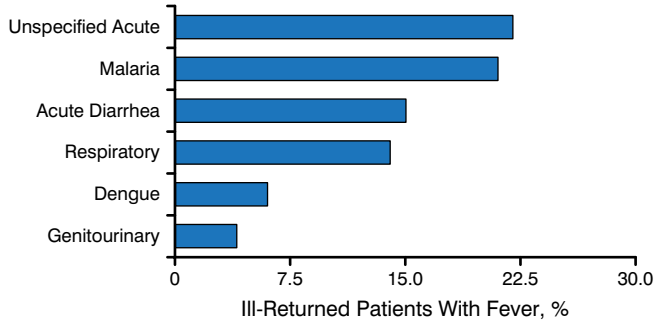
Figure 1. Many Febrile Patients Present After Travel With Unspecified Acute Symptoms (n = 6957)



Adapted from Kotylar S et al. Fever in the returning traveler. *Emerg Med Clin North Am.* 2013;31:927-944. Republished with permission of Elsevier, Inc.

To conclude, physicians should become familiar with the framework for the safe evaluation of patients with suspected highly infectious pathogens in order to effectively manage patients and at the same time minimize the risk to physicians and other health care team members.

The Challenge of Anticoagulant Reversal

Written by Toni Rizzo

Colin G. Kaide, MD, Ohio State University, Columbus, Ohio, USA, discussed the treatment of acute bleeding in patients taking old and new anticoagulants. Warfarin reversal involves 2 phases: immediate reversal and sustained reversal. Options for immediate reversal include fresh-frozen plasma (FFP), prothrombin complex concentrate (PCC), and activated PCC (aPCC) factor VIII inhibitor bypassing activity (FEIBA; Table 1).

For sustained reversal of warfarin, vitamin K must be given. Vitamin K promotes generation of the active forms of factors II, VII, IX, and X; it can be administered orally or intravenously [Ansell J et al. *Chest.* 2008].

Unfractionated heparin (UFH) can be reversed with protamine, which binds to and inactivates heparin. Protamine is administered at 1 mg/100 U UFH to a maximum dose of 50 mg. Protamine is not fully effective against low-molecular-weight heparin (LMWH). For enoxaparin reversal, protamine should be administered at 1 mg/1 mg enoxaparin if LMWH was taken within the previous 8 hours or at 0.5 mg/1 mg enoxaparin if LMWH was taken within 8 to 12 hours, up to a maximum of 50mg. Dosing should be repeated if the bleeding has not stopped and antifactor Xa levels are elevated 2 to 4 hours after the last protamine dose [Hirsh J et al. *Chest.* 2001].

One study found the anticoagulant effect of the fondaparinux was shown to be reversible in healthy volunteers with the administration of rVIIa dosed at 90 µg/kg [Bijsterveld NR et al. *Circulation.* 2002]. Another study found that rVIIa did not significantly reverse markers of anticoagulation for fondaparinux, whereas markers were likely improved with administration of PCC and completely reversed with aPCC (Feiba) [Desmurs-Clavel H et al. *Thromb Res.* 2009].

Several new oral anticoagulants (NOACs) have been developed. Among them are the direct thrombin inhibitors, dabigatran, and the direct-factor Xa inhibitors, rivaroxaban and apixaban. Reversing the action of these agents is a challenge. Hemodialysis can stop the activity of dabigatran but not of rivaroxaban and apixaban (Table 2).

Specific reversal agents for the NOACs are under development. For dabigatran, a humanized monoclonal antibody fragment is currently being investigated in several

Table 1. Options for Immediate Warfarin Reversal

Reversal Agent	Studies Regarding Agent	Dosage	Features
FFP	Holland LL et al. *Am J Clin Pathol.* 2006	10-15 mL/kg, 4 U minimum	Lowest attainable INR with FFP = 1.5
PCC	Leissinger CA et al. *Am J Hematol.* 2008	Weight-based dosing: 25-50 U/kg INR-based dosing: 2-4 = 25 U/kg; 4-6 = 35 U/kg, > 6 = 50 U/kg [Pabinger I et al. *Thromb Haemost.* 2008] Absolute dosing: INR ≤ 5 = 500 U; INR > 5 = 1000 U [Yasaka M et al. *Thromb Res.* 2005]	Mix of nonactivated clotting factors 2 types of mixes: 3-factor and 4-factor INR reversal in 15 min Corrects lab values and clinical bleeding Small risk of disease transmission Rare thromboembolic events (1.5% in 14 studies) [Leissinger CA et al. *Am J Hematol.* 2008]
aPCC (FEIBA)	Wojcik C et al. *Int J Emerg Med.* 2009	INR< 5: 500 U; INR ≥ 5: 1000 U	Contains activated factors II, VII, IX, X

aPCC, activated prothrombin concentrate; FEIBA, factor VIII inhibitor bypassing activity; FFP, fresh-frozen plasma; INR, international normalized ratio; PCC, prothrombin complex concentrate; rVIIa, activated recombinant factor VII; U, units.

Table 2. Reversal of Dabigatran, Rivaroxaban, and Apixaban

NOAC	Reversal
Dabigatran [Siegal DM, Cuker A. *J Thromb Thrombolysis*. 2013; Lillo-Le-Louet A et al. *Thromb Haemost.* 2012]	rVIIa: Inconsistent results, likely not useful Dosing: 50-100 U/kg* 4-factor PCC: Inconsistent results aPCC (Feiba) Reversed markers and in animals* Complete reversal in volunteer ex vivo studies* Best option at this time*
Rivaroxaban and apixaban	rVIIa did not work in animal studies 4-factor PCC was effective in animal studies and is the best current option aPCC FEIBA reversed markers in animals

aPCC, activated prothrombin complex concentrate; NOAC, new oral anticoagulant; PCC, prothrombin complex concentrate; rVIIa, recombinant factor VIIa.

*On May 1, 2015, these lines were indented.

animal and in vitro studies. Clinical trials are currently underway studying the recombinant factor Xa derivative, and adexanet alfa, as a specific reversal agent for rivaroxaban [NCT02220725] and apixaban [NCT02207725]. This agent is a factor Xa decoy that targets and sequesters direct and indirect factor Xa inhibitors in the blood. Once bound, the factor Xa inhibitors cannot bind and inhibit native factor Xa, allowing restoration of normal hemostasis.

Platelet inhibitors, including salicylates, clopidogrel, and factor IIb/IIIa inhibitors may be somewhat reversed by transfusion of platelets [Vilahur G et al. *J Thromb Haemost.* 2007] and desmopressin [Leithouser B et al. *Clin Hemorheol.* 2008], but there is no definitive proof. If reversal is attempted using platelets, 2 to 3 pools of platelets should be used. ε-Aminocaproic acid is an antifibrinolytic agent used for hemophiliacs that might reverse fibrinolytics, but there are no data supporting this use [Stief T. *Clin Appl Thromb Hemost.* 2008].

Dr Kaide concluded that anticoagulant reversal should be attempted in situations where "maximal harm is already in progress" and the risk of bleeding outweighs the risk of reversal of anticoagulation. New antidotes for the NOACs are under development and will be available in the near future.

Bedside Ultrasonography Useful for Trauma Patients

Written by Phil Vinall

In the decades since the Focused Assessment with Sonography in Trauma examination was first proposed, the use of point-of-care ultrasonography has expanded further into the trauma world. Matt Dawson, MD, University of Kentucky, Lexington, Kentucky, USA, discussed the modern use of bedside ultrasonography in the initial evaluation of trauma patients.

Bedside ultrasonography has been shown to be equal to or more sensitive than other modalities for detecting traumatic injuries. In a randomized controlled clinical trial, patients presenting to the emergency department with suspected torso damage assessed with ultrasonography had considerably decreased time to operative care, improved resource use, and lower medical costs [Melniker LA et al. *Ann Emerg Med.* 2006]. A more recent study reported that bedside ultrasonography had higher sensitivity and similar specificity compared with chest radiography for the diagnosis of pneumothorax [Ding W et al. *Chest.* 2011].

Point-of-care ultrasonography has long been used for the assessment of hemoperitoneum and hemopericardium in emergency departments and operating rooms [Rippey JC, Royse AG. *Best Pract Res Clin Anaesthesiol.* 2009]. Ultrasonography can also be used to assess vascular injuries, musculoskeletal injuries, genitourinary injuries, and fetal viability in pregnant trauma patients. In addition, ultrasonography can be used to guide nerve blocks and vascular access in real time.

Another application that may be useful in the setting of trauma is the tracheal rapid ultrasound examination [Chou HC et al. *Resuscitation.* 2011]. Correct positioning of an endotracheal tube can be confirmed by a sonographer within 3 seconds of placement, with 100% sensitivity and specificity [Muslu B et al. *J Ultrasound Med.* 2011].

Another useful application of ultrasonography is as a noninvasive test for elevated intracranial pressure (ICP). Optic nerve sheath diameter > 5 mm as detected by ocular ultrasonography identifies patients with ICP > 20 cm H_2O and has been highly correlated with ventriculostomy measurements [Kimberly HH et al. *Acad Emerg Med.* 2008]. Third-ventricle midline shift as evaluated by transcranial color-coded sonography is more sensitive and specific than the pulsatility index in detecting large intracerebral hemorrhage and it is also a significant predictor of short-term functional outcome (OR, 2.09; 95% CI, 1.06 to 4.13) [Tang SC et al. *J Ultrasound Med.* 2006].

Point-of-care ultrasonography is particularly useful in settings in which traditional radiography is unavailable or undesired. Clavicle fracture, a common orthopedic injury in children, can be diagnosed with bedside ultrasonography with 95% sensitivity, 96% specificity, and 96% overall accuracy [Cross KP et al. *Acad Emerg Med.* 2010]. Even in the hands of physicians with minimal training, portable ultrasonography is useful for detecting fractures in a remote setting [Marshburn TH et al. *J Trauma*. 2004].

Ultrasonography has long been the standard for hemodynamically unstable patients with concerning mechanism of injury. However, ultrasonography is also