**Warfarin: Common Causes and Management Strategies for High INRs**

**Objective:**
To provide a summary of the most common causes of and management strategies for high international normalized ratios (INRs) for patients on long-term warfarin therapy.

<table>
<thead>
<tr>
<th>Common Causes of High INRs</th>
<th>Management Strategies</th>
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</thead>
<tbody>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>• Temporary drug interaction: temporary warfarin hold or dose reduction</td>
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<td>• Chronic drug interaction: reduce maintenance dose and increase frequency of INR tests until new stable INR is achieved</td>
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<td>• Although many drugs may interact with warfarin, avoidance of either warfarin or the interacting drug is usually not required</td>
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<td><strong>Altered Health States</strong></td>
<td>• Fever, acute illness, diarrhea, reduced food intake</td>
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<td>• Uncontrolled hyperthyroidism</td>
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<td>• CHF exacerbation</td>
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<td>• Temporarily reduce the dose and increase the frequency of INR testing until the patient’s health stabilizes</td>
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<td><strong>Malnutrition</strong></td>
<td>• (vitamin K deficiency)</td>
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<td>• Encourage patient to consume regular meals, including those containing vitamin K. Consider meal replacement beverage.</td>
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<td>• Reduce maintenance dose of warfarin and increase frequency of monitoring</td>
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<td><strong>Alcohol</strong></td>
<td>• A one-time moderate to large amounts of alcohol (more than 2 drinks) will transiently increase the INR (e.g. weekend party).</td>
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<td>• Continue usual maintenance dose</td>
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<td><strong>Non-compliance or Errors in Dosing</strong></td>
<td>• Review the doses of warfarin actually taken over the past several weeks</td>
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<td>(The patient mistakenly took a different dosage regimen than was prescribed)</td>
<td>• Use strategies to improve compliance: pill box, warfarin dosing calendar, patient education, simplify dosing regimen</td>
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**Common causes of high INRs and management strategies**

The most common reasons for supratherapeutic INRs and management principles are:

1. **Drug Interactions**
   - **Most common drugs that can increase INR:**
     - Antibiotics: sulfamethoxazole/trimethoprim, metronidazole, quinolones (ciprofloxacin, levofloxacin), amoxicillin, erythromycin, clarithromycin, azithromycin
     - Azole antifungals: fluconazole, miconazole, voriconazole
     - Cardiac drugs: amiodarone, some statins (fluvastatin), fenofibrate
     - Acetaminophen >1 g/day
     - Levothyroxine dose increases – full effect observed after 4-6 weeks of dose change
   - **Management strategy:**
     - If the interacting drug is temporary and significantly increases the INR, may temporarily hold and/or reduce the maintenance dose of warfarin until the interacting effect resolves.
     - If the interacting drug will be used chronically, modify the warfarin dose according to a dosing nomogram.
     - Although warfarin interacts with many drugs, virtually no drug requires complete avoidance in a patient who is also taking warfarin therapy (or vice versa). Increasing the frequency of INR tests, initially, allows for appropriate dosing adjustments, if necessary. There may be some exceptions to this approach. For example, patients receiving chemotherapy with emesis or infection may have INR fluctuation that is difficult to control. In such cases, switching the patient to a low molecular weight heparin (LMWH) until stabilization of the underlying condition is suggested.
     - Note: **Antiplatelet agents** (acetylsalicylic acid [ASA], clopidogrel, prasugrel, ticagrelor) and **Non-steroidal Anti-Inflammatory Drugs** (NSAIDs) significantly increase the risk of bleeding when combined with warfarin but generally do not change the INR. The indication and clinical necessity of using these agents should be carefully weighed against the increased bleeding risk. Refer to the Clinical Guide “Warfarin” for more information.

2. **Altered health states**
   - Transient infectious illness (fever and/or diarrhea):
     - **Fever** increases the metabolic state which may result in depletion of clotting factors and increased INR.
     - Being ill can also alter diet and may lead to a transient vitamin K deficiency.
   - Uncontrolled hyperthyroidism – leads to increased clearance of clotting factors, resulting in high INR.
   - Congestive heart failure (CHF) exacerbation (perhaps due to liver congestion).
   - **Management Strategy:**
     - Temporarily reduce the warfarin dose and increase the frequency of INR monitoring until the patient’s health state stabilizes

3. **Altered Nutritional Status**
   - Patients who are malnourished are commonly vitamin K deficient.
   - Sudden changes in diet may be due to social circumstances such as a death of a spouse/family member/pet or stressful work or health situations.
Management Strategy:
- Ask the patient to describe their eating pattern and intake.
- Recommend eating consistent meals or use of a meal replacement beverage (e.g. 4 cans of Ensure contain the required daily amounts of nutrients) or multivitamins containing vitamin K.
- If this is not successful, consider lowering the maintenance dose and increase the frequency of monitoring.

4. Errors in dosing
- The patient may have mistakenly taken a different dosage regimen than what was prescribed.
  
  Management Strategy:
  - Ask the patient exactly what doses they have taken in the past 2 weeks and review their dosing calendar.
  - Ask the patient to bring in all of their medications and pill box to ensure the correct drugs and doses are being taken. If the patient has a good relationship with their local pharmacy, ask the pharmacist to double check.
  - Use a warfarin dosing calendar. Encourage the patient to use a calendar to record their INRs and warfarin doses taken.
  - Use a warfarin dosette (pill box). The patient or caregiver puts the daily doses in a weekly pill box.
  - Simplify the dosing regimen. Use of a single tablet strength to avoid multiple strength confusion and strategically putting extra/reduced daily doses on days that are easy to remember (e.g. “Take 1 tablet every day except take 2 tables on Sundays.”

REFERENCES


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