Clinical Approach to Asymptomatic Patients with an Elevated INR

- There is no need to order a PTT/PT for any ED patient unless you suspect hemophilia, von Willebrand’s disease, or the patient is on home unfractionated heparin therapy. Warfarin may cause minimal elevations in the PTT. The INR is the only useful test to follow warfarin therapy.

- A more conservative approach to asymptomatic patients with elevated INRs — eschewing routine reversal of anticoagulation — has developed over the past years.

- It is generally agreed that low-risk asymptomatic patients with an INR from 5.0 to 9.0 do not require immediate reversal of anticoagulation. High-risk patients probably do require intervention, and as the INR reaches 9.0, intervention becomes more important.

- The INR returns to normal in a somewhat variable and unpredictable manner; almost all are in the therapeutic range (2.0-3.0) in four days.

- INRs in the 5.0 to 9.0 range can be handled by holding warfarin for two days with or without a small dose of oral vitamin K in high-risk patients.

- Most asymptomatic, over-anticoagulated patients can be treated as outpatients in the absence of bleeding or high-risk criteria.

- Be particularly careful about elevated INRs in the elderly.

- Subcutaneous vitamin K is no better than placebo in reversing coagulopathy.

- Order INRs very liberally on ED patients on maintenance warfarin therapy.

- Reverse all INRs greater than 9.0. Minor elevations in INR (less than 5.0) may not require a reduction in dosage.

- The risk of major bleeding with an INR less than 10 is about one percent to four percent in 30 days, with the risk increasing as the INR approaches 9.0.

- Excessive dose of vitamin K, though effective in stopping bleeding, can lower the INR more than necessary and lead to prolonged warfarin resistance.
not have spontaneous bleeding. While active bleeding generally requires reversal, exactly what to do with patients who seem to be tolerating an elevated INR without complications is less straightforward.

It is well known that the risk of bleeding increases as the INR rises and an INR over 4.0 is a specific risk factor. This article examined the 30-day risk of hemorrhage in patients with an excessively prolonged INR of greater than 5.0. Through a computer-based registry (the CoumaCare database of Bristol Myers Squibb), about 1000 patients with a first hemorrhage in patients with an excessively prolonged INR of greater than 5.0 were enrolled. Most were outpatients in a community-based cardiology practice. The INR was between 5.0 and 6.0 in 96 percent and less than 7.0 in 80 percent. About 40 percent were receiving warfarin for atrial fibrillation, 30 percent had a prosthetic heart valve, and the rest were being treated for DVT, CVA, and a variety of cardiac issues. The average age was 70. Intervention was usually merely stopping the warfarin and follow-

ing the INR, but some patients received vitamin K reversal.

Of the 976 patients identified with an INR greater than 5.0, 13 patients (1.3%) experienced a major hemorrhage during the first 30 days after the index INR was identified. The majority occurred within one week. Most events were gastrointestinal in origin, and none was fatal. One soft tissue hemorrhage and one retroperitoneal hemorrhage occurred. If the INR was greater than 9.0, the risk of hemorrhage was significantly increased.

The most common clinical approach (perhaps defining the current standard of care) was simply to withhold subsequent warfarin doses and follow the INR. When the warfarin was withheld, the INR was 2.0 or less within four to five days. Overall, intervention with vitamin K was minimal; only about nine percent of the patients were given the reversal agent. Although vitamin K was not routinely administered to most patients, 62 percent of those with an INR greater than 9 received low-dose oral vitamin K for reversal of coagulopathy. Because of the small number of complications, the authors were not able to assess the value of vitamin K use and the risk of hemorrhage.

The authors concluded that the risk of major hemorrhage within 30 days in asymptomatic patients with an INR greater than 5.0 is quite low, only 1.3 percent in this study. It is standard practice to avoid the administration of low doses of vitamin K despite the fact that such intervention returns the INR to the normal range without causing an over-reversal of the anticoagulation effect of warfarin. The authors suggest that this low bleeding rate and K therapy should be considered for patients with an INR greater than 5.0 who have other risks for hemorrhage. However, if the INR is less than 9, these data indicate that intervention to reverse the coagulopathy is not standard practice nor required.

Comment: The clinical approach to excess anticoagulation in patients taking warfarin has evolved into a rather consen-

sual stance. When I was a neophyte emergency physician, it was a general consensus that high INRs (then we used the PT) had to be reversed because of the potential of bleeding, particularly intracranial hemorrhage. Intracranial hemorrhage (spontaneous and secondary to trauma) is the most feared and least correctable bleeding complication. A CNS bleed is especially problematic in the elderly. I can remember giving 10 mg of IV vitamin K to patients with modest elevations in the INR, and fighting for admission with a recalibrant (and obvi-

ously overcorrected) time. Interests have changed.

Speaking of times changing, why would you ever order a PT/PTT in the ED? The PT is clearly a dinosaur, with no redeeming features. The PTT is only elevated in hemophilia, von Willebrand’s disease, and unfractinated heparin therapy (not Lovenox et al outpatient use). Old habits die hard, but get the PT/PTT off the templated order sheet and stop ordering useless tests. Let the lab tech concentrate on tests that actually have value in the ED.

Numerous other clinicians have addressed this exact issue: What do we do with patients who have excess warfarin anticoagulation and have no sign of hemorrhage? Hyleke et al were the first to intensely study the short-term risk of hemorrhage after an isolated finding of an INR greater than 6.0 in asymptomatic patients. (Arch Intern Med 2000;160: 1612.) That small study found a slightly higher rate of bleeding, with a 4.4 percent risk of major hemorrhage within two weeks when INRs greater than 6.0 were managed conservatively. The INR was high in the Hyleke et al. Garcia study, with a mean of 8.1 vs. 6.5, and 14 percent were greater than 10. Major hemorrhage was defined as a fatal bleed, intracranial hemorrhage, or bleeding requiring hospitalization and transfusion. Temporarily discontinuing warfarin therapy resulted in a normal INR in 90 percent of the patients within 96 hours, but the decline was variable and unpredictable. It appears that an INR greater than 5.0 to 6.0 is a consideration or action level for reversal by most clinicians for patients at high risk for hemorrhage. In the absence of high-risk criteria, watchful waiting seems to be the norm. The exact INR requiring treatment has crept up over the years, but I am comfortable with patients who have excess warfarin anticoagulation. — E. Lovell, MD, Chicago, IL

Dr. Roberts responds: Thanks to Dr. Lovell for the letter and literature review. I generally agree with you. You seem to advocate a head CT on every small infant (under 3 months) who is brought in for a check, even in the absence of any symptoms or swelling. Of course, you have to get a pristine history and actually examine the child and the scalp, not always accomplished, less often documented. An automatic CT is the only way to be 100 percent sure. We are 100 percent sure on essentially nothing in medicine, but certainly a head injured infant is an emotional and litigious issue. There is, however, no definitive answer. Even the famous Nexus criteria had a few spinal fractures slip through the cracks. This is similar to the argument to admit every patient with chest pain to avoid missing that two to three percent of patients with occult MI/unstable angina who are sent home in every study that ever attempted to use preset criteria or clinical judgment. If you read my article carefully, I pointed out that the use of screening skull films was a "reaso-

nable" pediatric recommendation, not necessarily an emergency medicine approach, and not usually my personal approach. Most ICUs that are truly clinically silent never amount to much except angst, but try telling that to a parent who gets a CT the next day when you refused the study in the ED. Maybe PECARN will settle this, but don’t bet the farm on it. I use CT scans liberally and eschew skull films, but nothing is automatic. The younger the kid, the more the CT scanner is used. If I live long enough, I am sure I will be sued by a parent of a child with cancer attributed to my excessive radiation. Little Johnny who did not require the brain/thyroid radiation in the first place. It’s easy to sell shoes, hard to be an ED doctor.

InFocus

Warfarin

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such are uncertain. Their conclusion was that patients with an INR greater than 6.0 could achieve an early return to the INR target range with oral or IV vitamin K (but not subcutaneous vitamin K). Routine intervention was not suggested because the risks and benefits were unclear; no help here for the EP faced with the patient in the ED.

The most recent recommendations from the American College of Chest Physicians (ACCP) for the management of supratherapeutic INR among patients treated with warfarin are presented in the table. It is clear, however, that most physicians do not adhere to the ACCP guidelines but take a more conservative approach of watchful waiting. Clinical experience has concluded that one can be rather conservative with INR in the 5 to 9 range.

With regard to the asymptomatic patient who presents in the ED with an elevated INR, it appears reasonable to follow the ACCP guidelines. Many physicians do not know these guidelines, and some don’t follow them anyway, and the caveat that every patient should be individualized is stressed. I would be much more hesitant to allow an untreated INR of 8.0 in an 80-year-old man who lives alone than I would be for a 40-year-old who had a valve replacement and has little other morbidly. For me, an INR of 6.0 is certainly less of a concern than 8.5. I could find no recommendation on admission versus outpatient follow-up, but it seems that there is an overwhelming consensus that outpatient treatment is safe and universal. Most studies evaluate reliable and compliant private practice patients, not exactly my clientele. I have had patients take extra warfarin when they get sick because by their reasoning, “if more is good, three must be better.” Of course, you could always consult your local expert or the patient’s primary physician to coordinate the best clinical approach for that patient. The approach to the patient who is bleeding with an elevated INR will be covered in future columns.

The risk factors for major bleeding in patients treated with warfarin include age greater than 70 years, history of stroke or prior GI bleeding, or serious comorbid conditions, such as recent MI, renal failure, or severe anemia. It’s unknown whether the risk of bleeding can be reduced in high-risk patients without reducing the benefit of warfarin therapy. In short, there is no easy answer. It is clear that all physicians must respect the potential complications of warfarin therapy, and the emergency physician is in the mix even if we do not prescribe or follow outpatients.

Summary: Patients treated with warfarin can become excessively anticoagulated in a rather surreptitious and clandestine fashion. Even if the INR has been stable for many months, there are just too many variables in maintaining a proper INR to allow patients and clinicians to eschew INR testing on a regular basis. This is especially true in ED patients. My advice has always been to do an INR on almost any patient taking warfarin who presents to the ED with almost any complaint or issue. If nothing else, you give them a free coagulation update. Particularly at risk for erratic

Continued on next page

### Clinical Management of an Elevated INR

<table>
<thead>
<tr>
<th>INR</th>
<th>Bleeding</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 5.0</td>
<td>No</td>
<td>Lower warfarin dose. or Omit one to two doses and resume warfarin at a lower dose when INR is in therapeutic range. or Follow INR and do not reduce dose if INR is only minimally prolonged.</td>
</tr>
<tr>
<td>&gt;5.0 to 9.0</td>
<td>No</td>
<td>Omit the next one to two doses of warfarin, monitor INR more frequently, and resume treatment at a lower dose when INR is in therapeutic range. or Omit a dose and administer 1 mg·2.5 mg oral vitamin K1.</td>
</tr>
<tr>
<td>&gt;9.0</td>
<td>No</td>
<td>Hold warfarin.1 Administer 5 to 10 mg oral vitamin K1. Monitor INR more frequently and administer vitamin K1 as needed. Resume warfarin at a lower dose when INR is in therapeutic range.</td>
</tr>
<tr>
<td>&gt;20</td>
<td>No</td>
<td>Hold warfarin.1 Administer 10 mg vitamin K1 by slow IV infusion; supplement with prothrombin complex concentrate, fresh frozen plasma, or recombinant human factor VIIa, depending on clinical urgency. Repeat INR daily.</td>
</tr>
</tbody>
</table>

1. Preferred for high-risk patients (elderly, higher INR, history of bleeding, stroke, CHF, cancer, renal insufficiency, anemia, hypertension).
2. Most can be followed as outpatients. Admit all high-risk patients.
3. Admission or prolonged observation in high-risk patients; close follow-up in low-risk patients.
4. Admit to hospital.

Sources: Cheet 2004;126:204; Up to Date database http://scientific.thomson.com/products/idocs/complete.

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In Brief

Rangel and Dingel: Health IT Bill Endangers Privacy

Representatives Charles B. Rangel (D-NY) and John D. Dingel (D-MI) said the health information technology bill recently passed by House Republicans could jeopardize the privacy of medical records for millions of patients. The bill also does little to improve the current use of IT in health care, the Congressmen said in a statement.

“In fact, the Congressional Budget Office cautions that the bill would not significantly change the rate at which health IT will grow or how well the technology will be designed and implemented,” Rep. Rangel said. “There’s no question that we need to improve IT, but this bill sacrifices patient privacy for the sake of politics.”

HR 4157, introduced by Rep. Nancy L. Johnson (R-CT) with 58 cosponsors, establishes a National Coordinator for Health Information Technology in the Office of the Secretary of HHS. The coordinator will direct and oversee continuous improvements in a strategy of HHS. The coordinator will “serve as an advisor to the Secretary of Health and Human Services, facilitate adoption of a nationwide system for electronic exchange of health information, establish standards for the system, ensure coordination of HHS policy with ‘relevant executive branch agencies,’ coordinate outreach and consultation, and advise the President about specific federal health information technology programs.”

Like HR 4157, though, the language of S 1418 is vague and does not specify how and under what circumstances patients’ privacy is to be protected.

Majority of Medicare Enrollees May Fall into ‘Doughnut Hole’

Nearly seven million seniors and people with disabilities who purchased standalone prescription drug coverage are now at risk of falling into a “doughnut hole,” said three long-time Congressional Democrats. This latest setback comes after older people have struggled for months with confusing and inaccurate information about the new Medicare prescription drug program.

According to a report from senior Democrats on the House Ways and Means Committee, led by Ranking Member Rep. Charles Rangel (D-NY), Health Subcommittee Ranking Member Rep. Pete Stark (D-CA), and Social Security Subcommittee Ranking Member Rep. Sander Levin (D-MI), nearly 88 percent of new drug plan enrollees are at risk of losing coverage for their medications while they continue to pay monthly premiums to their insurers. The report describes how few individuals have enrolled in plans without doughnut holes, presumably because of the prohibitive cost of such plans. The hole requires seniors trapped inside it to pay for drug insurance and pay the entire cost of the drugs they buy.

Under the Medicare Part D rules, out-of-pocket prescription expenses between the annual amounts of $2,251 and $5,100 are not covered; and this nearly $3,000 gap has been termed the “doughnut hole.”

Another key finding of the report was that 88 percent of prescription drug plan enrollees who purchased non-HMO coverage are enrolled in plans with the doughnut hole. Eighty-four percent of private drug plans have a gap in coverage, and in 26 states, some 90 percent of beneficiaries are enrolled in plans with a gap. Nationally, only 12 percent of beneficiaries (fewer than one million people) with new coverage are enrolled in plans that provide any coverage at all in the doughnut hole, and premiums are, on average, more than 250 percent higher for a plan with full coverage.
**WARFARIN**

Continued from previous page

INR evaluations are elderly, noncompliant patients and those with excessive comorbidity (and that probably defines almost anyone on warfarin). Even minor changes in diet can wreak havoc with a previously stable INR. Those otherwise healthy lean green vegetables contain vitamin K that can negate warfarin effect. Of course, almost any drug you prescribe, even antibiotics, will bump the INR one way or another, usually to the upside.

The asymptomatic patient with an elevated INR presents a common issue for emergency physicians. If the INR is less than 9.0 (previously a rather scary number to me), the estimated risk of major hemorrhage within the next 30 days is about one percent. Risk is likely higher as the INR approaches 9.0, the recommended action level. There are two options for such patients: stop the warfarin or stop the warfarin and add a small dose of oral vitamin K. It may be quite difficult to ferret out the exact reason for this elevated INR. But it is well known that once the INR is over 6, there is a high chance of future coagulopathy and hemorrhage in this individual.

For most patients, it seems reasonable to opt for ED discharge and simply hold the warfarin dose for at least two days, and then repeat the INR. You can give them a prescription for the test at your lab and have it ready for the follow-up at the primary physician’s busy practice. Response to warfarin interruption is variable, and some patients will still be excessively anticoagulated after two days. Holding warfarin for four days brings the INR into line for most, if not, think liver disease. It appears that old age, a higher index INR, a lower maintenance dose of warfarin, and active cancer or heart failure increase the chance of a tardy return to a therapeutic INR.

Aministering 1 to 2.5 mg of oral vitamin K is one option for high-risk patients who are not bleeding but have an INR between 5.0 and 9.0. This corrects the excess anticoagulation more rapidly than simply stopping the warfarin, and it doesn’t render the patient resistant to further warfarin therapy. There is no need to give parenteral vitamin K in these patients. In fact, subcutaneous vitamin K is probably no better than placebo, and it should not be used. (Ann Intern Med 2002;137:251.) The oral and intravenous routes are equally effective, and the small risk of anaphylaxis with the IV route makes the oral regimen preferable.

If the INR is excessive, generally defined as greater than 9.0, oral vitamin K in a 5 mg to 10 mg dose is generally prudent. It’s unclear whether such patients need to be admitted to the hospital, so I would treat each as an individual. It seems prudent to opt for admitting those at high risk. If the INR is greater than 20, most experts recommend reversal with IV vitamin K, even in the absence of hemorrhage.

Finally it’s interesting to note that the size of vitamin K tablets generally available are 5 mg, scored to allow administration of 2.5 mg. One can give 1 mg of the intravenous preparation (2 mg/ml) by mouth, and accomplish the same effect as giving the pill. Note that some IV vitamin preparations are much more concentrated (10 mg/ml).

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**February 2007**

Questions:

1. An INR of greater than 9.0 in an asymptomatic patient is an indication for reversal of the coagulopathy

   - True
   - False

2. Most nonbleeding patients with an INR of less than 9.0 will have a therapeutic INR if warfarin is withheld for four days.

   - True
   - False

3. Low-dose oral vitamin K is the preferred intervention for asymptomatic elevations of the INR less than 9.0.

   - True
   - False

4. The risk of bleeding at 30 days in asymptomatic patients with an elevated INR (greater than 50) is about 50 percent.

   - True
   - False

5. Elderly patients (over age 75) are at higher risk for serious bleeding than younger patients with a similar INR.

   - True
   - False

Your evaluation of this CME activity will help guide future planning. Please respond to the following questions:

1. Did the content of this activity meet the stated learning objectives?

   - Yes
   - No

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   - 5
   - 4
   - 3
   - 2
   - 1

3. As a result of meeting the learning objectives of this educational activity, will you be changing your practice behavior in a manner that improves your patient care? If yes, please explain.

   - Yes
   - No

4. Did you perceive any evidence of bias for or against any commercial products? If yes, please explain.

   - Yes
   - No

5. How long did it take you to complete this CME activity? ______ hour(s) ______ minutes

6. Please state one or two topics that you would like to see addressed in future issues.

   ________________________________________________________________
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