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Therapeutic Drug Monitoring

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CCTC Clinical Chemistry Trainee Council

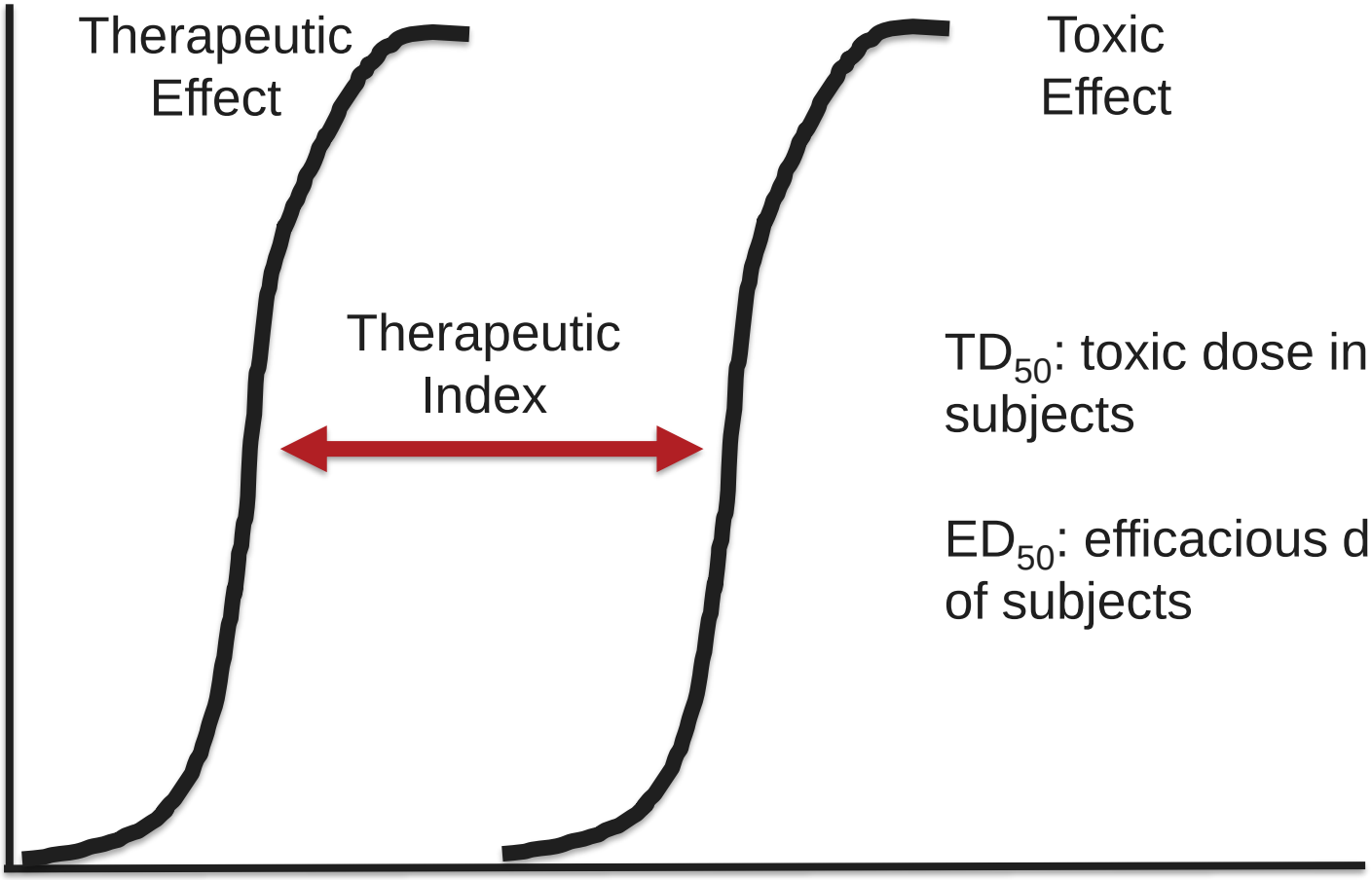
Learning Objectives

- Discuss the rationale for therapeutic drug monitoring (TDM)
- Describe how drug therapy is impacted by pharmacokinetics, pharmacodynamics and pharmacogenetics
- List various classes of drugs that require TDM
- Discuss analytical methods available for TDM

What is TDM?

- The practice of individualized drug dosing:
  - To enhance drug efficacy and reduce the risk of toxicity
  - Reserved for drugs with a well-established relationship between blood concentration and clinical effect
  - Targeted for drugs with unpredictable pharmacokinetic-pharmacodynamics relationship with dose
  - Drugs with a narrow therapeutic index

Therapeutic index = TD50 / ED50



TD_{50}: toxic dose in 50% of subjects

ED_{50}: efficacious dose in 50% of subjects

Indications for TDM

- Monitor patient adherence to prescribed medication
- To ensure that the patient drug concentrations are within the therapeutic range
- Assess toxicity or adverse drug reactions
- Improve patient care through directed decontamination efforts

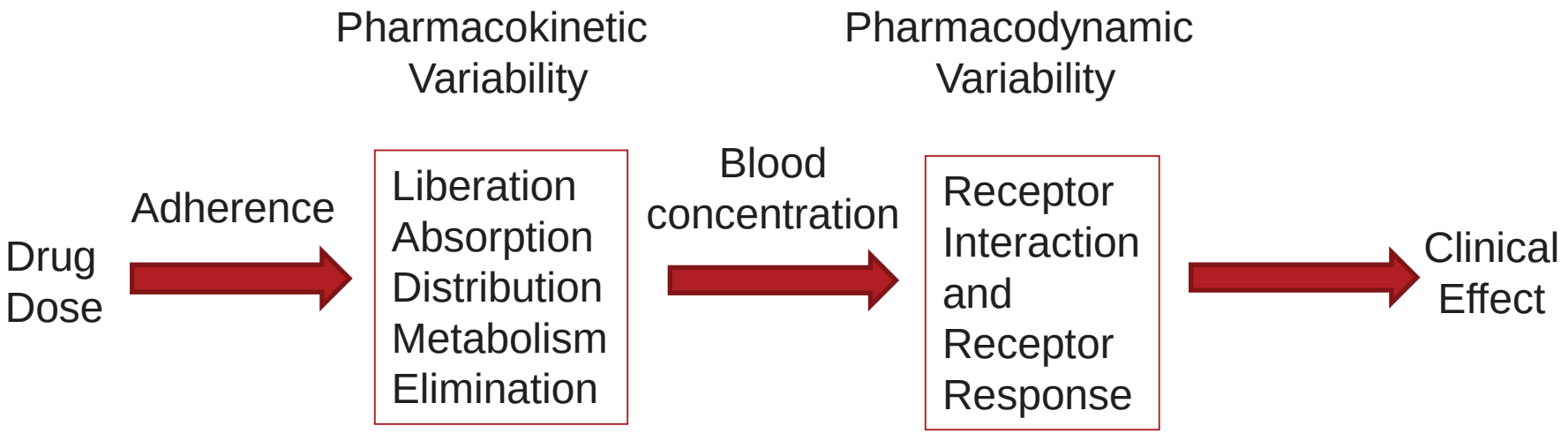
Recommended Drug Classes for TDM

- Antiarrhythmics
- Antibiotics
- Anti-cancer drugs
- Antidepressants
- Antiepileptics
- Antipsychotics
- Bronchodilators
- Cardiac drugs
- HIV drugs
- Immunosuppressant drugs
- Lithium

THESE ARE GUIDELINES

Actual TDM services should be based on needs of clients and current literature

Drug Therapy is Impacted by Pharmacokinetics and Pharmacodymanics



- Pharmacokinetics (PK)
  What the body does to the drug: ADME - evaluated by drug levels
- Pharmacodynamics (PD)
  What the drug does to the body: response, mechanism(s) of action
  evaluated by clinical response, biomarkers
- Pharmacogenetics (PG)
  How genes affect drug metabolism and clinical effect

Drugs Must Be Absorbed into blood circulation

- **Routes of Administration**
  - Oral
  - Sublingual
  - Rectal
  - Transdermal
  - Intravenous
  - Parenteral
  - Subcutaneous
  - Intramuscular
  - Intrathecal
  - Inhalation
- **Factors that affect Absorption**
- Drug solubility
- Patient: pathology, gastric emptying time, pH
- Drug characteristics: polarity, molecular weight, concentration, formulation
  - Ionization
  - Protein binding
  - Drug transport

Volume of Distribution (Vd)

- Describes the amount of drug that enters the plasma compartment, and where it goes in the body

- Drug distribution is dependent on drug and compartment
  - Drug
    - polar drugs = water soluble → circulation → kidneys
    - nonpolar drugs = lipid soluble → CNS, tissue, fat → liver/bile

  - Compartment
    - minutes: plasma and well-perfused organs (heart, liver, kidney, brain)
    - minutes to hours: muscle, skin
    - hours to days: fat

Bioavailability (F)

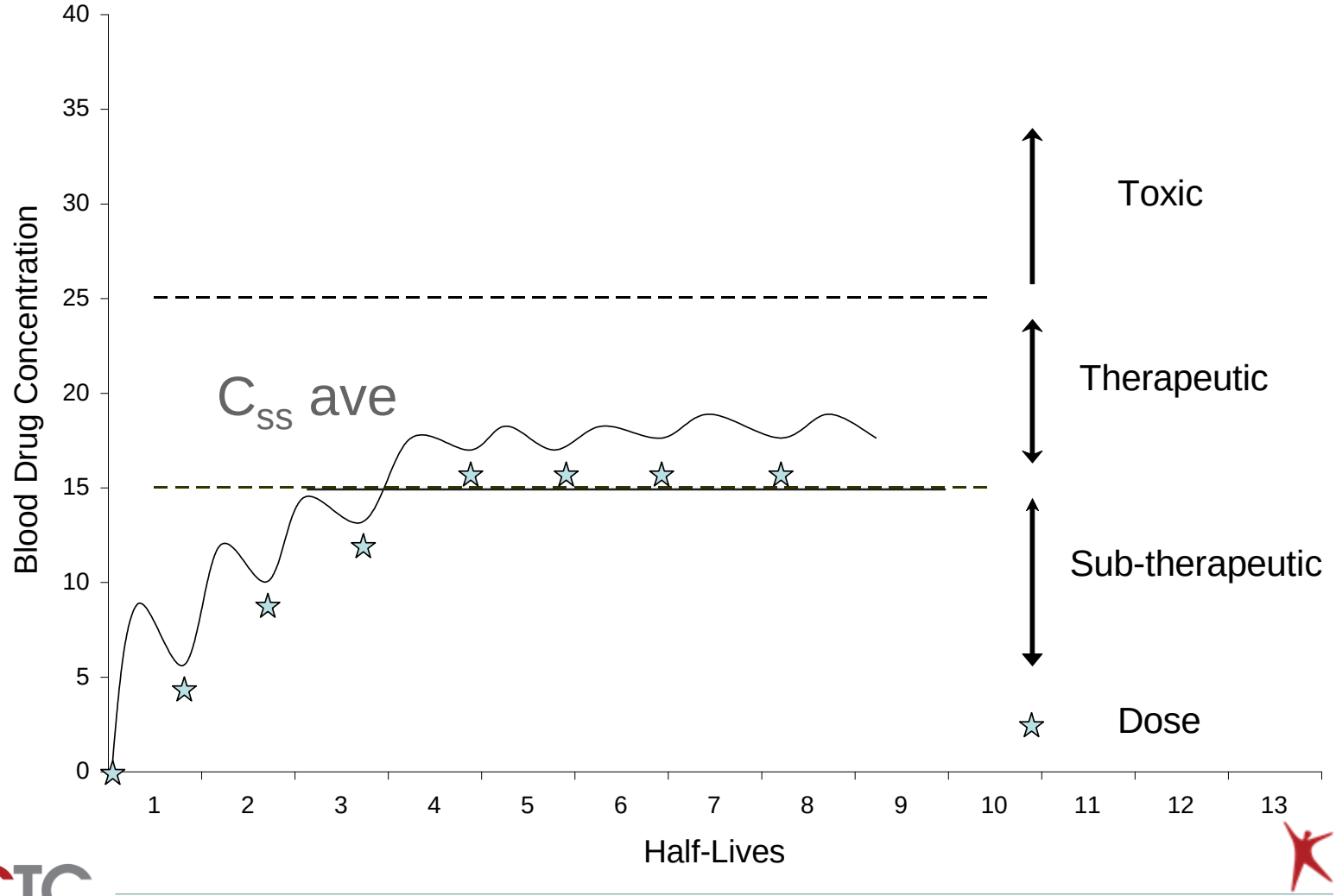
- The amount of drug that reaches systemic circulation
  - Blood concentration of the drug
- Oral drugs – undergo first-pass metabolism → a decrease in bioavailability
- Drugs administered IV – bypass first-pass metabolism → 100% bioavailability

Volume of Distribution (Vd)

- Relates the amount of drug in the body to the concentration of drug in the blood or plasma

Steady state (C_{ss}):

amount of drug in = amount of drug out, requires 5-7 $t_{1/2}$



Drug Metabolism

- Purpose – convert drugs into more hydrophilic metabolites to enhance elimination from the body

- Effects
  - Terminates pharmacological activity of drug
  - Activate pharmacological activity of a drug (codeine → morphine)
  - Decreases bioavailability (first pass metabolism)

- TDM tests should measure parent compound and/or metabolites

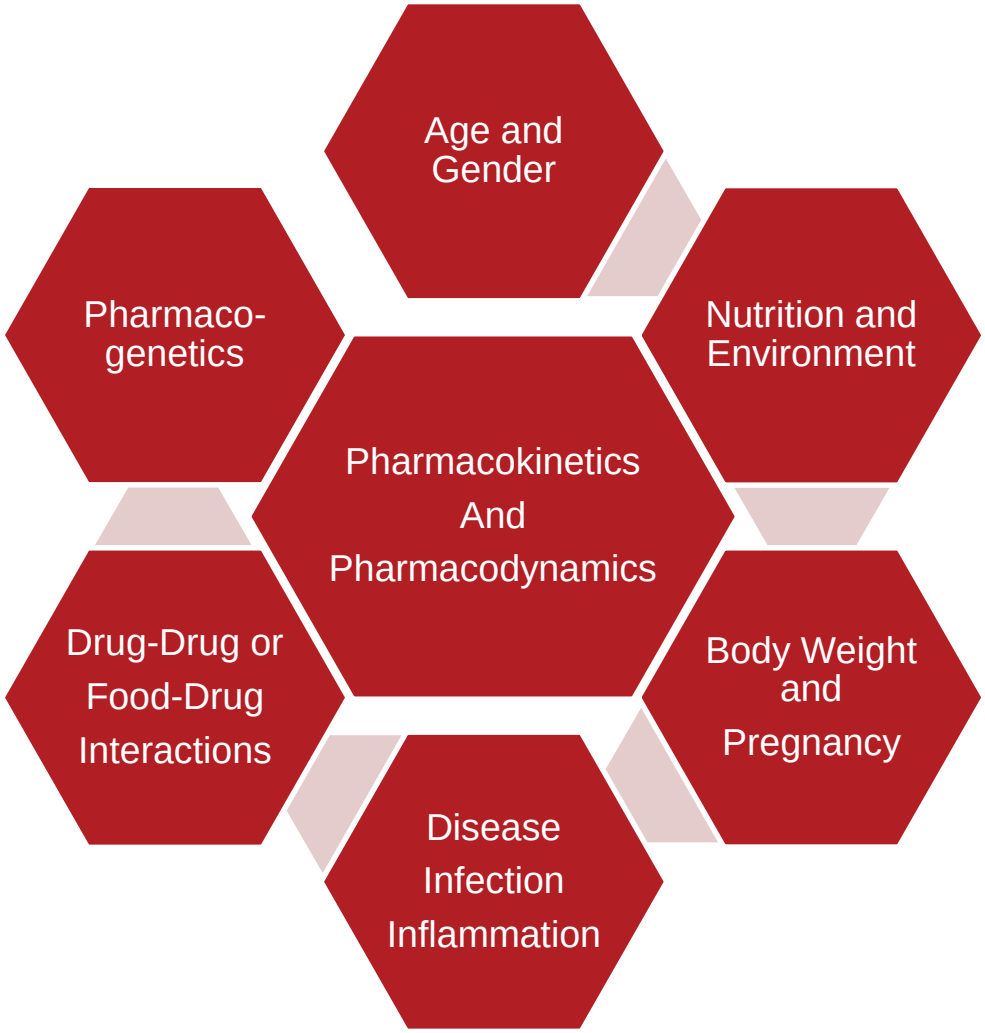
Drug Metabolism

- Phase I reactions (oxidation, reduction, hydrolysis)
  - cytochrome P450 (CYP3A4/5,2D6, 1A2, 2A6,2B6,
  - 2C8, 2C9, 2C19, 2D6, 2E1)
  - monoamine oxidase
  - alcohol dehydrogenase
  - dopamine ß-hydrolase

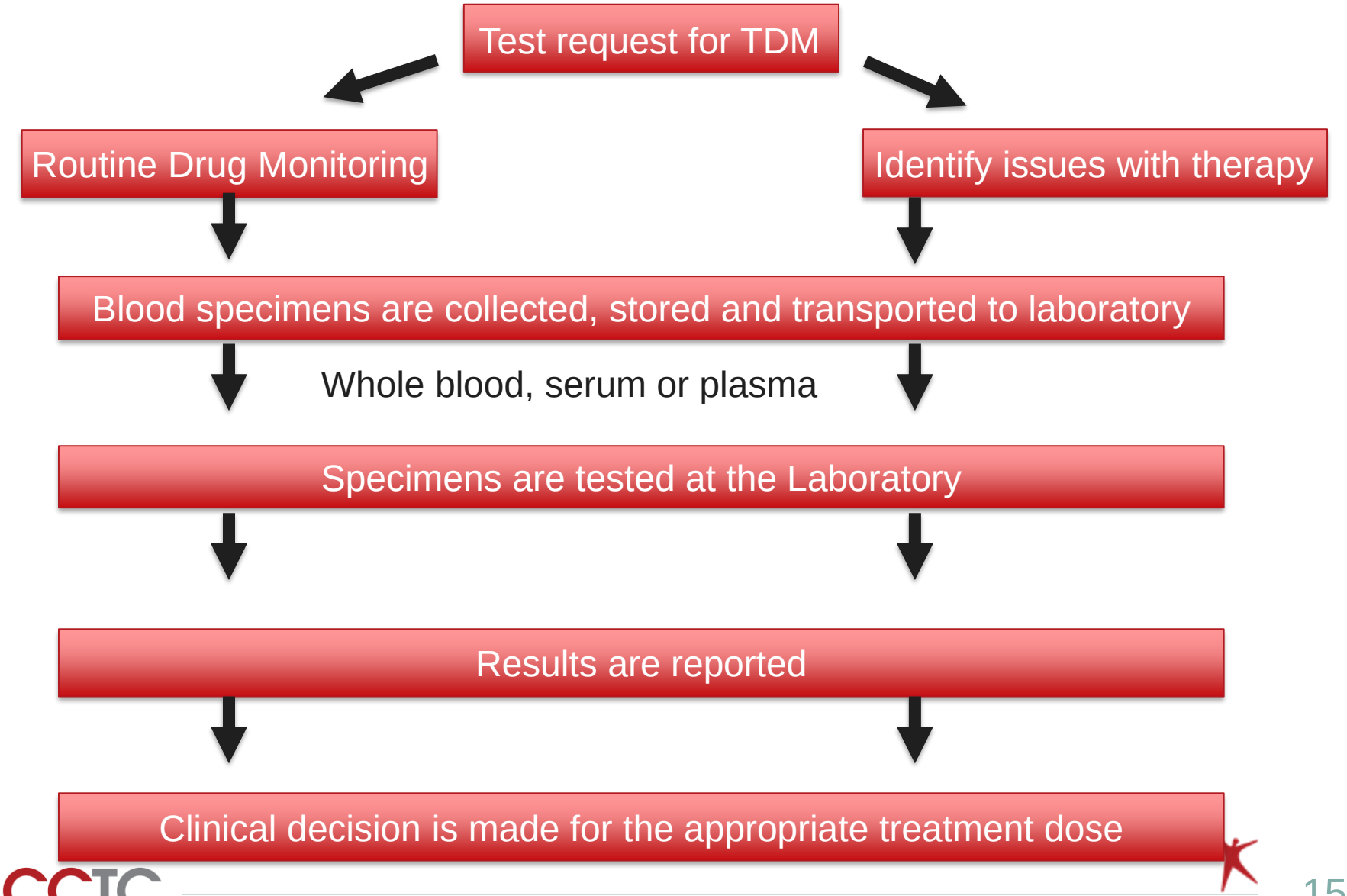
- Phase II reactions - conjugations with glutathione, glucuronide, sulfate, methyl group, acetyl group
  - GSTs, UGTs, SULT, MT, TPMT, NAT

- Sites for Drug Metabolism
  - Liver, GI tract, lung nasal mucosa, skin, etc.

Factors that Affect PK and PD



TDM Workflow



Timing of Specimen Collection

- Specimens – serum/plasma, blood, dried blood spots, oral fluid

- Specimens are drawn at either –
  - Peak, pre-dose (trough), or random
  - Majority of drugs are collected at pre-dose (trough)

- Peak collection (aminoglycosides)
  - Drugs administered intravenously
  - Patient experiences signs of toxicity after dose

- For drugs with a long distribution phase
  - Random specimen is collected
  - Digoxin

Monitoring Free (Unbound) Drug

- Patients with Renal failure
  - Toxins can displace protein-bound drug in uremic patients
- Patients with Liver Disease
- Patients with hypoalbuminemia
  - critically ill
  - burn patients
  - AIDS patients
- Patients where drug concentrations do not correlate with clinical expectation (drug-drug interactions, pregnancy, stress).

Pre-analytical variables

- Hemolyzed specimens
- Clotted specimens
- Interferences –
  - Lipemia
  - Icterus
  - Hemoglobin
- Collection tubes - Avoid gel separator tubes
- Specimen collection conditions
  - preservatives,
  - temperature
  - light
  - freeze/thaw cycles, etc.

Dasgupta et al. (1994) Am J Clin Path 101:456-461.

Drug-Drug Interactions – Affect Efficacy

- Synergism – two drugs are administered with the same effects → response to drug is enhanced
- Antagonism – two drugs with opposing actions interact → reducing the effectiveness of one or both drugs
- Enzyme saturation – two drugs are administered and are metabolized by the same CYP450 liver enzyme → metabolism of one drug can inhibit metabolism of the other

Drug-Drug Interactions

- Induction – a drug can enhance the metabolism of a drug or it's own metabolism
  - (ex. Rifampin (antibiotic) → induces CYP450 2B6, 2C8, 2C9, 2C19, 2D6, 3A4)

- Alteration – one drug may alter how the body absorbs, metabolize, or excrete another drug

Analytical Methods

- GC-MS
- LC-MS
- HPLC
- Immunoassays
- Spectrophotometry

Summary

- TDM is the practice of individualized drug dosing
  - Should be interpreted with respect to patient's clinical presentation

- TDM results are influenced by:
  - Patient's physiological condition
  - PK, PD, PG
  - Concomitant medications
  - Diet / supplements
  - Pre-analytical, Analytical and Post-analytical variables
  - Analytical methods

References

1. Tietz textbook of Clinical Chemistry and Molecular Diagnostics, Sixth edition, Chapter 40 – Therapeutic Drugs and their Management

2. Contemporary Practice in Clinical chemistry, Third edition, Chapters 44 and 45

- Pharmacokinetics for the Practicing Clinical Chemist
- Therapeutic Drug Monitoring

Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- **Employment or Leadership**: No disclosures
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