Warfarin Management - Adult - Inpatient
Clinical Practice Guideline

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Executive Summary

Guideline Overview

This guideline outlines the evidence for managing anticoagulation therapy with oral vitamin K antagonist (warfarin). Evidence is based on recommendations from the Antithrombotic Therapy and Prevention of Thrombosis, 9th edition: American College of Chest Physicians Clinical Practice Guidelines. It provides recommendations for how to initiate, dose adjust and monitor warfarin therapy.

Key Practice Recommendations

1. Initial warfarin dosing should be tailored based on patient bleed risk, potential sensitivity to warfarin, indication, goal INR range, and if potential drug interactions are present.
2. Daily warfarin dose adjustments should be based on current INR measurements and prior to making a dose adjustment assess for any missed doses, drug interactions, dietary intake or supplements, documentation of bleeding, or other changes that may affect the INR.
3. Table 4 and 5 provide recommendations for warfarin dosing for INR goals of 2-3 and 2.5 -3.5.

Companion Documents

1. Warfarin Management – Adult – Ambulatory Clinical Practice Guideline
2. Atrial Fibrillation – Adult – Inpatient/Ambulatory Clinical Practice Guideline
3. Antithrombotics in Non-Valvular Atrial Fibrillation – Adult – Inpatient/Ambulatory Clinical Practice Guideline
4. HealthDecision$_{TM}$ Atrial Fibrillation Risk Stratification Tool
5. Mechanical Circulatory Device (MCD) – Adult – Inpatient/Ambulatory Clinical Practice Guideline
6. Indications for Blood Product Transfusion – Adult – Inpatient/Ambulatory

Pertinent UW Health Policies & Procedures

1. UWHC Policy #2.3.1 Anticoagulation Monitoring by UW Anticoagulation Clinic Pharmacists

Patient Resources

1. Health Facts For You #6900: Warfarin (Coumadin, Jantoven)
2. Health Facts For You #322: Food-Drug Interactions: Coumadin & Warfarin Diet Interactions
3. Health Facts For You #6915: Heparin (Unfractionated and Low Molecular Weight)

Scope

Disease/Condition(s):
This guideline will apply to any disease or condition requiring anticoagulation with oral vitamin K antagonist (warfarin) therapy

Clinical Specialty:
General Medicine/Hospitalist
Cardiology
Pharmacy

Intended Users:
Physicians
Advanced Practice Providers
Pharmacists
Nurses

Objective(s):
To provide a strategy for the management of warfarin therapy in adult hospitalized patients using a standardized process while offering an individualized assessment.

Target Population:
Adult inpatients either being initiated on warfarin or continued on home warfarin therapy during hospitalization.

Interventions and Practices Considered:
This guideline provides strategies and recommendations designed to assist clinicians in developing warfarin management plans. It begins with providing recommendations for target INR ranges based on indication for use. It focuses on how to dose warfarin based on individual patient risk factors, INR response, drug interactions, and dietary interactions.

Major Outcomes Considered:
Thromboembolic events while initiating and maintaining warfarin therapy
Hemorrhagic events while initiating and maintaining warfarin therapy
Need for reversal agents in the event of a bleeding event or emergent surgery/procedure.

Guideline Metrics:
Metrics will include time to target INR range, sub and supratherapeutic INR values, critical INR values, appropriate dose adjustments based on drug and dietary interactions while receiving warfarin therapy.

Methodology

Methods Used to Collect/Select the Evidence:

(1) completing a comprehensive literature search of electronic databases; (2) conducting an in-depth review of relevant abstracts and articles; (3) conducting thoughtful discussion and interpretation of findings; (4) ranking strength of evidence underlying the current recommendations that are made.

Methods Used to Assess the Quality and Strength of the Evidence:

A similar grading system for the recommendations from the American College of Chest Physicians was utilized.

Rating Scheme for the Strength of the Evidence:

For all other recommendations a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) developed by the American Heart Association and American College of Cardiology (Figure 1.) has been used to assess the Quality and Strength of the Evidence in this Clinical Practice Guideline.[1]

Definitions

1. Baseline INR: For scheduled surgical patients the INR must be resulted within the electronic medical record and within the past 30 days and for all other patients the INR must be within 72 hours of warfarin order and prior to verification of the warfarin dose.
2. Current INR: an INR reported on the same calendar date as the scheduled warfarin dose

Introduction

Warfarin is a medication with a narrow therapeutic index that relies on a targeted range for efficacy and reduction of complications.[2] With this narrow therapeutic range, warfarin is associated with bleeding complications, longer lengths of stays, adverse drug reactions, and higher hospitalization costs.[2,3] It is recommended to use standardized and validated dosing and monitoring tools for most patients on warfarin therapy.[4]

Warfarin inhibits the reduction of vitamin K epoxide which limits the activation of vitamin K dependant clotting factors II, VII, IX and X. Warfarin is highly protein bound with a half-life of 36-42 hours. It is metabolized by the cytochrome P450 enzymes: 2C9, 1A2, and 3A4.[2]

This guideline provides recommendations that are based on the evidence outlined from the Antithrombotic Therapy and Prevention of Thrombosis 9th edition: American College of Chest Physicians Clinical Practice Guidelines (CHEST).[2,4-8]

Recommendations

1. INR goals and duration of therapy listed in Table 1 are recommended by the CHEST guidelines.[2,4-8] ***(Class I, Level B)***

1.1. Exceptions include orthopedic surgery INR goals which are recommendations provided by UW Health Orthopedic surgeon consensus and based on the American Association of Orthopedic Surgeons clinical guideline on Prevention of Symptomatic Pulmonary Embolism in Patients Undergoing Total Hip or Knee Arthroplasty[9] ***(Class IIb, Level C)***

1.2. Alternative INR goals may be chosen for specific patients when bleeding risk outweighs clotting risk and will be determined by the individual's provider ***(Class IIb, Level C)***

Table 1. Indications for Antithrombotics, INR Ranges, and Duration of Therapy[2,4-9]

Indication	INR (Range)	Duration	Comments
Thrombophilia with Thromboembolic Event[4]			
Antiphospholipid Syndrome	2.5 (2-3)	Chronic	
Homozygous Factor V Leiden	2.5 (2-3)	Chronic	
Deficiency of Protein C, S or Anti-Thrombin	2.5 (2-3)	Chronic	
Atrial Fibrillation (AF)/ Atrial Flutter[5]			
$CHA_2DS_2VASc = 0$; Low stroke risk	None		May choose aspirin 75-325 mg daily
CHA_2DS_2 VASc ≥ 1; Intermediate/High stroke risk	2.5 (2-3)	Chronic	Anticoagulation CI: aspirin 75-325 mg and clopidogrel 75 mg daily
Pre-cardioversion (AF or flutter >48 hours)	2.5 (2-3)	3 weeks	
Post-cardioversion (in NSR)	2.5 (2-3)	4 weeks	
Ischemic Stroke[6]			
Non-cardioembolic stroke or TIA	None	Chronic	Use antiplatelet therapy
Cardioembolic stroke or TIA			
-With warfarin CI	None	Chronic	Aspirin 81-325 mg daily
-With cerebral venous sinus thrombosis	2.5 (2-3)	3-6 months	
- With patent foramen ovale	None	Chronic	Use antiplatelet therapy
Thromboembolism (DVT, PE) symptomatic or asymptomatic[7]			
Provoked VTE event	2.5 (2-3)	3 months	
Unprovoked: 1st VTE event			
- Proximal or Distal DVT	2.5 (2-3)	3 months	After 3 months evaluate risk-benefit for extended therapy
- PE	2.5 (2-3)	> 3 months	After 3 months evaluate risk-benefit for extended therapy
Unprovoked: 2nd VTE event			
- DVT or PE	2.5 (2-3)	> 3 months	Consider chronic
With malignancy	2.5 (2-3)	> 3 months	LMWH preferred over warfarin Consider chronic
Acute Upper Extremity DVT			
- Associated with central venous catheter that was removed	2.5 (2-3)	3 months	
- Associated with central venous catheter that was NOT removed	2.5 (2-3)	Extended	Continue anticoagulation until catheter removed
- Not associated with a central venous catheter	2.5 (2-3)	3 months	
Spontaneous superficial vein thrombosis	None	45 days	Prophylaxis LMWH or Fondaparinux

Valvular Disease[8]			
Rheumatic mitral valve disease			
- Left atrial diameter < 55 mm	None		
- With AF, left atrial thrombus, or left atrial diameter > 55 mm	2.5 (2-3)	Chronic	
Valve Repair			
Aortic	None		Aspirin 81 mg daily
Mitral	None	3 months	Antiplatelet therapy
Valve Replacement - Bioprosthetic			
Aortic or TAVI*	None		Antiplatelet therapy
Mitral	2.5 (2-3)	3 months	Followed by aspirin 81 mg daily
* If other indication for anticoagulation exist – see specific indication for therapy recommendations			
Valve Replacement - Mechanical			
Aortic	2.5 (2-3)	Chronic	Low bleed risk: add aspirin 81 mg
Mitral	3 (2.5-3.5)	Chronic	Low bleed risk: add aspirin 81 mg
Dual Aortic and Mitral Valve	3 (2.5 -3.5)	Chronic	Low bleed risk: add aspirin 81 mg
Orthopedic Surgery[9]			
Total Knee or Hip Arthroplasty*	1.8-2.2	10-14 days	INR goal per UWHC Orthopedics
Hip Fracture Surgery*	1.8-2.2	10-14 days	INR goal per UWHC Orthopedics
Trauma Surgery*	1.8-2.2	35 days	INR goal per UWHC Orthopedics
* If other indication for anticoagulation exist - INR goal should be clarified			

AF- atrial fibrillation; CAD – coronary artery disease; CI- contraindications; DVT- deep vein thrombosis; LMWH- low molecular weight heparin; NSR- normal sinus rhythm; PE- pulmonary embolism; TIA- transient ischemic attack; TAVI - transcatether aortic valve transplantation; VTE – venous thromboembolism

Patient Assessment

2. Patients newly started on warfarin should be assessed for risk factors that may make them more sensitive to the effects of warfarin. If multiple high sensitivity risk factors are present then a lower initiation dose or reduced maintenance dose may be needed.[2,4] ***(Class IIb, Level C)***
   2.1. Table 2 identifies risk factors that may increase either INR response or bleeding risks.

Table 2. Factors for Identifying Warfarin Sensitive Patients[2,4,10]

Increased Warfarin Sensitivity	
Increased INR Response	Increased Bleeding Risk
Baseline INR ≥ 1.5	Current antiplatelet therapy
Age > 65	Thrombocytopenia: platelet <75 K/uL
Actual body weight < 45 kg or actual < ideal	Significant hepatic disease: cirrhosis or total bilirubin.>2.4 mg/dL
Malnourished/ NPO >3 days	Alcohol abuse history
Hypoalbuminemia <2 g/dL	End stage renal disease
Chronic diarrhea	GI bleed within past 30 days
Significant drug interactions	Surgery within past 2 weeks
Decompensated heart failure	Intracranial bleed within past 30 days

Initial Warfarin Dosing

3. Initial warfarin dosing should be tailored based on patient bleed risk, potential sensitivity to warfarin, indication, goal INR range and if potential drug interactions are present[2] ***(Class I, Level C)***
4. Warfarin should not be administered until a baseline INR has been resulted within the medical record. ***(Class IIb, Level C)***
5. A dose larger than the anticipated maintenance dose (loading dose) is inappropriate and should not be used in most patients[4] ***(Class IIb, Level C)***
   5.1 In healthy patients with acute VTE warfarin 10 mg for the first 2 days may be considered followed by dosing based on INR measurements[4,11,12] ***(Class IIb, Level C)***
6. Daily warfarin dose adjustments should be based on current INR measurements[2,4] ***(Class I, Level A)***)
7. Prior to making a dose adjustment assess for any missed doses, drug interactions, dietary intake or supplements, documentation of bleeding, or other changes that may affect INR[2,4] ***(Class I, Level C)***)
   7.1 Tables 3 and 4 provide recommendations for warfarin dosing in the first 5 days of therapy for INR goals of 2-3 or 2.5-3.5.
8. If appropriate, patients should receive another form of anticoagulation such as LMWH for at least 5 days and until they are therapeutic on warfarin for 24-48 hours[2,7] ***(Class I, Level B)***)

Table 4. Warfarin Dosing Protocol with INR Goal 2-3 ***(Class IIb, Level C)***

	High Sensitivity to Warfarin		**Low Sensitivity to Warfarin**	
	INR Value	**Dose**	**INR Value**	**Dose**
Day 1	<1.5	2.5 - 5 mg	<1.5	5 - 7.5 mg
Day 2	<1.5 ≥1.5	2.5 - 5 mg 0 - 2.5 mg	<1.5 ≥1.5	5 - 7.5 mg 0 - 5 mg
Day 3	<1.5 1.5-1.9 2-2.5 ≥2.6	5 mg 2.5 mg 1 mg 0 (no dose)	<1.5 1.5-1.9 2-2.5 ≥2.6	7.5 mg 5 mg 2.5 mg 0 (no dose)
Day 4	<1.5 1.5-1.9 2-3 > 3	7.5 mg 5 mg 2.5 mg 0 - 1 mg	<1.5 1.5-1.9 2-3 >3	10 mg 7.5 mg 5 mg 0-2.5 mg
Day 5	<1.5 1.5-1.9 2-3 3-3.5 >3.5	10 mg yesterday's dose + 1 mg yesterday's dose yesterday's dose – 1 mg 0 (no dose)	<1.5 1.5-1.9 2-3 3-3.5 >3.5	12.5 mg yesterday's dose + 2.5 mg yesterday's dose yesterday's dose – 2.5 mg 0 (no dose)

If at any time INR increases > 0.5 consider reducing dose or if > 1 point consider holding dose
If holding for a high INR, restart warfarin at a reduced dose when INR is trending downward

Table 5. Warfarin Dosing Protocol with INR Goal 2.5-3.5 ***(Class IIb, Level C)***

	High Sensitivity to Warfarin		**Low Sensitivity to Warfarin**	
	INR Value	**Dose**	**INR Value**	**Dose**
Day 1	< 1.5	2.5 - 5 mg	< 1.5	5 - 7.5 mg
Day 2	< 1.5 ≥ 1.5	2.5 - 5 mg 0 - 2.5 mg	< 1.5 ≥ 1.5	5 - 7.5 mg 0 - 5 mg
Day 3	< 1.5 1.5-1.9 2.0-2.5 ≥ 2.5	5 - 7.5 mg 5 mg 2.5 mg 0 (no dose)	< 1.5 1.5-1.9 2.0-2.5 ≥ 2.5	7.5 - 10 mg 7.5 mg 5 mg 0 (no dose)
Day 4	< 1.9 2.0-2.4 2.5-3.5 ≥ 3.6	7.5 mg 5 mg 2.5 mg 0 - 1 mg	< 1.9 2.0-2.4 2.5-3.5 ≥ 3.6	10 mg 7.5 mg 5 mg 0-2.5 mg
Day 5	< 1.9 2.0-2.4 2.5-3.5 3.6-4.0 ≥ 4.0	10 mg yesterday's dose + 2.5 mg yesterday's dose yesterday's dose – 2.5 mg 0 (no dose)	< 1.9 2.0-2.4 2.5-3.5 3.6-4.0 ≥ 4.0	12.5 mg yesterday's dose + 2.5 mg yesterday's dose yesterday's dose – 2.5 mg 0 (no dose)

If at any time INR increases > 0.5 consider reducing dose or if > 1 point consider holding dose
If holding for a high INR, restart warfarin at a reduced dose when INR is trending downward

Maintenance Warfarin Dosing

9. For patients on warfarin prior to admission and if there are no changes to medications or medical condition that would affect the INR, their home dose may be resumed. ***(Class I, Level C)***
10. Warfarin should be adjusted based on current INR measurements[2,4] ***(Class I, Level A)***
11. Prior to making a dose adjustment assess for any missed doses, drug interactions, dietary intake or supplements, documentation of bleeding, or other changes that may affect the INR level.[2,4] ***(Class I, Level C)***

Laboratory Monitoring

12. INR
    - 12.1 A baseline INR must be resulted in the EMR prior to verification of the first dose of warfarin ***(Class IIb, Level C)***
    - 12.2 A current INR must be resulted in the EMR prior to verification of the warfarin dose adjustment ***(Class IIb, Level C)***
    - 12.3 Obtain daily INR for patients with daily warfarin dosing ***(Class IIb, Level C)***
    - 12.4 Obtain a weekly INR (at minimum) for patients who have been maintained on a consistent warfarin dose with no changes in medications or medical condition that would affect the INR. ***(Class IIb, Level C)***
    - 12.5 Upon discharge from the hospital an INR should be obtained within 3-4 days or at the next scheduled INR visit if there are no changes in medications or medical conditions that would affect the INR ***(Class IIb, Level C)***

13. CBC should be obtained prior to initiating warfarin (baseline) and a minimum of every 3 days thereafter ***(Class IIb, Level C)***

14. Urine HCG (pregnancy test) should be obtained for women of child bearing age before initiating warfarin.[2,4] ***(Class IIb, Level C)***

Drug Interactions

Most drug interactions with warfarin will start to have an effect within 3-5 days of concomitant therapy. There are some notable exceptions which include amiodarone, carbamazepine, and rifampin which have a delayed effect after 7-14 days of dual therapy.[2,4,13,14] Tables 6 and 7 outlines potential drug-drug, drug-food, and drug-herb interactions. Bolded medications are considered significant interactions. This table is not all inclusive.

15. For most drug interactions with warfarin it is recommended to either increase or decrease (based on expected INR response) the weekly dose by 30% ***(Class IIb, Level C)***
    - 15.1 For amiodarone target a 50% *reduction* in weekly maintenance dose for warfarin after 7-14 days of dual therapy[13] or if initiating warfarin start at 2.5 mg dose. ***(Class IIb, Level C)***
    - 15.2 For rifampin target a 50% *increase* in weekly maintenance dose for warfarin after 7-14 days of dual therapy.[13] ***(Class IIb, Level C)***

Table 6. Medications, dietary supplements and food that **INCREASE** INR or bleeding risk.[2,4,13,14]

Drug Class	Known Interaction	Probable Interaction	Possible Interaction	Unlikely Interaction
Anti-Infective	Ciprofloxacin Erythromycin **Fluconazole** Isoniazid **Metronidazole** Miconazole Miconazole Vaginal Suppository Moxifloxacin **Sulfamethoxazole** Voriconazole	Amoxicillin/clavulanate Azithromycin Clarithromycin Itraconazole Ketoconazole Levofloxacin Ritonavir Tetracycline	Amoxicillin Chloramphenicol Darunavir Daptomycin Etravirine Ivermectin Nitrofurantoin Norfloxacin Ofloxacin Saquinavir Telithromycin Terbinafine	Cefotetan Cefazolin Tigecycline
Cardiovascular	**Amiodarone*** Clofibrate Diltiazem Fenofibrate Propafenone Propranolol	Aspirin Fluvastatin Quinidine Ropinirole Simvastatin	Disopyramide Gemfibrozil Metolazone	
Analgesics, Anti-Inflammatory	Piroxicam	Acetaminophen Aspririn Celecoxib Tramadol	Indomethacin Propoxyphene Sulindac Tolmentin Topical Salicylates	Methylprednisolone Nabumetone
CNS Drugs	Alcohol Citalopram Entacapone Sertraline	Disulfiram Chloral hydrate Fluvoxamine Phenytoin	Felbamate	Diazepam Fluoxetine Quetiapine

GI Drugs and Food	Cimetidine Mango Omeprazole	Grapefruit	Orlistat	
Herbal Supplement	Fenugreek Feverfew Fish Oil Ginkgo Quilinggao	Dandelion Danshen Don Quai Lycium PC-SPES Red or Sweet Clover	Capsicum Forskolin Garlic Ginger Turmeric	
Other	Anabolic Steroids Capecitabine Zileuton	Fluorouracil Gemcitabine Levamisole Paclitaxel Tamoxifen Tolterodine	Acarbose Cyclophosphamide Danazol Iphosphamide Trastuzumab	Etoposide Carboplatin Levonorgestrel

Table 7. Medications, dietary supplements and food that **DECREASE** INR.[2,4,13,14]

Drug Class	Known Interaction	Probable Interaction	Possible Interaction	Unlikely Interaction
Anti-Infective	Griseofulvin Nafcillin Ribavirin **Rifampin***	Dicloxacillin Ritonovir Rifapentine	Terbinafine Nelfinavir Nevirapine	Cloxacillin Rifaximin Teicoplanin
Cardiovascular	Cholestyramine	Bosentan	Telmisartan	Furosemide
Analgesics, Anti-Inflammatory	Mesalamine	Azathioprine	Sulfasalazine	
CNS Drugs	Barbiturates Carbamazepine	Chlordiazepoxide		Propofol
GI Drugs and Food	High content vitamin K food Avocado	Soy milk Sucralfate	Sushi containing seaweed	
Herbal Supplement	Alfalfa	Ginseng Multivitamin St. John's Wort Parsley Chewing Tobacco	Co-Enzyme Q10 Yarrow Licorice	Green Tea
Other	Mercaptopurine Chewing Tobacco	Chelation Therapy Influenza vaccine Raloxifene	Cyclosporine Etretinate Ubidecarenone	

Dietary Interactions

Patients on long term warfarin therapy can be sensitive to the fluctuating levels of vitamin K from both external dietary sources and internal gastrointestinal sources. Increased dietary intake of vitamin K from either food sources or nutritional supplement sources can reduce the effectiveness of warfarin and decrease the INR. Since warfarin is a high protein bound drug with up to 99% of the drug bound to plasma proteins, patients who are malnourished with low albumin levels will have higher concentrations of unbound drug and may experience faster INR response. Conversely, patients receiving enteral nutrition will have more bound drug due to the high protein concentration in these products.[2,13,15-17]

16. Promote consistent intake of dietary vitamin K and not avoidance[2] ***(Class I, Level C)***

17. For enteral nutrition hold the tube feed 1 hour before and 1 hour after warfarin administration[15,17] ***(Class IIa, Level B)***
    - 17.1 If unable to hold enteral nutrition, increase warfarin dose until a therapeutic INR is achieved[17] ***(Class IIb, Level B)***
    - 17.2 If on cycled tube feeding, administer warfarin at a time when tube feeds are off[17,18] ***(Class IIa, Level B)***

Warfarin Reversal

The treatment for warfarin reversal should be based on the indication for use, location of bleed, severity of bleed and the extent of INR elevation. Guidelines for reversal of warfarin are available within the UW Health Adult Procoagulant Therapy for Treatment of Non-Hemophiliac Bleeding Clinical Practice Guideline.[2,4]
http://www.uwhealth.org/files/uwhealth/docs/anticoagulation/Procoagulant_Guideline.pdf

Transitioning to Outpatient Management

18. Communication describing either warfarin initiation and/or management during the inpatient stay, along with the expected next INR check, should be communicated to the next provider of care.***(Class IIb, Level C)***
    - 18.1 Communication may occur electronically for patients who are managed in a UW Health clinic or by phone/fax for a patient who is managed in a non-UW Health clinic.

UW Health Implementation

Potential Benefits:
This guideline will provide a resource for standardizing the approach to warfarin management for an individual patient. Individualization of a warfarin management plan should result in lower incidence of supra-therapeutic and critical INR results, minimize the risk for bleeding events and provide guidance for managing drug and dietary interactions.

Potential Harms:
Warfarin is a complex medication that requires close monitoring to prevent adverse events. While significant bleeding more commonly occurs when the INR is above the therapeutic range, it, may also occur when the INR is within or slightly below target INR range. Bleeding is the most common adverse event of warfarin for which to monitor. Additionally, if the INR remains sub-therapeutic for an extended time there is the risk for thromboembolic events.

Qualifying Statements
Despite providing recommendations to manage many common scenarios, there may be external factors that can influence the INR and dosing of warfarin that are not provided in this guideline. Since standardization of warfarin management is unrealistic, clinical judgement should be used when indicated to prevent unwanted adverse events

Implementation Plan/Tools

Recommendations provided in this guideline will be disseminated to inpatient staff through a variety of venues including newsletters, pharmacy inservice and additional tools as described below:

1. Guideline will be housed on U-Connect in a dedicated folder for CPGs.
2. Guideline will also be posted on UW Health Anticoagulation Website: www.uwhealth.org/anticoagulation
3. Release of the guideline will be advertised in the Pharmacy Department weekly newsletter.
4. Links to this guideline will included in the Warfarin – Adult – Supplemental Order Set and included in the Warfarin Management protocol

Disclaimer

CPGs are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This Clinical Practice Guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

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Appendix A: Quality of Evidence and Strength of Recommendation Grading Matrix