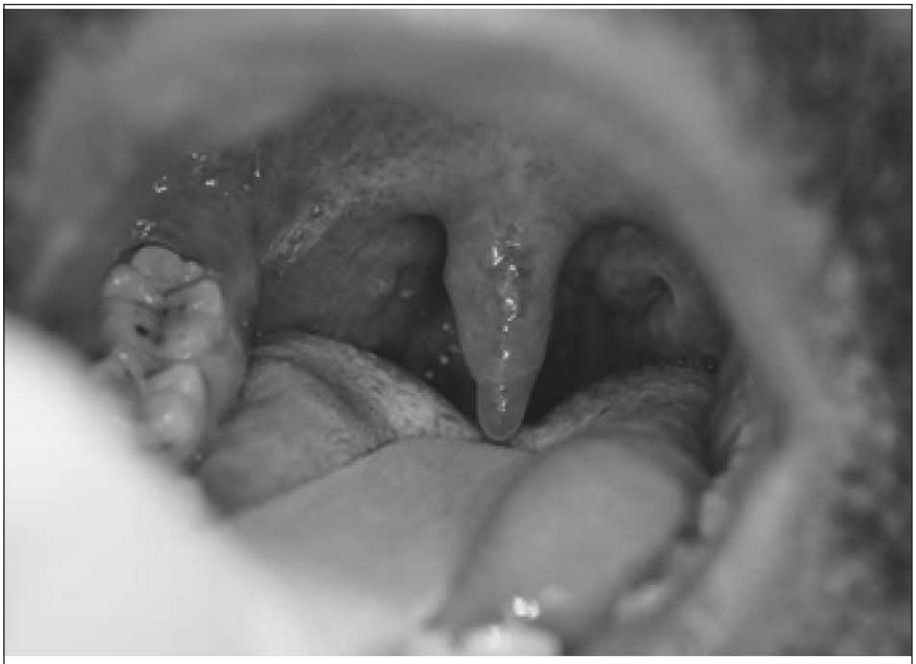
infectious process. Symptoms vary by individual, with the most common complaint being a sore throat. Other complaints include a feeling of neck fullness, difficulty breathing, and inability to swallow. Patients may also have the typical "hot potato voice" due to the swelling of the pharynx.

Hereditary Angioedema (HAE)

In the absence of medications, allergic reactions, trauma, or infection, one may consider hereditary angioedema (HAE) as a cause for uvular edema. The uvula in this case is rarely erythematous, but rather it bears a similar appearance to that of a white grape.[9] Bradykinin is a vasodilator thought to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain. The C1-esterase-inhibitor is a key regulator of the factor XII/kallikrein proteolytic cascade that leads to bradykinin production. When the C1 esterase inhibitor is absent or dysfunctional, a bradykinin cascade is triggered, leading to vasodilation and edema of the tissue. Most concerning is concurrent involvement of the larynx and airway compromise. Screening for the enzyme deficiency can be done by ordering a C3 and C4 level. A normal C3 and low C4 would suggest the condition.[10] Unfortunately, hereditary and ACE-inhibitor-induced angioedema do not respond to corticosteroids, antihistamines, or epinephrine. Instead, interventions to decrease bradykinin activity are indicated.[10,11] Some physicians have successfully used fresh frozen plasma (FFP) to reverse the effects (*see Table 2*). FFP contains kininase II, which breaks down bradykinin, rendering it ineffective. It also contains a C1 esterase inhibitor, making it effective for hereditary angioedema.[10,12] Most symptoms appear to resolve within a matter of hours; however, there are only case reports currently available. No studies to date have been performed to assess a large group's response to FFP.

There are currently at least two medications available that act on the bradykinin cascade, ecallantide and icatibant. Ecallantide is a kallikrein inhibitor, which reduces the conversion of kininogen to bradykinin, thereby reducing the amount of swelling and pain. Icatibant is a bradykinin receptor antagonist that was approved by the FDA in 2011 for use in severe asthma attacks as well as for treatment of hereditary angioedema. It is a competitive antagonist selective for the bradykinin B2 receptor and has an affinity similar to bradykinin. Icatibant inhibits bradykinin from binding the B2 receptor and, consequently, treats the clinical symptoms of an acute, episodic attack of HAE. The bradykinin cascade is stopped, thereby preventing systemic vasodilation and edema.[10,12-14] In a study by Bas et al, 30 mg of icatibant was given subcutaneously to eight patients with angioedema. The average time to

Figure 1: Isolated Edema of the Uvula



Isolated edema of the uvula in a 30-year-old male who presented to the emergency department complaining of a swollen uvula and a sore throat. The patient denied a fever or recent illness and indicated that his uvula felt "irritated from scratching."

initial improvement of symptoms was 50.6 minutes, with complete resolution of symptoms within 4.4 hours.[14] In addition, Schmidt et al presented a case of a patient who was given steroids, diphenhydramine (Benadryl), and epinephrine. The patient's symptoms did not respond. As a last resort, they gave the patient 30 mg of icatibant. Symptoms resolved rapidly, which avoided placement of an advanced airway.[15] Randomized, controlled trials have proven icatibant's efficacy for hereditary angioedema. As the pathways are similar for ACE inhibitor angioedema, it is hoped that icatibant will be likewise effective.[13]

Allergic

Allergic reactions or type 1 hypersensitivity reactions can cause uvulitis. Due to an IgE-mediated response, the reaction causes a sudden release of mast cells and vasodilation, causing urticaria, angioedema, or anaphylaxis.[5,6,8] A typical patient may present with systemic hives, edema, and difficulty breathing. Wheezes may or may not be present, although the patient may have inspiratory stridor. Treatment involves corticosteroids, antihistamines, H1 and H2 blockers, and epinephrine.[7] The patient should be monitored for a minimum of 6 hours after these therapeutic interventions to evaluate for a latent reaction phase.

Other Causes

There are other non-infectious causes of uvular edema. Myxedematous infiltration in hypothyroidism is well documented in the literature. A variety of pharmaceuticals, both illegal and legal, can lead to uvulitis. Alcoceba et al performed a prospective study identifying characteristics of individuals developing uvular edema. Of these, several were related to drug reactions, namely nonsteroidal anti-inflammatory drugs (NSAIDS), angiotensin-converting-enzyme inhibitors (ACE inhibitors), cocaine and marijuana use, as well as glucosamine sulfate, ipratropium bromide, and the juice from *Ecballium elaterium* (home remedy for sinusitis).[5,8] It is difficult to identify the difference between a medication reaction and an allergic reaction. Thus, initial management should include diphenhydramine, steroids, and, possibly, epinephrine. If ACE inhibitors are involved, the edema is usually due to the same bradykinin cascade as seen in hereditary angioedema and may not be responsive to the aforementioned treatment.

Table 1: Potential Diseases and Conditions of the Uvula

1. Angioedema
    a. Isolated angioedema or Quincke's disease
    b. Hereditary angioedema (HAE)
    c. Allergic
    d. Ace inhibitor and other drug associated angioedema
    e. Myxedematous changes of hypothyroidism
2. Burns
    a. Thermal
        i. Smoke inhalation injuries
        ii. Cocaine or marijuana smoking
        iii. Sauna exposure
    b. Chemical
3. Infections
    a. Viral
    b. Bacterial
    c. Mycobacterium
    d. Trauma
4. Postsurgical Uvula
    a. Surgical complications
        i. Orotracheal intubation associated
        ii. Suctioning or bronchoscopy
    b. Cultural uvulectomy
5. Hematologic and Oncologic
    a. Hemangiomas
    b. Oncologic
6. Congenital Variants
    a. Bifurcate uvula
    b. Elongated uvula
7. Vascular
    a. Superior vena cava syndrome
    b. Internal carotid artery ligation
    c. Lymphatic duct ligation
    d. Kawasaki syndrome

Burns: Thermal

Cannabis sativa contains a chemical, hashish, which burns much hotter than tobacco products. This is particularly irritating to the oropharynx, leading to swelling and erythema of the entire pharyngeal cavity, especially the uvula.[16,17] Symptoms occur within hours after heavy smoke exposure and may last up to 24 hours.[17,18] Boyce et al presented a clinical case of a patient who presented with difficulty breathing after smoking marijuana. The physical exam showed an edematous uvula. The patient was treated with antihistamines and corticosteroids and discharged home. The presumed etiology was either an inhalation burn or an allergic reaction to the cannabis.[19]

Cocaine or crack also burns at a higher temperature than typical tobacco products and can cause inflammation as well. In fact,

Table 2: Pharmaceuticals Used to Treat Uvular Diseases

Hereditary Angioedema		
FFP	2 units IV (adult)	Anecdotal cases reports, response takes hours, not currently recommended as first-line therapy
C1 inhibitor human (Berinert®)	20 units/kg infused slowly	Used for acute attacks, response within 30-120 min
Icatibant (Firazyr®)	30 mg SC in the abdomen	Bradykinin receptor antagonist, response within 30-120 min
Ecallatide (Kalabitor®)	30 mg (3 mL), SC in three 10 mg (1 mL) injections in thigh, abdomen and upper arm	Kallikrein inhibitor, response within 30-120 min Anaphylaxis observed in 4%
Thermal Burns and Adjunct to Infectious Uvulitis		
Dexamethasone	0.1 mg/kg IV (max dose 12 mg) q6-12 hours	Continue until swelling stabilizes
Bacterial Uvulitis		
Ceftriaxone	1 g IV (adult)	

breathing in any air that is extremely hot can cause uvulitis. There have even been reported cases following sauna exposures.[9] Treatment involves administration of steroids, in particular dexamethasone, as its anti-inflammatory potency is 25 times greater than hydrocortisone and it has a half life of 36 to 72 hours.[17] Dexamethasone can be given continuously with 0.1 mg/kg given every 6-12 hours, but not exceeding 12 mg in any dose.[17]

Burns: Chemical

Chemical burns to the uvula can occur following ingestion of toxic substances during accidental or purposeful ingestions. Multiple toxic acid or base (alkaline) agents can injure the oral mucosa to include the uvula. Acids typically cause a coagulation necrosis by denaturing proteins. The resulting eschar or coagulum can limit the penetration of the acid. However, bases tend to produce liquefaction necrosis and cause a more severe injury. Denaturing of proteins and saponification of fats occur without forming an eschar to limit tissue penetration.

Infections: Viral

Viral infections of the oropharynx tend to occur more commonly than bacterial ones do. However, there is not a plethora of research involved in identifying the individual viruses that can cause pharyngeal irritation. Human herpesvirus 6 (HHV6) is the virus that causes exanthem subitum (ES), a viral illness characterized by a high fever for approximately four days followed by a diffuse rash. In the early 1990s, uvulo-palatoglossal junction ulcers (UPJ) were identified as an early marker for the disease. The uvulo-palatoglossal junction is located where the palatoglossal folds approximate with the base of the uvula. K.B. Chua et al performed a study in Malaysia identifying UPJ ulcers as a pathognomonic finding in HHV6. They recruited a total of 46 children, 20 of whom had UPJ ulcers. Of the 19 patients who followed up, 17 of them had subsequently progressed to the full-blown symptoms of ES.[20] Many other viral agents including Coxsackie A may be associated with a sore throat and often involve the uvula.

In contrast to ulcer formation, human papillomavirus 6 (HPV-6) and human papillomavirus 11 (HPV-11) can lead to papillomas of the oral cavity. Though typically occurring on the tongue or palate, they can also cause lesions on the uvula. The papillomas form fibrous lesions that can lead to uvular elongation and a sense of choking in the patient. These can be removed surgically and rarely lead to cancer of the oropharynx.[21]

Infections: Bacterial

Infections of the uvula often accompany tonsillitis and, in the past, were seen relatively commonly with epiglottitis. Uvula infections can also occur as isolated infections. Infections are perhaps the most concerning cause of uvular edema. Bacterial infections are the most common, namely due to group A streptococcus, although it can also be caused by *Streptococcus pneumoniae*, and, in some individuals, *Haemophilis influenzae*.[8,22] In the case of *H. influenzae*, it is not the uvular edema that is the primary concern so much as it is the epiglottitis, which can concurrently develop, resulting in airway compromise. In adults this is rarely the case; however, in the pre-vaccine era it was not uncommon in children. Currently, it can still be seen in those who have not been vaccinated.[8,9,22] Patients typically present with a sore throat and fever. However, symptoms may be even more severe, including presentation of an individual with a hot potato voice, respiratory distress, drooling, and dysphagia. Current recommendations for any patient with both fever and uvular edema are to obtain lateral soft tissue films of the neck.[8,9,22] If signs of epiglottitis are evident, namely the typical "thumb print sign," further investigation with laryngoscopy and

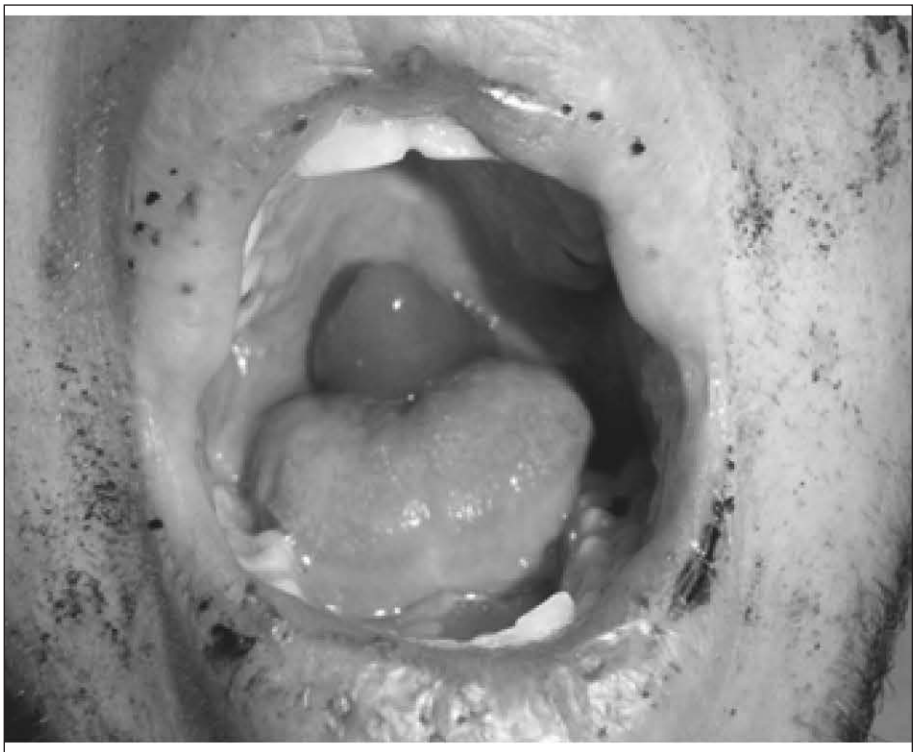
consultation with an ear, nose, and throat specialist (ENT) and surgery are advised.[9] While waiting for the consultant, a complete blood count (CBC), blood cultures, and oropharyngeal cultures should be obtained, and the patient should be started on ceftriaxone and dexamethasone.[9] As a precaution, if the patient is not tolerating oral secretions and appears in respiratory distress, then the patient should be kept calm and allowed to remain in any position that is most comfortable for him or her. In this case, obtaining an oropharyngeal culture should be deferred until the patient is taken to the operating room for intubation, although antibiotics should be started as soon as possible.

Diphtheria is a historical disease in the developed world that also involves the uvula. However, in underdeveloped countries the disease can still be found and is associated with the bacterium *Corynebacterium diphtheriae* (a pleomorphic Gram-positive rod). Diphtheria predominantly involves the nasopharyngeal mucosa and presents as a dirty gray membrane covering the tonsils, tonsillar pillars, soft palate, and uvula. Bleeding with attempts at removal of the membrane and a "bull-neck" appearance secondary to cervical adenopathy are commonly described. The case mortality rate for diphtheria is up to 12%.

Mycobacterium

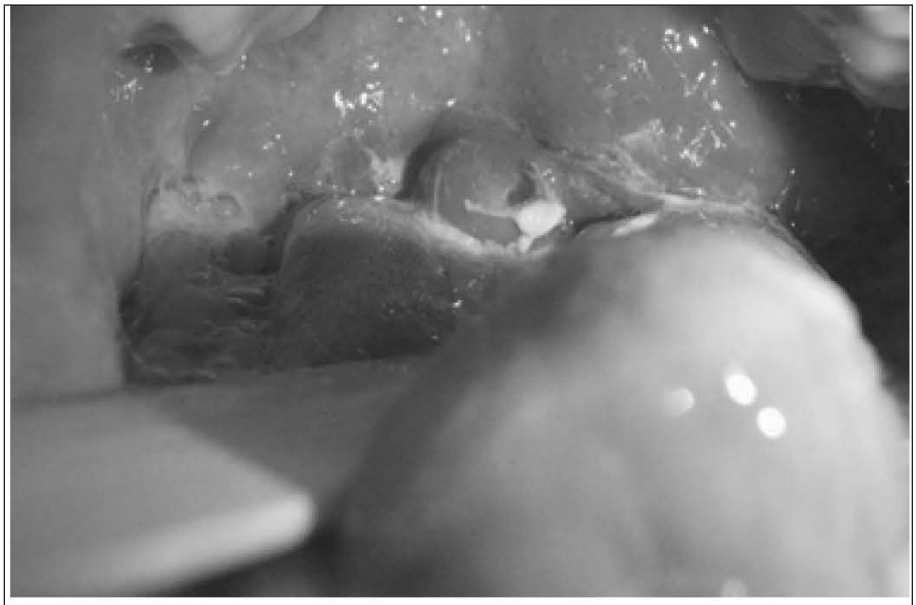
An additional consideration in immunocompromised patients is the presence of *Mycobacterium tuberculosis.* Although oral cavity *M. tuberculosis* typically occurs in the tongue and mandible, some cases have been reported with primary sites involving the uvula. Signs of infection can range from a single ulcer to a yellow discharge to a nodular mass. The workup should include a chest X-ray, purified protein derivative (PPD) test, and a culture and stain for acid fast bacilli. After confirming the diagnosis, treatment should be started with a six-month course of rifampin, ethambutol, isoniazid, pyrazinamide, and streptomycin.[23-25]

Figure 2: Edema and Inflammation of the Uvula



A 26-year-old male who presented for evaluation following an assault. He demonstrated marked edema and inflammation of the uvula, and he admitted to smoking marijuana with a crack pipe.

Figure 3: Tonsillitis with Uvula Swelling and Inflammation

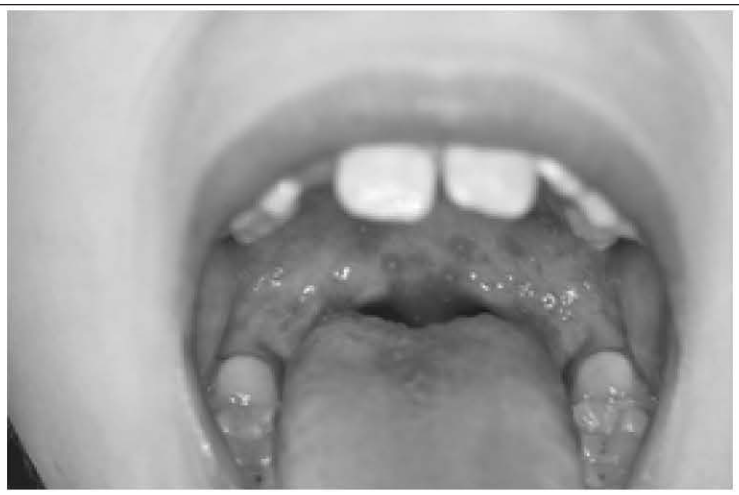


Tonsillitis along with uvula swelling and inflammation of unknown etiology in an 18-year-old male who presented for evaluation of severe throat pain. The rapid streptococcal test was negative.

Fungal

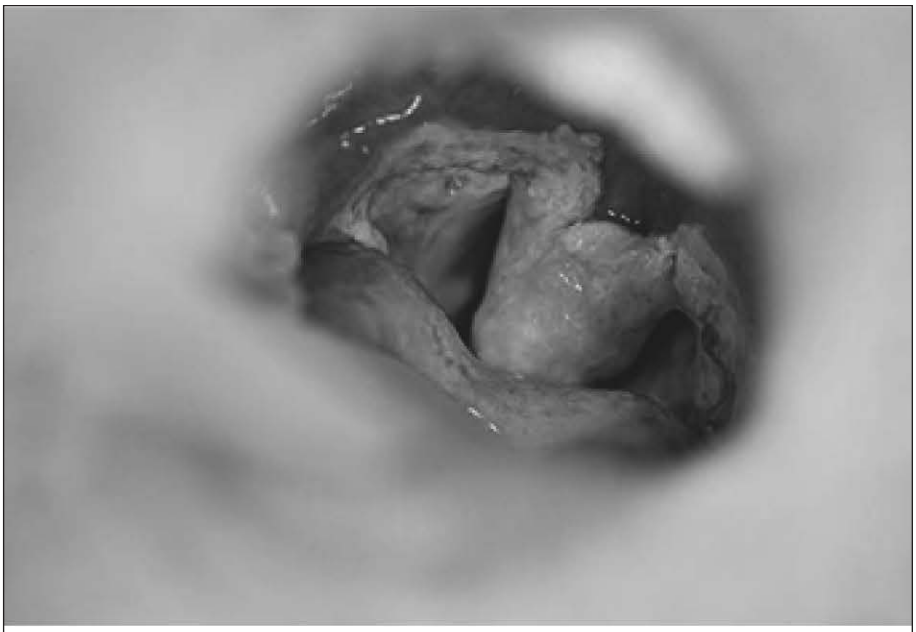
Candida, in addition to causing thrush in infants, can also be isolated to the uvula. The presentation

Figure 4: Lesions on Palate and Uvula Consistent with Herpangina



Eight-year-old female presenting with the chief complaint of fever, cough, rhinorrhea, and a sore throat. The lesions demonstrated on the palate and uvula were consistent with herpangina, which is typically caused by the Coxsackie A virus.

Figure 5: Eschar of the Uvula



Eschar of the uvula in a 17-year-old girl four days following tonsillectomy and adenoidectomy.

may be an erythematous uvula in the absence of other findings or white plaques isolated to the uvula. The investigation should include neck films to evaluate for epiglottitis and possibly uvular cultures. Treatment is nystatin, which leads to a resolution of symptoms within a few days.[26]

Trauma: Post-surgical Uvula

Tonsillectomy is one of the oldest and most commonly performed surgeries in the pediatric population. Originally performed in an attempt to prevent recurrent pharyngitis, it is now used in cases for obstructive sleep apnea.[27] Occasionally these pediatric patients will present to the ED after having their tonsils and adenoids removed. To the untrained eye, the posterior pharynx may look severely infected. However, the normal healing process involves the formation an eschar over the incised area, usually extending across the entire posterior pharynx and appearing yellow, white, and occasionally black in some places. This usually sloughs off in 5 days. Bleeding from this area may occur. Patients are advised to initially try icing; however, if there is a large amount of bleeding, the patient should return to the emergency department. Overnight observation is typically warranted to ensure hemostasis, and about half of these patients need to be taken the OR for revision. Tweedie et al performed a retrospective review of post-operative complications. Those at highest risk of post-operative complications were patients with Down syndrome, cardiac disease, obesity, cerebral palsy, craniofacial anomalies, mucopolysaccharidoses, and hemoglobinopathy.[28] The most common complaint was respiratory distress, especially in the aforementioned patients. Other complaints include fever, odynophagia, and uvular edema.[27] Of the 1735 patients, only seven returned to the operating room for hemorrhage.[28] Gallagher et al performed a study involving surgical techniques in 4776 children. Post-operative bleeding was more common in older children compared to younger kids.[27]

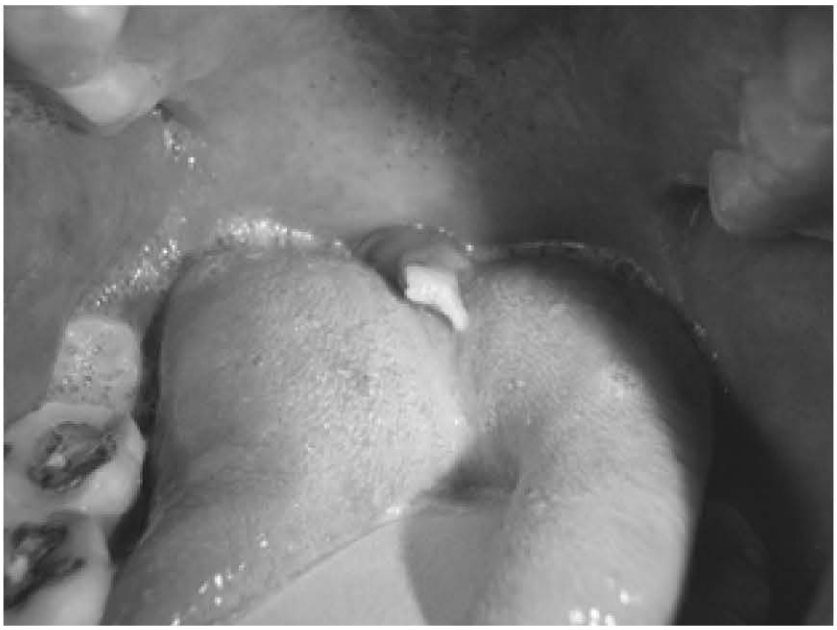
Surgical Complications

One complication of adenoidectomy is uvular necrosis. Most often this is iatrogenic, due to intubation. However, isolated cases have also been reported in patients undergoing endoscopy.[29-33] It is thought that ischemia occurs due to impingement of the uvula against the hard palate or posterior oropharynx either by the scope or by the orotracheal tube during the procedure. The uvula then swells and may become necrotic or even ulcerate. It often appears elongated, with the tip of the uvula

turning white.[34] Patients complain of a sore throat persisting past the usual duration for post-operative throat pain, as well as a sensation of a foreign body in their mouth.[29] After 5-14 days, the patient should report relief of symptoms, often with the tip slouching off.[30-33]

Aside from oropharyngeal intubation and endoscopy, isolated cases of uvular necrosis have also been reported in patients after undergoing aggressive oropharyngeal suctioning,[29,32] bronchoscopy,[34] or even after use of a laryngeal mask airway.[35] Regardless of the cause of uvular necrosis, conservative management is recommended, usually with observation, pain control, steroids, and in some cases epinephrine.[29-31,35] If conservative management is ineffective, surgical removal of the uvula is advised.

Figure 6: Idiopathic Necrosis of the Uvula



Idiopathic necrosis of the uvula in a 31-year-old male who presented for evaluation of physical changes noted to his uvula. The patient denied any trauma or infections.

Cultural Uvulectomy

Since ancient times, the uvula has been thought to contribute to a range of maladies, including cough, upper respiratory infections, and reflux.[39] Some cultures traditionally remove the uvula in infancy while others may wait for persistent disease manifestations attributed to the uvula.[40-42] Prual et al reported that by the age of 5 years, almost 20% of children in Niamey, capital of Niger, had undergone removal of the uvula.[41] Some African cultures believe that removal of the uvula facilitates breast feeding and speech development. Removal is done by traditional medicine, sometimes using a special knife or by tying a horse hair tied around the tissue. Complications include throat pain, aspiration into the airway of the cut uvula, hemorrhage, and infections such as neck abscesses and tetanus.[41,42] Obstructive sleep apnea and snoring caused by palatal stenosis resulting from traditional uvulectomy during childhood has been reported.[43]

Hemangiomas

Cavernous hemangiomas involve rapid proliferation of blood vessels during early childhood, followed by slow involution. They are usually soft and painless and rarely resolve completely. Most develop in the head and neck region, usually sparing the oral mucosa. However, adult hemangiomas occur more frequently in the oral mucosa in areas of trauma, namely the tongue or lips, although rare cases have been reported with involvement of the uvula. Most hemangiomas do not necessitate surgery. Management includes treatment with steroids, sclerotherapy, cryotherapy, or surgical removal. Two separate laser techniques are used: CO2 laser therapy and neodymium:yttrium-aluminum garnet (Nd-YAG).[36] In an isolated case reported by Thong et al, a middle-aged man presented with a chief complaint of sleep apnea. On examination, the individual had a large, bluish-colored uvula. Nasal endoscope showed extension to the nasal portion of the soft palate. Removal of the uvula using CO2 laser therapy resolved the patient's symptoms.[36]

Oncologic

Cancer of the uvula is rare. The most common type is papillomas secondary to a viral infection, namely HPV-6 and HPV-11. This typically causes a fibrous protrusion on the uvula, which may result in elongation and a choking/gagging sensation. Surgical incision leads to resolution of symptoms.[21]

Carcinomas of the oropharynx typically involve the tongue and oral mucosa. Rarely, they involve the uvula, although they are considered a very aggressive tumor when they do. Restrepo et al performed a retrospective study evaluating the frequency and characteristics of uvular carcinomas, as well as patient outcome. They found that most patients presented with T1 or T2 size lesions. Despite primarily being only T1 or T2, many tumors were able to metastasize, as the tumor may have been more developed, but was restricted visibly by the size of the uvula. Metastasis is via the lymphatic system, although lymphadenopathy may be absent, unilateral, or bilateral. In lesions greater than 1 cm, cervical lymph node metastasis was present 92.9% of the time. The treatment of choice for uvular carcinoma is uvula removal with bilateral

cervical lymph node dissection. Patients diagnosed with stage I and II of the disease have a good chance of surviving without any disease complications. However, of the individuals diagnosed in stage III and IV, 78.5% ended up dying of further disease complications.[37]

Goldman et al described a case of neuroendocrine carcinoma. Although carcinoid tumors rarely involve the head and neck, they are sometimes found in the larynx. In this case, the patient presented with a feeling of something being stuck in the back of his throat. On exam, the patient had a 2 cm lesion on the uvula, as well as bilateral cervical adenopathy. A biopsy of the uvular lesion showed a poorly differentiated carcinoma of unknown type, but subsequent neck dissection did not show any lymph node involvement.[38]

Congenital Variants

Not all abnormal-appearing uvulas are a sign of pathology. There are some normal variants that occur, including the bifurcate uvula and elongated uvula. The bifurcate uvula occurs when the uvula undergoes partial fusion, resulting in a single trunk and two tips. In and of itself, it has no impact on development or speech in the individual and is merely an interesting deviation. However, when the uvula is split completely in half, this may be indicative of incomplete palatal fusion.[1]

Additionally, the uvula can also grow longer, sometimes reaching the level of the vocal cords. This can cause irritation, cough, vomiting, dysphagia, and sleep apnea. If asymptomatic, no treatment is necessary. However, if symptoms persist, a uvulectomy may be performed.[2] Although generally considered a benign disorder, uvular elongation can be fatal. Nachman et al present a case in which an infant died of asphyxiation due to an elongated uvula becoming lodged between the vocal cords. Another concern for uvular elongation is that there may be a correlation in patients having an increased risk of developing uvulitis.[5]

Vascular

Vascular alterations such as superior vena cava syndrome, ligature of the internal jugular vein, and obstruction of lymphatic flow after ligature of the thoracic duct have been reported to cause uvular swelling.[5] Additionally, uvula swelling can occur as part of the presentation of a vasculitis such as Kawasaki syndrome.[44]

Conclusion

The posterior pharynx is often visualized to evaluate for pharyngitis, coxsackie viruses, or for petechiae. The uvula itself is commonly overlooked, except in cases in which it looks vastly abnormal. Some may be regular anatomical variants, while others may be indicators of a life-threatening illness. All patients presenting with isolated uvulitis should have a thorough history and physical exam, in particular noting any recent drug use (legal or illegal), surgical procedures, or recent fevers/illness. If the patient presents with fever and an erythematous uvula, a lateral soft-tissue film should be obtained to evaluate for epiglottitis, and antibiotics should be started. If an ACE inhibitor is involved or there is a concern for hereditary angioedema, the patient should be examined with a fiberoptic endoscope to evaluate for concurrent laryngeal edema. The physician should also inquire about recreational drug use, as there have been many reports of isolated angioedema due to cannabis and crack inhalation injuries.

References

1. Friedman O, Wang T, Milczuk H. Chapter 186: Cleft Lip and Palate. In: Flint, Cummings. *Otolaryngology Head & Neck Surgery*, 5th edition, 2010.
2. Marom T, Roth Y, Cinamon U. Elongated uvula. *Ear Nose Throat J* 2010;89(7):E38.
3. Woodson G. Chapter 56: Laryngeal and Pharyngeal Function. In: Flint, Cummings. *Otolaryngology Head & Neck Surgery*, 5th edition, 2010.
4. Finkelstein Y, Meshorer A, Talmi YP, Zohar Y, Brenner J, Gal R. The riddle of the uvula. *Otolaryngol Head Neck Surg* 1992;107(3):444-450.
5. Alcoceba E, Gonzalez M, Gaig P, Figuerola E, Auguet T, Olona M. Edema of the uvula: Etiology, risk factors, diagnosis, and treatment. *J Investig Allergol Clin Immunol* 2010;20(1):80-83.
6. McNamara RM. Clinical characteristics of acute uvulitis. *Am J Emerg Med* 1994;12(1):51-52.
7. Mohseni M, Lopez MD. Images in emergency medicine. Uvular angioedema (Quincke's disease). *Ann Emerg Med* 2008;51(1):8, 12.
8. Huang CJ. Isolated uvular angioedema in a teenage boy. *The Internet Journal of Emergency Medicine*. 2007;3(2). Last accessed 26 January 2013.
9. Le Blanc C, Jenkins C, Godsoe S. Acute uvulitis in the ED. *Canadian Journal of Diagnosis* 2008. Last accessed 26 January 2013.
10. Banerji A. Hereditary angioedema: Classification, pathogenesis, and diagnosis. *Allergy Asthma Proc* 2011;32(6):403-407.
11. Vasekar M, Craig TJ. ACE inhibitor-induced angioedema. *Curr Allergy Asthma Rep* 2012;12(1):72-78.
12. Stewart M, McGlone R. Fresh frozen plasma in the treatment of ACE

Emergency Medicine Reports

CME Objectives

Upon completion of this educational activity, participants should be able to:

- recognize specific conditions in patients presenting to the emergency department;
- apply state-of-the-art diagnostic and therapeutic techniques to patients with the particular medical problems discussed in the publication;
- discuss the differential diagnosis of the particular medical problems discussed in the publication;
- explain both the likely and rare complications that may be associated with the particular medical problems discussed in the publication.

inhibitor-induced angioedema. *BMJ Case Rep* 2012; Aug 24.
13. Illing EJ, Kelly S, Hobson JC, Charters S. Icatibant and ACE inhibitor angioedema. *BMJ Case Rep* 2012; Aug 30.
14. Bas M, Greve J, Stelter K, Bier H, Stark T, Hoffmann TK, Kojda G. Therapeutic efficacy of icatibant in angioedema induced by angiotensin-converting enzyme inhibitors: A case series. *Ann Emerg Med* 2010;56(3):278-282.
15. Schmidt PW, Hirschl MM, Trautinger F. Treatment of angiotensin-converting enzyme inhibitor-related angioedema with the bradykinin B2 receptor antagonist icatibant. *J Am Acad Dermatol* 2010;63(5):913-914.
16. Tennant FS Jr, Prendergast TJ. Medical manifestations associated with hashish. *JAMA* 1971;216(12):1965-1969.
17. Mallat A, Roberson J, Brock-Utne JG. Preoperative marijuana inhalation — an airway concern. *Can J Anaesth* 1996;43(7):691-693.
18. Guarisco JL, Cheney ML, LeJeune FE Jr, Reed HT. Isolated uvulitis secondary to marijuana use. *Laryngoscope* 1988;98(12): 1309-1312.
19. Boyce SH, Quigley MA. Uvulitis and partial upper airway obstruction following cannabis inhalation. *Emerg Med* (Fremantle) 2002;14(1): 106-108.
20. Chua KB, Lam SK, AbuBakar S, Lim ST, Paranjothy M, Koh MT, Lee WS. The predictive value of uvulo-palatoglossal junctional ulcers as an early clinical sign of exanthem subitum due to human herpesvirus 6. *J Clin Virol* 2000;17(2):83-90.
21. Goodstein LA, Khan A, Pinczewski J, Young VN. Symptomatic squamous papilloma of the uvula: Report of a case and review of the literature. *Case Report Otolaryngol* 2012;2012:329289. Epub 2012 Apr 17.
22. McNamara R, Koobatian T. Simultaneous uvulitis and epiglottitis in adults. *Am J Emerg Med* 1997;15(2):161-163.
23. Baruah B, Goyal A, Shunyu NB, Lynrah ZA, Raphael V. Tuberculosis of nose and palate with vanishing uvula. *Indian J Med Microbiol* 2011;29(1):63-65.
24. Kumar V, Singh AP, Meher R, Raj A. Primary tuberculosis of oral cavity: A rare entity revisited. *Indian J Pediatr* 2011;78(3):354-356.
25. Kakisi OK, Kechagia AS, Kakisis IK, Rafailidis PI, Falagas ME. Tuberculosis of the oral cavity: A systematic review. *Eur J Oral Sci* 2010;118(2):103-109.
26. Krober MS, Weir MR. Acute uvulitis apparently caused by *Candida albicans*. *Pediatr Infect Dis J* 1991;10(1):73.
27. Gallagher TQ, Wilcox L, McGuire E, Derkay CS. Analyzing factors associated with major complications after adenotonsillectomy in 4776 patients: Comparing three tonsillectomy techniques. *Otolaryngol Head Neck Surg* 2010;142(6):886-892.
28. Tweedie DJ, Bajaj Y, Ifeacho SN, Jonas NE, Jephson CG, Cochrane LA, Hartley BE, Albert DM, Wyatt ME. Peri-operative complications after adenotonsillectomy in a UK pediatric tertiary referral centre. *Int J Pediatr Otorhinolaryngol* 2012;76(6):809-815.
29. Calikapan GT, Karakus F. Uvula necrosis after endotracheal intubation for rhinoplasty. *Aesthetic Plast Surg* 2008;32(4):710-711.
30. Shores NJ, Bloomfeld RS. Images in clinical medicine. Uvular necrosis after endoscopy. *N Engl J Med* 2009;361(12):e20.
31. Evans DP, Lo BM. Uvular necrosis after orotracheal intubation. *Am J Emerg Med* 2009;27(5):631.
32. Tang SJ, Kanwal F, Gralnek IM. Uvular necrosis after upper endoscopy: A case report and review of the literature. *Endoscopy* 2002;34(7): 585-587.
33. Commins DJ, Whittet H, Okoli UC, Ewart M. Postintubation uvular necrosis. *Anaesthesia* 1994;49(5):457-458.
34. Sunio LK, Contractor TA, Chacon G. Uvular necrosis as an unusual complication of bronchoscopy via the nasal approach. *Respir Care* 2011;56(5):695-697.
35. Emmett SR, Lloyd SD, Johnston MN. Uvular trauma from a

Now You Can Complete Your Test with Each Issue

Here's a change we know you'll like: From now on, there is no more having to wait until the end of a 6-month semester or calendar year to earn your continuing education credits or to get your credit letter.

Log on to www.cmecity.com to complete a post-test and brief evaluation after each issue. Once the completed evaluation is completed, a credit letter is e-mailed to you instantly.

If you have any questions, please call us at (800) 688-2421, or outside the U.S. at (404) 262-5476. You can also email us at: customerservice@ahcmedia.com.

CME Instructions

HERE ARE THE STEPS YOU NEED TO TAKE TO EARN CREDIT FOR THIS ACTIVITY:

1. Read and study the activity, using the provided references for further research.
2. Scan the QR code below, or log on to **www.cmecity.com** to take a post-test; tests can be taken after each issue or collectively at the end of the semester. *First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice, or renewal notice.*
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the test, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. **Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.** You will no longer have to wait to receive your credit letter.

laryngeal mask. *Br J Anaesth* 2012;109(3):468-469.

36. Thong JF, Pang KP, Siow JK. Haemangioma of the uvula causing loud habitual snoring — a rare entity. *Med J Malaysia* 2008;63(5):408-409.
37. Espinosa Restrepo F, Martínez Capoccioni G, Martín Martín C. T1-T2 squamous cell carcinoma of the uvula: A little big enemy. *Otolaryngol Head Neck Surg* 2012;146(1):81-87.
38. Goldman NC, Barnes RE Jr. Atypical carcinoid (moderately differentiated neuroendocrine carcinoma) of the uvula. *Ear Nose Throat J* 2012;91(2):75-76.
39. Nachman R, Krispin A, Nnoli M, Hiss J. Infantile asphyxia due to aberrant uvula — an anatomic misadventure. *J Forensic Leg Med* 2010;17(7):401-403.
40. Hodes R. Cross-cultural medicine and diverse health beliefs. Ethiopians abroad. *West J Med* 1997;166(1): 29-36.
41. Prual A, Gamatie Y, Djakounda M, Huguet D. Traditional uvulectomy in Niger: A public health problem? *Soc Sci Med* 1994;39(8):1077-1082
42. Adeyi A, Nimkur TL. The traditionally amputated uvula amongst Nigerians: Still an ongoing practice. *ISRN Otolaryngology* 2011;125(9):982-986.
43. Ravesloot MJ, de Vries N. "A good shepherd, but with obstructive sleep apnoea syndrome": Traditional uvulectomy case series and literature review. *J Laryngol Otol* 2011;125:982-986.
44. Kazi A, Gauthier M, Lebel MH, Farrell CA, Lacroix J. Uvulitis and supraglottitis: Early manifestations of Kawasaki disease. *J Pediatr* 1992;120(4 Pt 1):564.

CME Questions

1. Icatibant is most effective in treating which of the following?
   A. allergic angioedema
   B. uvulitis due to hashish exposure
   C. papillomas from HPV-6
   D. hereditary angioedema
   E. diphtheria

2. The most effective treatment regimen currently in practice for cocaine burns is:
   A. 25 mg Benadryl PO q6 hours
   B. 20 mg famotidine PO q12 hours
   C. 1 mg/kg dexamethasone IV q6-12 hours
   D. 30 mg icatibant subcutaneously, once
   E. 0.3 mg epinephrine IM PRN acute swelling

3. Which of the following is the most common cause of infectious uvulitis?
   A. HHV-6
   B. HPV-6
   C. *Haemophilus influenzae*
   D. *Streptococcus pneumoniae*
   E. group A Streptococcus

4. All of the following are used to treat infectious causes of uvulitis *except*:
   A. ecallantide
   B. nystatin
   C. ethambutol
   D. ceftriaxone
   E. dexamethasone

5. Which of the following surgical procedures has *not* been known to cause uvular necrosis?
   A. endoscopy
   B. tonsillectomy
   C. intubation
   D. laryngeal mask airway
   E. aggressive suctioning

6. Uvular necrosis is one complication of adenoidectomy.
   A. true
   B. false

7. Which treatments are recommended for uvular necrosis?
   A. observation
   B. pain control
   C. steroids
   D. epinephrine in some cases
   E. all of the above

8. Which of the following should be evaluated in patients presenting with isolated uvulitis?
   A. recent drug use
   B. recent surgical procedures
   C. recent fever
   D. recent illness
   E. all of the above

9. In some cultures, the uvula is though to cause which disorders
   A. upper respiratory infections
   B. Coughing
   C. Sleep apnea
   D. Reflux
   E. All of them

10. Current recommendations for any patient with fever and uvular edema are to obtain lateral soft tissue films of the neck.
   A. true
   B. false

In Future Issues

Oncologic Emergencies

Emergency Medicine Reports™ (ISSN 0746-2506) is published biweekly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326. Telephone: (800) 688-2421 or (404) 262-7436.

Editorial Director: Lee Landenberger

Executive Editor: Shelly Morrow Mark

Managing Editor: Leslie Hamlin

GST Registration No.: R128870672

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to *Emergency Medicine Reports*, AHC Media LLC, PO Box 550669, Atlanta, GA 30355

Back issues: $31. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Multiple copy prices: One to nine additional copies, $359 each; 10 to 20 additional copies, $319 each.

Subscriber Information

Customer Service: 1-800-688-2421

Customer Service E-Mail:
customerservice@ahcmedia.com

Editorial E-Mail:
shelly.mark@ahcmedia.com

World Wide Web page:
http://www.ahcmedia.com

Subscription Prices

1 year *with* 65 ACEP/65 AMA/39 AAFP Category 1/Prescribed credits: $564

1 year *without* credit: $419
Add $19.99 for shipping & handling

Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

All prices U.S. only.
U.S. possessions and Canada, add $30 plus applicable GST. Other international orders, add $30.

Accreditation

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of *65 AMA PRA Category 1 Credits™*. Each issue has been designated for a maximum of 2.50 *AMA PRA Category 1 Credits™*. Physicians should claim only credit commensurate with the extent of their participation in the activity.

Approved by the American College of Emergency Physicians for a maximum of 65.00 hour(s) of ACEP Category I credit.

This enduring material activity, *Emergency Medicine Reports*, has been reviewed and is acceptable for up to 39 Prescribed credits by the American Academy of Family Physicians. AAFP certification begins January 1, 2014. Term of approval is for one year from this date with the option of yearly renewal.

Each issue is approved for 1.50 Prescribed credits. Credit may be claimed for one year from the date of each issue. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Osteopathic Association has approved this continuing education activity for up to 65 AOA Category 2-B credits.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

This CME activity is intended for emergency and family physicians. It is in effect for 36 months from the date of the publication.

AHC Media

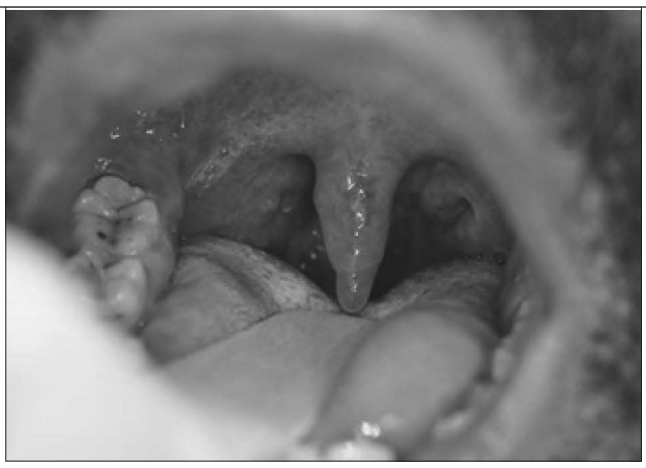
Emergency Medicine Reports
Practical, Evidence-Based Reviews in Emergency Care

Disease Presentations of the Uvula

Potential Diseases and Conditions of the Uvula

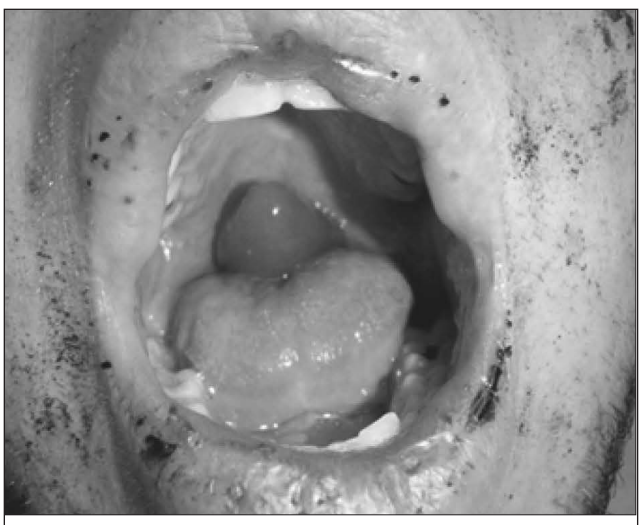
1. Angioedema
    a. Isolated angioedema or Quincke's disease
    b. Hereditary angioedema (HAE)
    c. Allergic
    d. Ace inhibitor and other drug associated angioedema
    e. Myxedematous changes of hypothyroidism
2. Burns
    a. Thermal
        i. Smoke inhalation injuries
        ii. Cocaine or marijuana smoking
        iii. Sauna exposure
    b. Chemical
3. Infections
    a. Viral
    b. Bacterial
    c. Mycobacterium
    d. Trauma
4. Postsurgical Uvula
    a. Surgical complications
        i. Orotracheal intubation associated
        ii. Suctioning or bronchoscopy
    b. Cultural uvulectomy
5. Hematologic and Oncologic
    a. Hemangiomas
    b. Oncologic
6. Congenital Variants
    a. Bifurcate uvula
    b. Elongated uvula
7. Vascular
    a. Superior vena cava syndrome
    b. Internal carotid artery ligation
    c. Lymphatic duct ligation
    d. Kawasaki syndrome

Isolated Edema of the Uvula



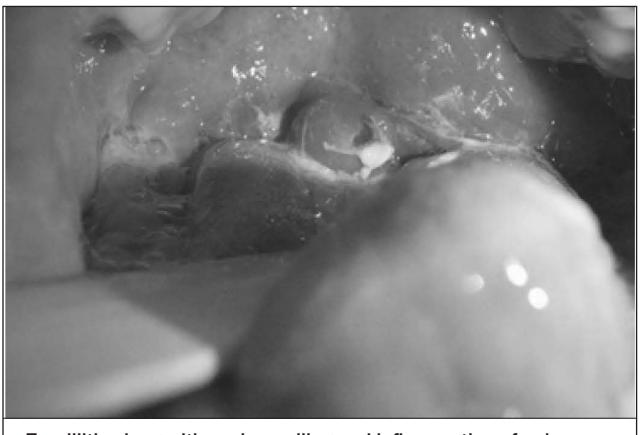
Isolated edema of the uvula in a 30-year-old male who presented to the emergency department complaining of a swollen uvula and a sore throat. The patient denied a fever or recent illness and indicated that his uvula felt "irritated from scratching."

Edema and Inflammation of the Uvula



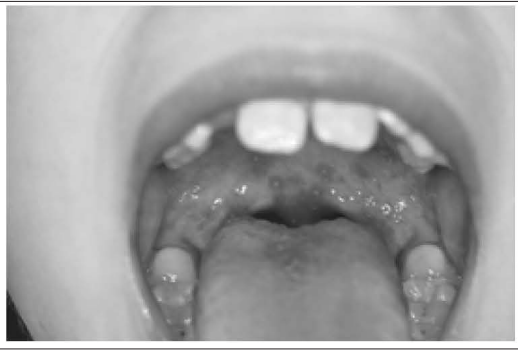
A 26-year-old male who presented for evaluation following an assault. He demonstrated marked edema and inflammation of the uvula, and he admitted to smoking marijuana with a crack pipe.

Tonsillitis with Uvula Swelling and Inflammation



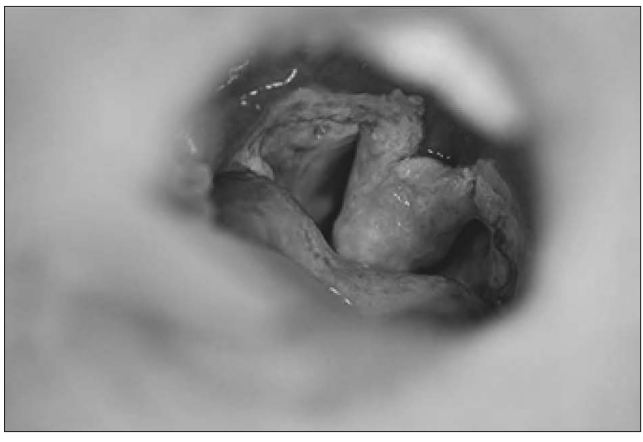
Tonsillitis along with uvula swelling and inflammation of unknown etiology in an 18-year-old male who presented for evaluation of severe throat pain. The rapid streptococcal test was negative.

Lesions on Palate and Uvula Consistent with Herpangina



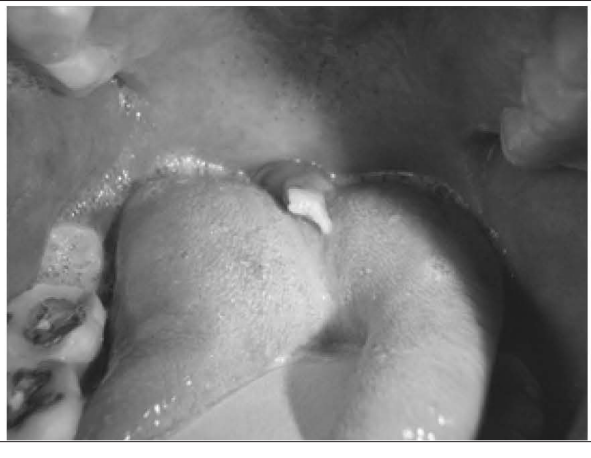
Eight-year-old female presenting with the chief complaint of fever, cough, rhinorrhea, and a sore throat. The lesions demonstrated on the palate and uvula were consistent with herpangina, which is typically caused by the Coxsackie A virus.

Eschar of the Uvula



Eschar of the uvula in a 17-year-old girl four days following tonsillectomy and adenoidectomy.

Idiopathic Necrosis of the Uvula



Idiopathic necrosis of the uvula in a 31-year-old male who presented for evaluation of physical changes noted to his uvula. The patient denied any trauma or infections.

Supplement to *Emergency Medicine Reports*, July 13, 2014: "Disease Presentations of the Uvula."
Authors: **Roselynn Gentles, MD**, St. James Healthcare, Butte, MT; and **Larry Mellick, MD, MS, FAAP, FACEP**, Professor, Department of Emergency Medicine and Pediatrics, Georgia Regents University, Augusta, GA.

Trauma Reports

PRACTICAL, EVIDENCE-BASED REVIEWS IN TRAUMA CARE

Volume 15, Number 4 **July/Aug 2014**

Authors:

Zachary Ginsberg, MD, MPP, Fellow, Trauma Critical Care, R Adams Cowley Shock Trauma Center, Baltimore, MD.

Jay Menaker, MD, Associate Professor, Department of Surgery and Emergency Medicine, University of Maryland School of Medicine, Medical Director Lung Rescue Unit, Physician Director of Quality Management, R Adams Cowley Shock Trauma Center, Baltimore, MD.

Peer Reviewer:

Robert Falcone, MD, FACS, Clinical Professor of Surgery, Ohio State University, Columbus.

Statement of Financial Disclosure

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Dietrich (editor in chief), Dr. Ginsberg (author), Dr. Menaker (author), Dr. Falcone (peer reviewer), and Ms. Behrens (nurse reviewer) report no relationships with companies related to this field of study. Ms. Mark (executive editor), and Ms. Hamlin (managing editor) report no relationships with companies related to the field of study covered by this CME activity.

AHC Media

Trauma Resuscitation: The Use of Blood and Blood Products

Trauma is the most common cause of death for young people, with hemorrhage being a substantial cause of the mortality. The best resuscitative fluid and amount of fluid that is appropriate in the trauma setting is controversial. This issue explores the use of blood and blood products in a trauma resuscitation.

— Ann M. Dietrich, MD, Editor

Introduction

In the United States, trauma is the leading cause of death for people younger than age 45 years.[1] Hemorrhage is the second leading cause of mortality following injury, behind only traumatic brain injury.[2]

Classifications of shock have traditionally been defined by vital signs and physiologic parameters. Based on these definitions, the severity of shock can be determined prior to any laboratory data, and appropriate resuscitation can be initiated. The American College of Surgeons Committee on Trauma has defined the classes of shock as follows (*see Table 1*):

- Class I shock is characterized by 750 mL of blood loss or 15% of blood volume, pulse rate < 100, normal blood pressure, a normal or increased pulse pressure, urine output of > 30 mL/hour, slightly anxious mental status, and a respiratory rate of 14-20.
- Class II shock is characterized by 750-1500 mL of blood loss or 15-30% of blood volume, pulse rate 100-120, normal blood pressure, decreased pulse pressure, urine output of 20-30 mL/hour, mildly anxious mental status, and a respiratory rate of 20-30.
- Class III shock is characterized by 1500-2000 mL of blood loss or 30-40% of blood volume, pulse rate 120-140, decreased blood pressure, decreased pulse pressure, urine output of 5-15 mL/hour, anxious or confused mental status, and a respiratory rate of 30-40.
- Class IV shock is characterized by > 2000 mL of blood loss or > 40% of blood volume, pulse rate > 140, decreased blood pressure, decreased pulse pressure, negligible urine output, confused or lethargic mental status, and a respiratory rate of > 35.

Undifferentiated shock in trauma should be assumed to be hemorrhagic until proven otherwise. Hemorrhage represents 30-40% of mortality of trauma and may require significant volume to resuscitate.[2] Classic crystalloid resuscitation has been called into question because it is associated with a metabolic acidosis,[3,4] and blood components may offer a superior option to reverse shock. In this paper, the authors discuss the use of blood and blood products during a trauma resuscitation.

Resuscitative Goals: To What End?

While blood pressure is one of the most readily available measurements in the resuscitative environment, it may provide false reassurance of end organ perfusion. Markers that reflect tissue perfusion may facilitate initial assessment and

Executive Summary

- Undifferentiated shock in trauma should be assumed to be hemorrhagic until proven otherwise. Hemorrhage represents 30-40% of mortality from trauma and may require significant volume to resuscitate.
- One pre- and post-intervention of a massive transfusion protocol showed improved outcomes with the 1:1 FFP:PRBC transfusion protocol for critically ill trauma patients at 24 hours and 30 days, and lower bleeding complications, with 18% and 21% absolute mortality reduction, respectively.
- Rapid depletion of fibrinogen has been shown in patients with significant blood loss exceeding 20% of their calculated blood volume, and fits within the conceptual understanding of the mechanism of traumatic consumptive coagulopathy.
- If thromboelastography can identify specific functional deficiencies of the traumatic coagulopathy, one can adapt the massive transfusion to simultaneously reverse the coagulopathy and shock while limiting the exposure to harm from excessive utilization of blood components.
- The most common side effects associated with PRBC transfusions reported in the CRIT trial were fever (1.9%), fluid overload (1.7%), and hypotension (1%). A pooled meta-analysis showed that the risk of developing an infectious complication was 1.8 times more likely and ARDS 2.5 times more likely with transfusion of blood.
- Clinical findings of TRALI are tachypnea, cyanosis, frothy pulmonary secretions, dyspnea, hypotension, tachycardia, and fever within 6 hours of transfusion, although most cases occur within 1-2 hours.

monitoring of a patient's response to resuscitation. Goals for a successful response to therapy are as follows:[8]

- arterial lactate < 2
- urinary output > 0.5 mL/kg/hr
- hematocrit > 25%
- normal arterial base deficit.

One study found a base deficit > 8 mEq/L or lactate > 2.5 mmol/L was an independent predictor of developing multisystem organ failure (MSOF).[9] While those who achieve optimal markers of perfusion have a better survival rate, a landmark trial found age alone is the strongest predictor of whether a patient will respond optimally to resuscitation or not. Additional attempts to resuscitate to supranormal levels (i.e., systolic blood pressure > 100 mmHg, hematocrit > 30%, base deficit < 3, or urinary output > 1 mL/kg/hr) resulted in more blood components and inotrope utilization without improving mortality.[10]

Table 1. Shock Classification

Class I

- **Shock is characterized by 750 mL of blood loss or 15% of blood volume, pulse rate < 100, normal blood pressure, a normal or increased pulse pressure, urine output of > 30 mL/hour, slightly anxious mental status, and a respiratory rate of 14-20.**

Class II

- **Shock is characterized by 750-1500 mL of blood loss or 15-30% of blood volume, pulse rate 100-120, normal blood pressure, decreased pulse pressure, urine output of 20-30 mL/hour, mildly anxious mental status, and a respiratory rate of 20-30.**

Class III

- **Shock is characterized by 1500-2000 mL of blood loss or 30-40% of blood volume, pulse rate 120-140, decreased blood pressure, decreased pulse pressure, urine output of 5-15 mL/hour, anxious or confused mental status, and a respiratory rate of 30-40.**

Class IV

- **Shock is characterized by > 2000 mL of blood loss or > 40% of blood volume, pulse rate > 140, decreased blood pressure, decreased pulse pressure, negligible urine output, confused or lethargic mental status, and a respiratory rate of > 35.**

Permissive Hypotension in Penetrating Trauma

In the setting of trauma, the body's earliest response is an attempt to form a clot to stop hemorrhage. In penetrating trauma, a focal site of hemorrhage is likely, and preventing clot disruption can reduce the overall blood loss a patient has before hemorrhage control can be achieved. Elevated blood pressures may disrupt the clot. Therefore, in penetrating trauma, practice tolerates a lower blood pressure to protect the tenuous clot providing hemostasis.

This is of greatest value in

hemorrhagic lesions in which rapid hemostasis is more difficult to achieve, such as liver or pelvic fractures.[8] Resuscitative hypotension tolerates a systolic blood pressure between 70 and 90 until source control of hemorrhage has been achieved, generally in the operating room (OR).[8,11] The physiology underlying resuscitative hypotension strategies optimizes perfusion without blunting compensatory mechanisms or disrupting early hemostatic control from initial clot formation at the source of bleeding.

In studies, resuscitative hypotension did not result in worse outcomes for patients and prevented the use of higher blood component volumes transfused with no significant difference in incidence or severity of coagulopathy, anemia, or thrombocytopenia, while encouraging the preservation of native hemostatic mechanisms, such as early clot formation, until hemorrhagic source control can be achieved.[8] Lower volumes of resuscitative fluids may maintain physiologic mechanisms such as endogenous catecholamines and vasoconstriction to prevent the lethal triad of hypothermia, coagulopathy, and acidosis.[12,13] (*See Figure 1.*)

Traumatic brain injury should not be resuscitated with permissive hypotension, as studies excluded this population, and hypotension in traumatic brain injury may aggravate anoxic brain injury.[14]

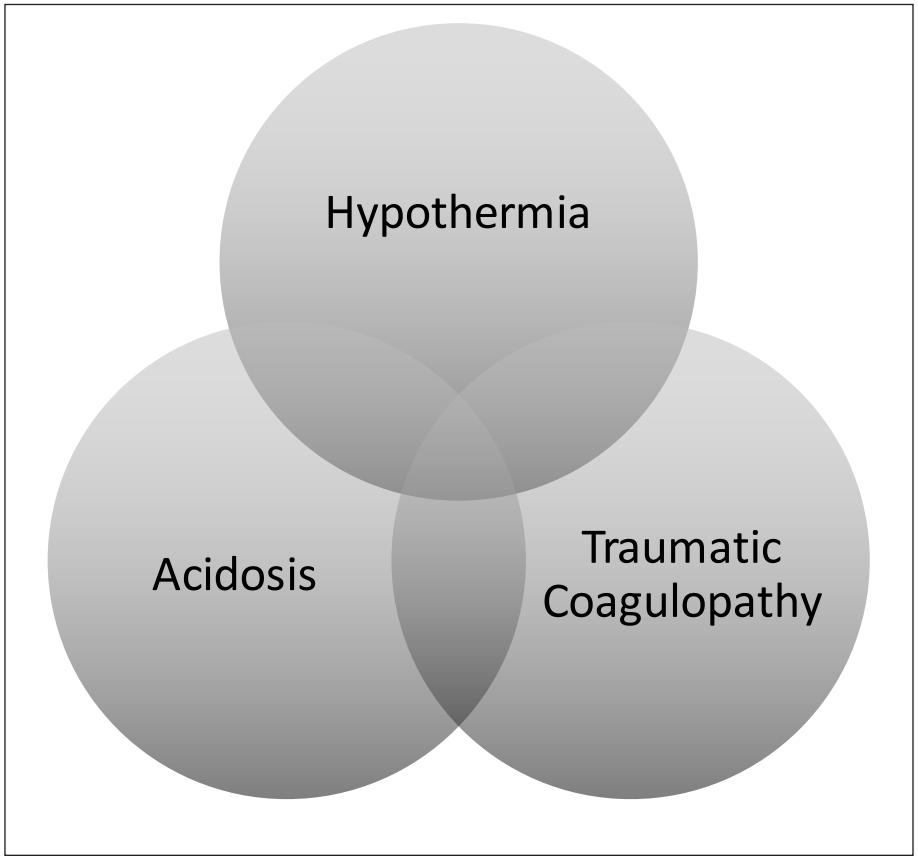
Traumatic Coagulopathy

Traumatic coagulopathy occurs in 25% of trauma patients.[6,15] The cause is multifactorial, including depletion and consumption of coagulation factors, dilution from resuscitative crystalloid, platelet dysfunction, and increased fibrinolysis ultimately compromising the coagulation system.[5,16,17] (*See Figure 2.*) Resuscitation should be tailored to restore function of the coagulation system, strengthen the clot, slow hemorrhage, replace volume losses, and improve oxygen delivery to tissues.[18]

The cell-based model defines three critical activation steps of primary hemostasis in trauma: initiation, amplification, and propagation.[19] The initiation phase of the traumatic coagulopathy is in response to endothelial injury exposing subendothelial prothrombogenic surface to platelets, which in turn form a loosely adherent plug. This plug acts as a catalyst for coagulation proteins: factor VII activates factors IX and X that convert prothrombin to thrombin. Thrombin subsequently activates factors V, VIII, and XI, amplifying the production of thrombin to sufficient levels to activate factor XIII, which forms fibrin cross-links to stabilize the clot.[18] This describes primary hemostasis in trauma with the initial clot formation of a "sticky platelet clot" on the endothelial surface at the site of injury.

This amplification of thrombin, however, also activates a counter-regulatory fibrinolytic process to prevent overactivation of the coagulation system. In normal settings, this breaks up fibrin to prevent excessive coagulation. In massive hemorrhage, the coagulation process capacity is overwhelmed and unable to maintain this balance, leading to the traumatic coagulopathy and uncontrollable hemorrhage associated with trauma.[17] Current evidence suggests that traumatic coagulopathy exists early in injury independent of clotting factor deficiency and may be a result of an injury complex triggered by tissue injury, cellular ischemia, dilution of clotting factors, hypocalcemia, hypothermia, acidosis, inflammation, and fibrinolysis, which the resuscitation should seek to reverse or contain early.[18]

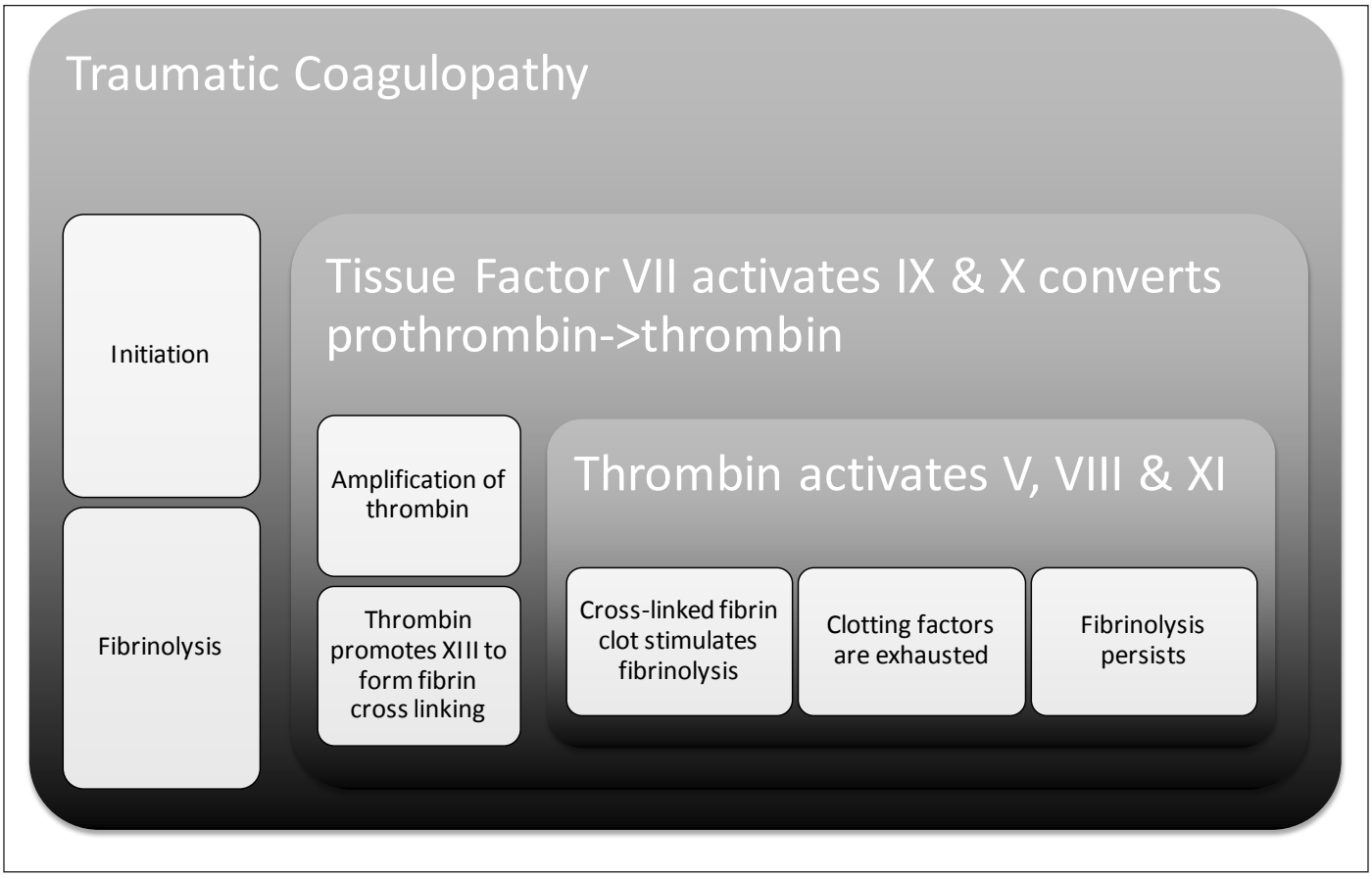
Figure 1. Lethal Triad



Balanced Resuscitation

Early in resuscitation, reversal of the traumatic coagulopathy improves patient outcomes and lessens the

Figure 2. Traumatic Coagulopathy



total blood components required. Trauma patients post-resuscitation had less coagulopathic problems in the ICU with early administration of higher plasma:PRBC ratios.[17,20,21] The likely benefit of plasma comes from replacing coagulation factors, which prevent or correct the coagulopathy that occurs in hemorrhage and shock. Rapid depletion of fibrinogen has been shown in patients with significant blood loss exceeding 20% of their calculated blood volume,[22] and fits within the conceptual understanding of the mechanism of traumatic consumptive coagulopathy.[17] Each unit of fresh frozen plasma (FFP) contains fibrinogen, and is an essential element of coagulation factor replenishment.[23] Plasma may also function as a buffer to help to counter the acidosis of traumatic shock.[7]

The literature is consistent that early reversal of traumatic coagulopathy improves outcomes. Recent literature has promoted a ratio between FFP to packed red blood cells (PRBCs) as close as possible to 1:1.9.[24-26] One study showed a survival difference of approximately 20%, with the majority of the difference occurring within the initial 6 hours and persisting through 30 days.[7] Another prospective, observational study showed no difference in mortality or ICU and hospital days,[27] while a third prospective cohort study showed that a high FFP:PRBC ratio (> 1:1.5) produced a significantly lower mortality risk within the first 24 hours in blunt trauma patients requiring more than 8 units of PRBC.[28] While the higher FFP:RBC ratio showed improved mortality, the study attributed this to reversal of traumatic coagulopathy and also found a higher incidence of ARDS. Other retrospective studies have shown a preferable FFP:PRBC ratio of 1:1 to 2:3 to improve mortality.[29] One of these studies showed an absolute mortality reduction of 55%.[30] One retrospective study of 252 soldiers receiving massive transfusion showed higher fibrinogen:PRBC ratios were independently associated with improved survival (odds ratio 0.37, $p = 0.013$).[23] While exact ratios are unclear, the evidence clearly supports that use of blood components in as close to a 1:1 to 2:3 FFP:PRBC ratio is preferable over crystalloid for the initial traumatic resuscitation. All studies to date are subject to survivor bias — those who receive the plasma survive long enough for it to thaw and become available.[31] To date, no prospective, randomized, controlled trial has investigated the optimal ratio; however, the PROPPR trial,[32]

a prospective, multi-center, randomized trial, is currently underway. While we await these results, the literature favors 1:1 FFP:PRBC ratios in those with massive PRBC transfusion requirements.[16,33]

The benefits of balanced transfusion show that the composition of blood components transfused in traumatic resuscitation may be as important as the volume itself. As soon as a patient is stabilized and hemorrhagic source control is achieved, one should attempt to avoid excessive transfusion of blood component therapy.[34]

Massive Transfusion Protocols

In an effort to pursue balanced resuscitation while avoiding overexposure to blood products and the associated risks, utilization of massive transfusion protocols (MTP) at many hospitals has been implemented for patients requiring in excess of 6-10 PRBC units. MTPs have decreased the incidence of transfusion-associated complications, reduced delays to activate massive transfusion protocols, reduced total volumes of blood products transfused, and improved patient mortality.[9,20,35-38] One pre- and post-intervention of a massive transfusion protocol showed improved outcomes with the 1:1 FFP:PRBC transfusion protocol for critically ill trauma patients at 24 hours and 30 days, and lower bleeding complications, with 18% and 21% absolute mortality reduction, respectively. The same study also showed a significant reduction in the incidence of traumatic coagulopathy.[20]

Research has sought to identify earlier the patients who require massive transfusion to improve the delivery of blood transfusion within the "golden hour" of trauma resuscitation.[39,40] The largest prospective, observational study of 1103 patients, identified the following variables that independently predicted the need for a massive transfusion (defined as greater than 10 units PRBC within the first 24 hours). Using regression analysis, they found significant correlation between systolic blood pressure (SBP) < 90 mmHg, SBP 90-120, free fluid in the peritoneum on FAST, clinically unstable pelvic ring fracture, and age older than 60 years increased the likelihood of requiring a massive transfusion.[41,42]

Thromboelastography (TEG)

The properties of an individual patient's ability to produce a clot can be assessed by thromboelastography,[43] allowing the resuscitation to adapt to a patient's coagulopathy. Additional research in trauma-associated coagulopathy advocates a resuscitation balancing blood components based on a specific patient's ability to form and maintain clot integrity using thromboelastography.[18,44,45] Thromboelastography assesses parameters of clot initiation, maximum strength, and rates of lysis in a more real-time manner to determine the strength and duration of clot in traumatic hemorrhage.[46] Resuscitation practices that have evolved to pursue a more physiologic balancing of blood components can now employ new laboratory data to tailor resuscitative strategies to the patient being treated.[18,46,47]

Existing laboratory coagulation studies were originally designed to evaluate for hemophilia and monitoring anticoagulation therapy. Furthermore, laboratory in vitro coagulation studies are buffered to a normal pH and a temperature of 37°C, which will not reflect the in vivo status of coagulation in a bleeding trauma patient.[17] Thus, these tests have not been proven in trauma and frequently take longer than is clinically useful for prompt correction of coagulopathy in traumatic resuscitations.[18]

Massive transfusion protocols have allowed for more rapidly balanced resuscitations and resulted in less total blood products, and, thus, fewer transfusion-related risks.[18,48] However, a predetermined ratio may result in higher proportionate use of FFP without benefit, as found in one center that combined TEG with their MTP.[29,43] While not statistically significant, this same center found a trend that their patients received less FFP in penetrating trauma than blunt trauma.[46] These findings support that massive transfusion protocols and TEG in trauma are not mutually exclusive but complementary.

Thus, in the appropriate population, a TEG tailored massive transfusion protocol resuscitation in trauma could theoretically offer real-time understanding of which blood product a patient needs next. If thromboelastography can identify specific functional deficiencies of the traumatic coagulopathy, one can adapt the massive transfusion to simultaneously reverse the coagulopathy and shock while limiting the exposure to harm from excessive utilization of blood components.[18,46-47]

Blood Components: Potential Harms

The above discussion has illustrated clearly that blood components have significant benefit in the appropriate ratios to resuscitate patients; however, these benefits are not without possible harms. All studies of blood component therapy suggest some immunomodulating effect as a possible cause of adverse outcomes. Collectively, they are known as Transfusion Related Immunomodulatory Response (TRIM), but the specific mechanism is not known. The risks associated with each blood component are discussed below. (*See Table 2.*)

Fresh Frozen Plasma and Cryoprecipitate

Fresh frozen plasma is the portion of blood that remains when whole blood is centrifuged and red blood cells removed. Each unit of FFP contains approximately 400 mg of fibrinogen.[23] Cryoprecipitate is the cold insoluble fraction formed when FFP is thawed at 4°C. Rich in factors VIII, XIII, vWF, and fibrinogen, the fibrinogen contained in one pooled cryoprecipitate pack is roughly equivalent to four units of FFP.

As the administration of FFP increases with the balanced blood component transfusions, so do the

Table 2. Blood Components and Potential Harms

Blood Component	Product Contents	Indications and Thresholds	Considerations and Volume	Complications
FFP	Contain all clotting factors	Most useful for traumatic coagulopathy	400 mg of fibrinogen Volume = 300 mL	Infectious and inflammatory complications
Cryoprecipitate	Contain factor 8, vWF, fibrinogen	Smaller volumes with focused delivery of specific clotting factors	250 mg of fibrinogen/ unit	Infectious and inflammatory complications
PRBC	Red blood cells improve oxygen-carrying capacity	TRIC trial transfusion threshold: hgb > 7.0 g/ dL TRACS and CCP establish threshold for cardiac patients hematocrit > 24%	Citrate solution can cause hypocalcemia. Cell lysis can cause hyperkalemia and acidosis. Volume = 250-330 mL	Fever, fluid overload, hypotension Infectious risk 4%/unit transfused
Platelets	Typically transfused in 6 packs of single-donor platelets	Function ultimately more important than total number	Thrombocytopenia occurs late in the course of hemorrhage	Most likely to cause TRALI

incidents of complications. A retrospective, case-control study showed an increased relative risk of infections with the transfusion of FFP, specifically severe ventilator associated pneumonia (VAP) (RR = 5.42), simple VAP (RR = 1.91), severe blood stream infection (RR = 3.35), simple blood stream infection (RR = 2.12), and undifferentiated sepsis (RR = 3.32).[49]

Platelets

Initially, ratios favored a higher ratio of platelet transfusion attempting to approximate ratios of components of whole blood.[7] However, this 1:1 ratio of platelets:PRBC has been criticized for excessive exposure to risk of transfusion-related adverse reactions, specifically Transfusion Related Acute Lung Injury (see below), and some have advocated a much reduced ratio of 1:5 for platelets:PRBC.[24,34] A significant relationship between platelet count and mortality from hemorrhage has not been shown,[6] and thrombocytopenia occurs late in the course of bleeding and massive transfusion.[50,51] The count itself may not be as relevant as the function, and this could be better assessed by thromboelastography.[18]

Packed Red Blood Cells (PRBC)

PRBCs are an important component of hemorrhagic resuscitation, as hemoglobin improves the blood's oxygen-carrying capacity to body tissues essential to maintain perfusion. PRBCs are the best initial transfusion to reverse shock, as they improve oxygen-carrying capacity while simultaneously providing volume that will not extravasate (in contrast to crystalloid) through permeable capillary membranes. In the initial trauma resuscitation, one should resuscitate to hemodynamic stabilization, hemorrhage control, and the physiologic end goals of resuscitation described above.

PRBC Side Effects

The accompanying fluid transfused alongside the red blood cells is by no means inert. The storage of blood exposes the red blood cells to "age lesions,"[52] leading to hyperkalemia with cell breakdown in some populations, and the anticoagulant citrate binds to the patient's calcium and may cause tetany, QT prolongation, and decreased myocardial contractility and should be monitored closely with an ionized calcium. Finally, the actual storage of blood leads to a pH of 7.0 in fresh units and decreases to 6.6 to 6.8 with age, which could in fact worsen acidosis.[13]

Another study examined 15,534 trauma patients over three years controlling for confounding shock variables and found transfusion to be an independent predictor of mortality with an odds ratio of 2.83 (1.82-4.40).[53] The risk of PRBC transfusions has been replicated in the CRIT trial, a prospective, multicenter, observational study among ICU patients showing PRBC transfusions were independently associated with worse clinical outcomes. The authors demonstrated a 15% increased incidence of death among those who received six or more units of PRBC as compared to those who received no transfusion.[54]

The most common side effects reported in the CRIT trial were fever (1.9%), fluid overload (1.7%), and hypotension (1%).[54] A pooled

meta-analysis showed that the risk of developing an infectious complication was 1.8 times more likely and ARDS 2.5 times more likely with transfusion of blood.[55] Another study found a 4% cumulative risk of infection for each unit of PRBC transfused.[49]

Complications of Transfusion

Aside from the risks associated with the specific blood components, complications of transfusing donor products can occur. Vigilance can assist with early recognition and management of these complications post-resuscitation. These complications broadly fall into the categories of pulmonary and hemolytic reactions, transmission of blood-borne pathogens, and problems associated with preparation and storage of blood products.

Transfusion Related Acute Lung Injury (TRALI)

Transfusion Related Acute Lung Injury (TRALI) is the leading cause of transfusion-related morbidity and mortality in the United States.[56] Clinical findings of TRALI are tachypnea, cyanosis, frothy pulmonary secretions, dyspnea, hypotension, tachycardia, and fever within 6 hours of transfusion, although most cases occur within 1-2 hours. Physiologic findings include PaO_2/FiO_2 ratios of < 300 mm Hg and decreased pulmonary compliance despite normal cardiac function. Chest radiographs will frequently show bilateral infiltrates.[48,56] Diagnosis is based on clinical criteria consistent with acute lung injury and treated similarly. In practice, it can be difficult to differentiate TRALI from Transfusion Associated Circulatory Overload (TACO), although a B-natriuretic peptide level more than 100 pg/dL and a post-transfusion to pre-transfusion ratio more than 1.5 can be suggestive of TACO over TRALI.[56] Generally, fluid management and volume adjustments are sufficient to address TACO.

TRALI is now the most frequent cause of transfusion-related mortality reported to the FDA. It is estimated to occur approximately 1 in every 5000 blood component transfusions, with mortality from 5-25%.[48,57] Two predominant theories exist. The first suggests the presence of leukocyte alloantibodies, cytokines, lipid or human leukocyte antigen (HLA) class I and II that accompany transfused blood components prime neutrophils and cause pulmonary damage.[48,58,59] The second theory suggests a predisposing condition such as surgery, trauma, infection, or proinflammatory event stimulates the release of cytokines and encourages neutrophils to attach to the vascular endothelium, particularly in the pulmonary capillaries. The second step is the same as the first theory except that the belief is that TRALI is a two-step process requiring the initial priming of the patient's baseline condition upon transfusion.[48,59,60]

FFP should be ABO typed as the first choice, but can be given to a different ABO group so long as it does not possess anti-A or anti-B activity.[58] Increasingly, the importance of HLA screening has been emphasized. The presence of leukocyte alloantibodies in donor plasma appears to contribute significantly to the development of the syndrome. Such alloantibodies develop most frequently in women after pregnancy and are entirely absent from male blood unless the patient has had prior transfusions. As a result, the United Kingdom has disqualified multiparous females from plasma donation, and the United States uses primarily males.[48,56,58]

The TRICC trial found an OR 1.5 (0.97-2.49) of developing TRALI with PRBC transfusion.[61] The largest retrospective study of 14,070 trauma patients found patients receiving 1-5 and 6-10 units of PRBC had an odds ratio of 1.70 and 2.24, respectively, to develop ARDS and TRALI. The study also found a 6% higher risk of ARDS for each unit of PRBCs transfused, although the ARDS group was more severely injured than the non-ARDS group prior to developing the syndrome. This same study found that receiving more than five units of FFP also had an odds ratio of 2.55 for development of ARDS.[62] High ratios of FFP:PRBC early in resuscitation were associated with almost a twofold higher risk of acute lung injury.[28] Additionally, a retrospective analysis focused on the incidence of TRALI in association with transfusions found FFP (OR = 2.48, 1.29-4.74) and platelets (OR = 3.89, 1.36-11.52) to be more likely than PRBCs to contribute to the development of TRALI.[63] Other series have found the following transfusion to be most contributory, in descending order of likelihood: whole blood platelets, FFP, PRBCs, whole blood, apheresis platelet concentrates, and intravenous immunoglobulin (IVIG).[48,60]

Hemolytic Reactions

Acute hemolytic transfusion reactions are estimated at approximately 1 in 76,000, and mortality related to transfusions at 1 in 1.8 million units transfused.[57]

Delayed hemolytic transfusion reactions are more common than acute reactions, occurring days after a transfusion, and they have an incidence of 1 in 6000 units transfused.[57] They frequently go unrecognized and are characterized by fever, declining hemoglobin, and mild jaundice. Delayed reactions occur when a patient previously sensitized by pregnancy or transfusion receives "incompatible red cells" because the low titer of circulating alloantibody escapes detection by pre-transfusion screening.

Transfusion-associated graft-vs-host disease occurs when immunocompetent allogeneic lymphocytes in transfused blood mount an attack against the host tissues. It occurs between 4 and 30 days after transfusion of any blood component. Diagnosis is suspected when circulating donor lymphocytes are identified in the recipient patient. It is confirmed by detecting donor DNA in the lab or biopsy specimen. Irradiating blood components with at least 25 Gy or chemophototherapy to inactivate donor T lymphocytes can reduce the incidence of transfusion associated graft-versus-host

disease. Nonetheless, if it occurs, treatment ranges from difficult to futile, with morality approaches 90% in full-blown syndromes.[57] Transfusion of FFP will not cause transfusion-associated graft-vs-host disease.[58]

Blood-borne Pathogens

Hepatitis C. In 1990, with the introduction of the first donor screening test for hepatitis C, the transfusion risk of transmission was 4%. Risk of hepatitis C is now calculated to be 1 case in every 1.5 million to 2 million transfusions.[57]

HIV. In 1987, among the known cases of HIV, 2% were from transfused adults. Since the implementation of donor screening, only 49 documented cases of transfusion-associated HIV transmission have occurred. The risk of acquiring HIV infection through blood transfusion is estimated conservatively to be one in 1.5 million.[64]

Bacterial contamination in PRBCs is 0.21 infections per million transfusions. Spirochetes do not survive in citrated blood.[57] The risks of platelet transfusion-associated septic reaction and fatality are 1 in 74,807 and 1 in 498,711 transfusions, respectively.[65]

Age of PRBCS

A recent 2012 meta-analysis reviewing the effects of older blood questioned the effects of age on stored blood.[52] A pooled meta-analysis of six studies with little heterogeneity showed a significant increase in multi-organ dysfunction (OR = 2.26 {1.56-3.25}) and pneumonia (OR = 1.17 {1.08-1.27}) with older blood (> 21 days on average). In another analysis of six papers on trauma patients, the pooled odds ratio of mortality for receiving older blood was 1.18 (1.02-1.35). The analysis showed that the use of "newer" blood would benefit one in 97 patients who received transfusions.

Leukoreduced PRBCS

In 2003, following universal adoption of leukoreduction in Canadian blood storage, Hebert showed a slight mortality benefit of 0.84% to leukoreduction, further suggestive of an immunomodulatory mechanism. This effectively equates to one life saved for every 120 patients who receive leukoreduced blood.[66] The study also showed a reduction in incidence of fever by 2.2%, and use of antibiotics for patients with the use of leukoreduced blood. Another study showed a cumulative risk of infection of 4% per unit of PRBC transfused.[49]

One study in western Europe showed an odds ratio of 1.37 increased mortality with blood transfusion in the ICU.[67] The next study by the same authors found no such increased mortality rate.[68] Both were prospective, multi-center, observational studies of 3534 and 1040 patients, respectively, and the authors attributed the leukodepletion of the transfused PRBC as the only difference supporting the immunomodulatory effect of PRBC units on mortality.[68] While leukoreduction offers benefit, considerable barriers to achieving a sufficient pool of leukodepleted blood globally exist without a significant enough benefit to pursue currently.

Special Populations

Post-resuscitation there are pre-existing conditions that may adjust the transfusion thresholds and end points of resuscitation. The landmark studies TRICC, CCP, and TRACS defined transfusion thresholds and special populations for whom higher hemoglobin levels are beneficial. Please note all these studies occurred after the initial resuscitation in stabilized patients. Moreover, a laboratory transfusion threshold should not exist in initial trauma with hemodynamic instability since the hemoglobin and hematocrit can take some time to equilibrate (even up to 24 hours).

ICU Patients. The landmark Transfusion Requirements in Critical Care (TRICC) established the safety of a hemoglobin level of 7.0 g/dL in critically ill hemodynamically stable patients. The trial randomized patients to a hemoglobin of 7.0 g/dL as a transfusion threshold as compared to the control group with a hemoglobin of 9.0 g/dL and found no difference in outcomes.[61] However, notable exclusions to the study included patients with active acute myocardial infarction.

Acute Myocardial Infarction. The Cooperative Cardiovascular Project (CCP) defined transfusion thresholds in stabilized patients with acute myocardial infarction. A cohort study of 78,974 patients who were 65 years of age or older and hospitalized with confirmed acute myocardial infarction showed transfusion was associated with a reduction in mortality with incrementally increasing hematocrit goals: hematocrit 24.0% or lower (OR 0.36 [0.15-0.83]), hematocrit 24.1-27.0 (OR 0.69 [0.47-1.01]), and hematocrit 27.1-30.0 (OR 0.75 [0.58-0.96]).[69] This is likely from compensatory mechanisms that redistribute coronary blood flow away from the endocardium during low hematocrit levels.[69]

Post-cardiac Surgery. The Transfusion Requirements After Cardiac Surgery (TRACS) randomized, controlled trial of 512 patients post-cardiac surgery randomized patients to a liberal and conservative transfusion goal of hematocrit > 30% and > 24%, respectively, and found no such protective effect of PRBC transfusion.[70] In fact, for each transfused unit, an increased risk of occurrence of respiratory complications (OR 1.27), infectious complications (1.20), and 25% increased likelihood of 30-day mortality, cardiogenic shock, ARDS, or renal injury requiring dialysis or hemofiltration were observed.[70] Since this is the only trial on post-cardiac surgery patients, many now utilize a hematocrit threshold of 24%.

Conclusion

Early reversal of the shock state with a targeted resuscitation can prevent the lethal triad — acidosis, coagulopathy, and hypothermia — and improve patient outcomes by restoring perfusion and reversing the coagulopathy of trauma.[5,6,7] While

blood component transfusion is not without risk, a variety of components in blood offer the ability to target specific functional deficiencies in a patient's ability to form and maintain a clot or achieve hemorrhage control.

References

1. National Center for Injury Prevention and Control, Centers for Disease Control and Prevention WISQARS Database accessed March 15, 2014. Web http://webappa.cdc.gov/sasweb/ncipc/leadcaus10_us.html
2. Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: An overview of epidemiology, clinical presentations, and therapeutic considerations. *J Trauma* 2006;60Supplement2006: S3–S11.
3. O'Dell E, et al. Hyperchloremia is the dominant cause of metabolic acidosis in the postresuscitation phase of pediatric meningococcal sepsis. *Crit Care Med* 2007;35:2390–2394.
4. Gheorghe C, et al. Hyperchloremic metabolic acidosis following resuscitation of shock. *Chest* 2010;138:1521–1522.
5. HenslerT, et al. Immunologic alterations associated with high blood transfusion volume after multiple injury: Effects on plasmatic cytokine and cytokine receptor concentrations. *Shock* 2003; 20.6: 497–502.
6. MacLeod JBA, et al. Early coagulopathy predicts mortality in trauma. *J Trauma: Injury, Infection, and Critical Care* 2003;55.1:39–44.
7. Holcomb JB, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. *Ann Surg* 2008;248.3: 447–458.
8. Dutton RP, Mackenzie CF, Scalea TM. Hypotensive resuscitation during active hemorrhage: Impact on in-hospital mortality. *J Trauma* 2002; 52.6:1141–1146.
9. Cotton BA, et al. Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. *J Trauma* 2009; 66.1: 41–48; discussion 48–49.
10. Velmahos GC, Demetriades D, Shoemaker WC. Endpoints of resuscitation of critically injured patients: Normal or supranormal? A prospective randomized trial. *Ann Surgery* 2000;232.3: 409–418.
11. Bickell WH, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med* 1994;331.17:1105–1109.
12. Morrison CA, et al. Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: Preliminary results of a randomized controlled trial. *J Trauma* 2011;70.3:652–663.
13. Sihler KC, Napolitano LM. Complications of massive transfusion. *Chest* 2010;137.1:209–220.
14. Brain Trauma Foundation Guidelines. *J Neurotrauma* 2007;24.supplement 1.
15. Brohi K, et al. Acute traumatic coagulopathy. *J Trauma: Injury, Infection, and Critical Care* 2003;54.6 :1127–1130.
16. Duchesne JC, et al. Review of current blood transfusions strategies in a mature Level I trauma center: Were we wrong for the last 60 years? *J Trauma* 2008;65.2:272–276; discussion 276–278.
17. Spahn DR, Rossaint R. Coagulopathy and blood component transfusion in trauma. *Br J Anaesthesia* 2005;95.2:130–139.
18. Kashuk JL, et al. Postinjury coagulopathy management: Goal directed resuscitation via POC thrombelastography. *Ann Surgery* 2010;251.4: 604–614.
19. Hoffman M, Monroe DM. A cell-based model of hemostasis. *Throm Haemost* 2001;85:958–965.
20. Dente CJ, et al. Improvements in early mortality and coagulopathy are sustained better in patients with blunt trauma after institution of a massive transfusion protocol in a civilian Level I trauma center. *J Trauma: Injury, Infection, and Critical Care* 2009;66.6:1616–1624.
21. Gonzalez EA, et al. Fresh frozen plasma should be given earlier to patients requiring massive transfusion. *J Trauma: Injury, Infection, and Critical Care* 2007;62.1: 112–119.
22. Hiippala ST, Myllyla GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. *Anesth Analg* 1995;81:360–365.
23. Stinger HK, et al. The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an Army Combat Support Hospital. *J Trauma* 2008;64.2 Suppl: S79–85; discussion S85.
24. Gunter OL, Jr, et al. Optimizing outcomes in damage control resuscitation: Identifying blood product ratios associated with improved survival. *J Trauma* 2008;65.3: 527–534.
25. Maegele M, et al. Red-blood-cell to plasma ratios transfused during massive transfusion are associated with mortality in severe multiple injury: A retrospective analysis from the trauma registry of the Deutsche Gesellschaft Für Unfallchirurgie. *Vox Sanguinis* 2008;95.2: 112–119.
26. Maegele M, et al. Early coagulopathy in multiple injury: An analysis from the German Trauma Registry on 8724 patients. *Injury* 2007;38.3 :298–304.
27. Scalea TM, Bochicchio KM, Lumpkins K, et al. Early aggressive use of fresh frozen plasma does not improve outcome in critically injured trauma patients. *Ann Surg* 2008;248:578–584.
28. Sperry JL, et al. An FFP:PRBC transfusion ratio >/=1:1.5 is associated with a lower risk of mortality after massive transfusion. *J Trauma* 2008;65.5:986–993.
29. Kashuk JL, et al. Postinjury life threatening coagulopathy: Is 1:1 fresh frozen plasma:packed red blood cells the answer? *J Trauma* 2008;65.2: 261–270; discussion 270–271.
30. Borgman MA, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma: Injury, Infection, and Critical Care* 2007;63.4: 805–813.
31. Snyder CW, et al. The relationship of blood product ratio to mortality: Survival benefit or survival bias? *J Trauma: Injury, Infection, and Critical Care* 2009;66.2: 358–364.
32. Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial. http://cetir-tmc.org/research/proppr.
33. Scalea TM, et al. Early aggressive use of fresh frozen plasma does not improve outcome in critically injured trauma patients. *Ann Surgery* 2008;248.4 (2008): 578–584.
34. Sambasivan CN, et al. High ratios of plasma and platelets to packed red blood cells do not affect mortality in nonmassively transfused patients. *J Trauma* 2011;71.2 Suppl 3 :S329–336.
35. Malone DL, Hess JR, Fingerhut A. Massive transfusion practices around the clobe and a suggestion for a common massive transfusion protocol. *J Trauma* 2006;60.6 Suppl:S91–96.
36. Enticott JC, et al. A review on decision support for massive transfusion: Understanding human factors to support the implementation of complex interventions in trauma: Human factors and massive transfusion. *Transfusion* 2012;52.12:2692–2705.
37. Fitzgerald M, et al. Trauma resuscitation errors and computer-assisted decision support. *Arch Surg* 2011;146.2:218–225.
38. Cotton BA, et al. Damage control hematology: The impact of a trauma exsanguination protocol on survival and blood product utilization. *J Trauma: Injury, Infection, and Critical Care* 2008;64.5:1177–1183.
39. Nunez TC, et al. Early prediction of massive transfusion in trauma: Simple as ABC (assessment of blood consumption)? *J Trauma* 2009;66.2:346–352.
40. Yücel N, et al. Trauma Associated Severe Hemorrhage (TASH)-Score: Probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. *J Trauma* 2006;60.6:1228–1236; discussion 1236–1237.
41. Ruchholtz S, et al. The Emergency Room Transfusion Score (ETS): Prediction of blood transfusion requirement in initial resuscitation after severe trauma. *Transfusion Medicine* 2006;16.1:49–56.
42. Kuhne CA, et al. Emergency Transfusion Score (ETS): A useful instrument for

prediction of blood transfusion requirement in severely injured patients. *World J Surgery* 2008;32.6:1183–1188.

43. Tapia NM, et al. TEG-guided resuscitation is superior to standardized MTP resuscitation in massively transfused penetrating trauma patients. *J Trauma Acute Care Surg* 2013;74.2:378–386.
44. Johansson PI. Coagulation monitoring of the bleeding traumatized patient. *Curr Opin Anaesthesiology* 2012;25.2:235–241.
45. Schöchl H, et al. Practical application of point-of-care coagulation testing to guide treatment decisions in trauma. *J Trauma Acute Care Surg* 2013;74.6:1587–1598.
46. Holcomb JB, et al. Admission rapid thrombelastography can replace conventional coagulation tests in the emergency department: Experience with 1974 consecutive trauma patients. *Ann Surgery* 2012;256.3:476–486.
47. Holcomb JB, et al. Damage control resuscitation: Directly addressing the early coagulopathy of trauma. *J Trauma: Injury, Infection, and Critical Care* 2007;62.2:307–310.
48. Silliman CC, Ambruso DR, Boshkov LK. Transfusion-related acute lung injury. *Blood* 2005;105.6:2266–2273.
49. Sarani B, et al. Transfusion of fresh frozen plasma in critically ill surgical patients is associated with an increased risk of infection. *Crit Care Med* 2008;36.4: 1114–1118.
50. Hiippala ST, Myllylä GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. *Anesthesia and Analgesia* 1995;81.2:360–365.
51. Counts RB, et al. Hemostasis in massively transfused trauma patients. *Ann Surgery* 1979;190.1:91–99.
52. Wang D, et al. Transfusion of older stored blood and risk of death: A meta-analysis: Outcomes using old vs. new stored blood. *Transfusion* 2012;52.6: 1184–1195.
53. Malone DL, et al. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. *J Trauma: Injury, Infection, and Critical Care* 2003;54.5:898–907.
54. Corwin HL, et al. The CRIT Study: Anemia and blood transfusion in the critically ill — Current clinical practice in the United States. *Crit Care Med* 2004;32.1: 39–52.
55. Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: A systematic review of the literature. *Crit Care Med* 2008;36.9:2667–2674.
56. Triulzi DJ. Transfusion-related acute lung injury: Current concepts for the clinician. *Anesthesia & Analgesia* 2009;108.3: 770–776.
57. Alter HJ, Klein HG. The hazards of blood transfusion in historical perspective. *Blood* 2008;112.7:2617–2626.
58. O'Shaughnessy DF, et al. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematology* 2004;126.1:11–28.
59. Looney MR, Gropper MA, Matthay MA. Transfusion-related acute lung injury: A review. *Chest* 2004;126.1:249–258.
60. Toy P, et al. Transfusion-related acute lung injury: Definition and review. *Crit Care Med* 2005; 33.4:721–726.
61. Hébert PC, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999;340.6: 409–417.
62. Chaiwat O, et al. Early packed red bood cell transfusion and acute respiratory distress syndrome after trauma. *Anesthesiology* 2009;110.2:351–360.
63. Khan Hasrat, et al. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. *Chest* 2007;131.5:1308–1314.
64. Zou S, Dorsey KA, Notari EP, et al. Prevalence, incidence, and residual risk of human immunodeficiency virus and hepatitis C virus infections among United States blood donors since the introductions of nucleic acid testing. *Transfusion* 2010;50:1495-504.
65. Eder AF, et al. Bacterial screening of apheresis platelets and the residual risk of septic transfusion reactions: The American Red Cross Experience (2004-2006). *Transfusion* 2007;47.7: 1134–1142.
66. Hébert PC, et al. Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. *JAMA* 2003; 289.15: 1941–1949.
67. Vincent JL. Anemia and blood transfusion in critically ill patients. *JAMA* 2002;288.12: 1499.
68. Vincent JL, et al. Are blood transfusions associated with greater mortality rates? Results of the Sepsis Occurrence in Acutely Ill Patients Study. *Anesthesiology* 2008;108.1:31–39.
69. Wu WC, et al. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001;345.17:1230–1236.
70. Hajjar LA. Transfusion requirements after cardiac surgery: The TRACS Randomized Controlled Trial. *JAMA* 2010;304.14:1559.

CME/CNE Questions

1. What is the current ratio of blood products in traumatic resuscitation recommended by the literature?
   A. 1 unit PRBC to 1 unit FFP
   B. 2 units PRBC to 1 unit FFP to 1 pack of single donor platelets
   C. 1 unit of PRBC to 2 units FFP to 1 pack of single donor platelets
   D. 1 unit of PRBC to 1 unit FFP to 2 packs of single donor platelets
2. Permissive resuscitative hypotension should occur in which of the following settings?
   A. penetrating trauma with hemorrhage from easily compressible sites regardless of when hemostatic control is achieved
   B. penetrating trauma in difficult to achieve hemorrhagic lesions such as the liver or pelvic fractures, regardless of when hemostatic control is achieved
   C. penetrating trauma with hemorrhage from easily compressible sites up to the point when hemostatic control is achieved
   D. penetrating trauma in difficult to achieve hemorrhagic lesions such as the liver or pelvic fractures up to the point when hemostatic control is achieved
3. Which of the following patient characteristics predicts the need for massive transfusion?
   A. hypotension (systolic blood pressure < 90)
   B. mechanism of injury
   C. chest injury
   D. no free fluid on the FAST
   E. age younger than 50
4. What is the leading cause of transfusion-related morbidity and mortality in the United States?
   A. transfusion-related acute lung injury
   B. pneumonia
   C. fluid overload
   D. hypotension
5. Which is *not true* regarding Transfusion Related Acute Lung Injury (TRALI)?
   A. Clinical findings include tachypnea, cyanosis, frothy pulmonary secretions, dyspnea, hypotension tachycardia, and fever within 6 hours of transfusion, PaO2/FiO2 ratios of < 300 mm Hg, and decreased pulmonary compliance despite normal cardiac function.
   B. Higher FFP:PRBC ratios are associated with a higher incidence of TRALI.

CNE/CME Objectives

Upon completing this program, the participants will be able to:

- discuss conditions that should increase suspicion for traumatic injuries;
- describe the various modalities used to identify different traumatic conditions;
- cite methods of quickly stabilizing and managing patients; and
- identify possible complications that may occur with traumatic injuries.

C. TRALI occurs with a frequency of 1 in 5000, with morality rates up to 25%.
D. B-natriuretic peptide level more than 100 pg/dL and a post-transfusion to pre-transfusion ratio more than 1.5 indicate TRALI is most likely.

6. Which of the following *inaccurately* describes the risks of blood-borne pathogens from packed red blood cells?
   A. Risk of hepatitis C transmission is 1 in 1.5-2 million transfusions.
   B. Risk of HIV transmission is 1 in 1.5 million transfusions.
   C. Bacterial contamination is 1 in 4.75 million transfusions.
   D. Spirochetes in particular can survive in citrated blood, making these the most common blood-borne pathogen from transfusion.

7. The role of TEG in trauma is best described by which of the following?
   A. TEG identifies when sufficient volume has replaced hemorrhagic losses.
   B. TEG assesses function of the coagulation system to guide a targeted resuscitation of blood components.
   C. TEG assesses oxygen delivery to accurately restore perfusion to end organ tissues.
   D. There is no role for TEG in trauma.

8. Traumatic coagulopathy occurs in trauma as a result of which of the following?
   A. exposure of blood to open air during hemorrhage
   B. mixing of foreign material with blood causes intravascular coagulopathy
   C. infection that occurs after resuscitation causing inability for clotting factors to function
   D. depletion and consumption of coagulation factors and increased fibrinolysis

9. Which of the following correctly describes the transfusion threshold for a patient with cardiac history?
   A. Patients with active cardiac ischemia or recent cardiac surgery should be transfused when their hemoglobin is < 10.0 g/dL or hematocrit < 30%.
   B. Patients with active cardiac ischemia or recent cardiac surgery should be transfused when their hemoglobin is < 8.0 g/dL or hematocrit < 30%.
   C. Patients with active cardiac ischemia or recent cardiac surgery should be transfused when their hemoglobin is < 7.0 g/dL or hematocrit < 21%.
   D. Patients with active cardiac ischemia or recent cardiac surgery should not be transfused, as they are at highest risk of developing volume overload.

10. Which of the following best describes platelets?
    A. Platelets should be transfused to keep above a threshold of 50,000 in hemorrhagic shock.
    B. Platelet function matters more than quantitative volume.
    C. The literature universally indicates platelets should be transfused at a 1:1:1 ratio of PRBC:FFP:platelets.
    D. Platelets carry the least risk of transfusion-related immunomodulatory effects.

CNE/CME Instructions

HERE ARE THE STEPS YOU NEED TO TAKE TO EARN CREDIT FOR THIS ACTIVITY:

1. Read and study the activity, using the provided references for further research.

2. Scan the QR code below, or log on to **www.cmecity.com** to take a post-test; tests can be taken after each issue or collectively at the end of the semester. *First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice, or renewal notice.*

3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.

4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.

5. **Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.** You will no longer have to wait to receive your credit letter.

Trauma Reports™ (ISSN 1531-1082) is published bimonthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326. Telephone: (800) 688-2421 or (404) 262-7436.

Editorial Director: Lee Landenberger

Executive Editor: Shelly Morrow Mark

Managing Editor: Leslie Hamlin

POSTMASTER: Send address changes to *Trauma Reports*, P.O. Box 550669, Atlanta, GA 30355

Subscriber Information

Customer Service: 1-800-688-2421

Customer Service E-Mail:
customerservice@ahcmedia.com

Editorial E-Mail:
shelly.mark@ahcmedia.com

World Wide Web page:
http://www.ahcmedia.com

FREE to subscribers of *Emergency Medicine Reports* and *Pediatric Emergency Medicine Reports*

Subscription Prices

United States

$259 per year. Add $19.99 for shipping & handling

Multiple Copies

Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

All prices U.S. only. U.S. possessions and Canada, add $30 postage plus applicable GST.

Other international orders, add $30.

Accreditation

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 2.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Approved by the American College of Emergency Physicians for a maximum of 2.5 hour(s) of ACEP Category I credit.

The American Osteopathic Association has approved this continuing education activity for up to 30 AOA Category 2-B credits.

AHC Media is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity has been approved for 1.5 nursing contact hours using a 60-minute contact hour.

Provider approved by the California Board of Registered Nursing, Provider # 14749, for 1.5 Contact Hours.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

This CME/CNE activity is intended for emergency, family, osteopathic, trauma, surgical, and general practice physicians and nurses who have contact with trauma patients.

It is in effect for 36 months from the date of publication.

In Future Issues **Pelvic Trauma**

AHC Media

Dear *Trauma Reports* Subscriber:

This issue of your newsletter marks the start of a new continuing education semester and provides us with an opportunity to remind you about **the procedures for earning credit and delivery of your credit lette**r.

Trauma Reports, sponsored by AHC Media, provides you with evidence-based information and best practices that help you make informed decisions concerning treatment options. Our intent is the same as yours — the best possible patient care.

Upon completion of this educational activity, participants should be able to:

- discuss conditions that should increase suspicion for traumatic injuries;
- describe the various modalities used to identify different traumatic conditions;
- cite methods of quickly stabilizing and managing patients; and
- identify possible complications that may occur with traumatic injuries.

HERE ARE THE STEPS YOU NEED TO TAKE TO EARN CREDIT FOR THIS ACTIVITY:

1. Read and study the activity, using the provided references for further research.
2. Log on to **www.cmecity.com** to take a post-test; tests can be taken after each issue or collectively at the end of the semester. *First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice, or renewal notice.*
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. **Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.** You will not have to wait to receive your credit letter!

This activity is valid 36 months from the date of publication. The target audience for this activity includes emergency medicine physicians and nurses.

If you have any questions about the process, please call us at (800) 688-2421, or outside the U.S. at (404) 262-5476. You can also fax us at (800) 284-3291, or outside the U.S. at (404) 262-5560. You can also email us at: customerservice@ahcmedia.com.

On behalf of AHC Media, we thank you for your trust and look forward to a continuing education partnership.

Sincerely,

Lee Landenberger
Continuing Education Director
AHC Media