Standardizing INR Testing Can it be done?

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Objectives

Explain the INR, what it is, how it is calculated and when it should be used
 Describe reasonable expectations for INR agreement across platforms
 Evaluate different INR systems to maximize standardized patient care

Coagulation Testing

Monitoring hemostasis



Coagulation Made Simple



Coagulation Monitoring

Monitor with ACT / aPTT



Heparin versus Warfarin

Drug	Action	Mechan- ism	Moni- toring	Effective
Heparin	Direct Inhibition of Thrombin	AT cofactor	APTT ACT	Immediate
Warfarin	Decreases Production of factors	Vitamin K	PT	Delay 3-5 days

What is Warfarin?

Rat poison Cause of "sweet clover disease" Orally active anticoagulant



Warfarin Effects on Coagulation



- 1. KO-reductase warfarin sensitive
- 2. K-reductase relatively warfarin resistant

Adapted from Hirsh J, et al. Chest. 2001;119:85-215.

Why Monitor Warfarin?

 Functions by decreasing production of Vitamin K dependent clotting factors in liver

Delayed onset of anticoagulation

- Potency may vary by manufacturer
- Obse response varies by patient
 - > Dietary interactions
 - > Life-style influences

PT testing: 1935 – Quick, et. al.



Picture courtesy of Helena Laboratories

45 - 50 years pass Thromboplastin isolated from: > Different species pig; cow; human; etc. > Different organs brain; thymus; lung; etc. All yield different results > Results vary by instrument system in use Manual tilt tube "gold standard" Fibrometer; automated coagulation systems • PT ratios adopted to determine therapeutic range

PT Standardization

IPT - 1st IRP developed

- International reference thromboplastin preparation
- 1983 Kirkwood describes method to calibrate local thromboplastin to IRP
 - > Define reagent ISI
 - International sensitivity index

Iqual of the INR to standardize PT result reporting

INR

International Normalized Ratio (INR)

- > ISI = international Sensitivity Index
- > INR target ranges are specified by patient populations, e.g.,
 - DVT, Afib, Atrial MHV: INR= 2.0 3.0
 - Mitral mechanical heart valve: INR= 2.5 3.5
 - Individual variation

$$INR = \left(\frac{PT_{patient}}{PT_{meannormal}}\right)$$

ISI

Key variables

• ISI

- Initially determined by reagent manufacturer
- Traceable to IRP
 - International Reference thromboplastin Preparation
- > WHO defined process
 - Calibration up to INR = 4.5
 - manual tilt tube method reference
- Local calibrations can be performed to determine the instrument specific ISI¹

Mean normal PT

 The mean normal PT should be determined for each new batch of thromboplastin with the same instrument used to assay the PT¹

Antithrombotic therapy and prevention of thrombosis, 9th ed: ACCP guidelines. CHEST 2012; 141(2)(Suppl):e44S-e88S

Effect of Local Calibration

Local calibration may introduce variability



 Same sample yields different results depending on calibration method

ISI and MNPT from Poller et. al., J Thromb Haemost 2012; 10: 1379–84.

POC Calibration

 Manufacturer assigns ISI and mean normal PT (MNPT)
 Lot specific
 Traceable to IRP
 Often through secondary standard
 Cannot be changed by end user
 Does not vary by location of testing

Will POC Results Match the Lab?



but it WILL Correlate

Why not?

Point of Care

- > Whole Blood
- No Added Anticoagulant
- > No Dilution
- No Preanalytical Delay

- Laboratory
 - > Platelet Poor Plasma
 - Sodium Citrate
 Anticoagulant
 - > 1:9 Dilution
 - Variable Preanalytical Delay
- InstrumentClot detection

> Reagent

Preanalytic Variables

Lab Samples

- > Blood collection
 - venipuncture technique
 - citrate concentration
 - 3.2% should be used
- > Transport
 - temperature effects
 - exposure beyond 18 24°C affects result
 - cold temperatures significantly reduce PT
 - sample clotting
 - delay in testing
 - variable effects depending on ambient temperature, concomitant medications and time of delay

CLSI documents H03; H21 and H54



Preanalytic Variables (cont.)

Point of Care

- Blood collection
 - fingerstick technique
 - use of capillary tube for transfer

Analytic Variability



Thromboplastin	Analyzer	calibration	Thromboplastin	Analyzer	calibration
Innovin	CA1500	Local vs rTF/95	HepatoQuick	STA-R	Manufacturer
Recombiplastin	MLA1800	Local vs rTF/95	Thrombotest	KC10	Local vs OBT/79
Neoplastin Plus	STA-R	Manufacturer	Thromboplastin C Plus	CA1500	Manufacturer

Expectations Lab to Lab 10 OAT patients across 7 analyzer/ reagent combinations

McGlasson, DL 2003: Lab Med 34: 124 – 9.



Expectations POC to lab 36 patients over 4 visits each 3 POC; 1 lab

• Solvik et. al., 2010: Clin Chem 56:1618-1626 (2010)



Variability of Lab INR

Observed:
± 0.4 at INR = 2.0
± 0.8 at INR = 3.0
± 1.2 at INR = 4.0
Standardization as with glucose is unlikely
discrete analyte to be tested
versus a biologic process

Jacobson, J Thromb Thrombolysis (2008) 25:10-11

Why perform POC PT?

Results Available While Patient is Present
 Improved Anticoagulation Management
 Increased Time in Therapeutic Range
 Improved Standard of Care
 Staff Efficiency
 Immediate Retesting (if needed)
 Fingerstick Sampling

POCT - PT/INR Agreement

POCT 14A Consensus Candidate Limit

Source	INR Range	Agreement Limits
CLSI POCT 14A	1.0 to 2.5	<u>+</u> 0.4
CLSI POCT 14A	2.6 to 3.5	<u>+</u> 0.7
Literature	3.6 to 5.0	<u>+</u> 0.9
Literature	Above 5.0	<u>+</u> 1.2

Supportive Literature Citations

Lassen JF et al. INR for PT in patientsCritical difference and probability of significant change in consecutive measurements, *Clin Chem*. 1995.

Oral Anticoagulation Monitoring Study Group. POC PT measurement for professional and patient self-testing use, Am J Clin Path. 2001.

<u>Hobbs et al</u>. Is the INR reliable? A trialin hospital laboratory and primary care settings. J Clin Pathol, 1999. <u>Jacobson A</u>. Warfarin monitoring: POC INR limitations and interpretations. J Thromb Thrombolysis, 2008. <u>Ansell J et al</u>. Pharmacology and management of Vit K: Am Coll Chest Physicians Evidence Based Clinical Practice Guidelines. CHEST 2008.

How to Compare INR Results



Lower dose?
Keep same dose?
Raise Dose?

Test Again?Test more often?

Thrombotic and Hemorrhagic Reserve for a Patient with a target INR of 3.0



Adapted from Cannegeiter, et. al. N Engl J Med 1995; 333:11-17

PT/INR and Patient Management



Goal is to Maintain a Tight Therapeutic Range

- Practical Considerations
 - > A-Fib complications increase from 4% at age 65 to >15% at age 75

Patient Management

1. Understand limitations in the INR

- Whenever a patient undergoes duplicate testing on different systems, there is the potential for disagreement
- 2. Attempt to have patients managed with a consistent methodology

Jacobson, J Thromb Thrombolysis (2008) 25:10–11

LIMITATION!!!!!!!

INR was developed to monitor effect of vitamin K antagonists (warfarin, others) INR is inappropriate scale for monitoring coagulopathies Most POC PT/INR tests cleared ONLY for monitoring patients receiving oral anticoagulation therapy such as Coumadin or warfarin.

POC Coagulation Testing

Monitoring hemostasis





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