Biochemical Mechanisms of Drug Toxicity: Drug-induced Liver Injury (DILI)

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Presentation Outline

Adverse Drug Reactions

• Adverse Drug Reactions
• Drug-induced Liver Injury
  • Intrinsic vs. Idiosyncratic
• Systemic Drug Reactions
• Chemotherapy Adverse Reactions
• Teratogenic Reactions to Drugs
Adverse Drug Reaction (ADR)

Undesirable Drug Effect

• World Health Organization (WHO)
  • “a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function”
Adverse Drug Reaction (ADR)

Undesirable Drug Effect

FDA Warns About Teething Medication: Benzocaine

**FDA Drug Safety Communication: Reports of a rare, but serious and potentially fatal adverse effect with the use of over-the-counter (OTC) benzocaine gels and liquids applied to the gums or mouth**

**Safety Announcement**

- Additional information for Consumers
- Additional information for Healthcare Providers

**Reference**

- [FDA Guidance](https://www.fda.gov/Drugs/DrugSafety/ucm449967.htm)
- [Benzocaine Information](https://www.fda.gov/Drugs/DrugSafety/ucm449972.htm)

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**Fast Teething Pain Relief**

- FDA warns about teething medication: benzocaine.

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**Fast Facts**

- Benzocaine gels and liquids are used OTC under different brand names such as Anbesol,Hurricane, Orajel, Baby Orajel, Orabase, and others. Benzocaine is also sold in other forms such as ointment and spray solutions (also see separate Drug Safety Communication on Benzocaine Spray). These products are used to relieve pain from a variety of conditions, such as teething, caries, and irritation of the mouth and gums.

- Benzocaine-induced methemoglobinemia has been reported at all strengths of benzocaine gels and liquids, including concentrations as low as 7.5%. The cases occurred mainly in children aged two years or younger who were treated with benzocaine gel for teething. People who take methemoglobinemia may experience pain, shortness of breath, rapid breathing, bluish coloration of the skin, and other symptoms. In severe cases, symptoms of methemoglobinemia may not always be evident or attributed to the condition. The signs and symptoms usually appear within minutes to hours of applying benzocaine and may occur with the first application of benzocaine or after additional use. If you or your child has any of these symptoms after taking benzocaine, seek medical attention immediately.

- Benzocaine products should not be used on children less than two years of age, except under the advice and supervision of a healthcare professional. Healthcare professionals and consumers are advised to consider the American Academy of Pediatrics' recommendations for teething pain relief instead of using the benzocaine teething products.

- Give the child a teething ring chilled in the refrigerator.
- Gently rub or massage the child's gums with your finger to relieve the symptoms of teething in children. If these methods do not provide relief from teething pain, consumers should talk to a healthcare professional to select an alternative treatment.

- Adult consumers who use benzocaine gels and liquids to treat pain in the mouth should know the information in the product label. Consumers should also be aware that benzocaine products are not for use in children. FDA encourages consumers to talk to their healthcare professional about using benzocaine.

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Adverse Drug Reaction (ADR)

**Benzocaine and Drug-induced Methemoglobinemia**

- Benzocaine
  - Local anesthetic
  - Used as topical pain reliever or in cough drops
  - Active ingredient in many over-the-counter anesthetic ointments

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Principles of Clinical Pharmacology, ed. 3, ch.16, Fig. 16.2
Adverse Drug Reaction (ADR)

Undesirable Drug Effect

• World Health Organization (WHO)
  • “a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function”

• Contradictory effects of drugs
  • Therapeutic benefits and adverse effects (range from very insignificant to serious to fatal)

• Target locations of toxicity
  • Hepatotoxicity
  • Nephrotoxicity
  • Gastrointestinal Toxicity
  • Neurotoxicity
  • Ototoxicity
  • Dermatological Toxicity
  • Endocrine System
  • Hematological Toxicity
  • Pulmonary Toxicity
Drug-induced Liver Injury (DILI)

Adverse Drug Reactions

- Diverse set of responses after exposure to manufactured or natural chemical compounds
- Leading cause of acute liver failure or liver transplantation
- Common reason for regulatory actions concerning drugs

Etiology of Acute Liver Failure (ALF) in the USA

US ALFSG Adult Registry 1998-2014 (N= 2102)

Bernal W, Lee WM, Wendon J, Larsen FS, Williams R. J Hepatol. 2015 Apr; 62(1 Suppl), S112-S120
Drug-induced Liver Injury (DILI)

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Principles of Clinical Pharmacology, ed. 3, ch.16, Fig. 16.4.
Drug-induced Liver Injury (DILI)

*Adverse Drug Reactions*

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![Diagram of Drug Metabolism](image)

*Principles of Clinical Pharmacology, ed. 3, ch.16, Fig. 16.4.*
Drug-induced Liver Injury (DILI)

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Principles of Clinical Pharmacology, ed. 3, ch.16, Fig. 16.4.
Drug-induced Liver Injury (DILI)

Scheme for Adverse Drug Reactions

- Diverse set of responses after exposure to manufactured or natural chemical compounds
- Leading cause of acute liver failure or liver transplantation
- Common reason for regulatory actions concerning drugs

Drugs → Non-Toxic Metabolites → Excretion

Reactive Metabolites

- Oxidative Stress: GSH Depletion
- Apoptosis
- Necrosis

Pathways
A: Initial Mechanism of DILI
B: New Mechanism of DILI

- Tissue Necrosis
- Hypersensitivity Reaction
- Carcinogenesis
- Teratogenesis

Principles of Clinical Pharmacology, ed. 3, ch.16, Fig. 16.4.
Drug-induced Liver Injury (DILI)

Adverse Drug Reactions

- Diverse set of responses after exposure to manufactured or natural chemical compounds
- Leading cause of acute liver failure and transplantation
- Common reason for regulatory actions concerning drugs
- Both types are influenced by pharmacogenetics

<table>
<thead>
<tr>
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<th>Idiosyncratic DILI</th>
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<tbody>
<tr>
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<tr>
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Intrinsic DILI

Drug-induced Liver Injury (DILI)

• As exposure increase beyond the therapeutic dose, toxicity occurs
• Severity of liver injury increases as exposure increases (dose-dependent)
• Acetaminophen (APAP)
  • Over-the-counter analgesic and antipyretic
  • Dose-dependent hepatotoxicity
    • Safe at therapeutic concentrations but severe hepatotoxicity above therapeutic range
    • Leading cause of acute liver failure in United States
• Two Phase drug-induced toxicity
  • Metabolic Phase (bioactivation-initiating event)
  • Oxidative Phase
• Large variations in APAP susceptibility
  • Inflammatory stress (exposure to microbes)
  • Alcohol consumption (increase metabolic activation)

Etiology of Acute Liver Failure (ALF) in the USA
US ALFSG Adult Registry 1998-2014 (N= 2102)

Bernal W, Lee WM, Wendon J, Larsen FS, Williams R. J Hepatol. 2015 Apr; 62(1 Suppl), S112-S120
Roth R.A. and Ganey P.E. J Pharmacology and Experimental Therapeutics. 2010; 332(3), 692-697
Acetaminophen (APA)

Phase 1: Metabolic Phase (Bioactivation)

Metabolism via Phase II Conjugation

- Glucuronidation: 55-60%
- Sulfation: 20-30%
- N-acetylcysteine (NAC) 55-60%
- Mercapturic acid adduct APAP 20-30%

Major Metabolites (~85%): Inactive Forms (renal elimination)

Metabolism via Phase I Oxidation

- CYP2EI: 5%
- Glutathione (GSH) Depletion
- Catechol Derivative: 10%
- Eliminated in Urine
- N-acetylcysteine (NAC)
- Glutathione Conjugate APAP
- Cysteine adduct APAP

- N-acetyl-p-benzoquinone imine (NAPQI)

• Acetaminophen (APAP) $t_{1/2}$ = 2.0-2.5 hour
• With hepatic injury, APAP $t_{1/2}$ increase to >4 hour
• Daily dose of APAP:
  - Adult (>12 yrs.): 4 g/day
  - Children (<12 yrs.): 50-75 mg/kg/day
• Overdose of APAP:
  - Adult (>12 yrs.): >7.5 g/day
  - Children (<12 yrs.): >150 mg/kg/day

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Acetaminophen (APA)

Phase 1: Metabolic Phase (Bioactivation) and Phase 2: Oxidative Stress

Phase 1: Metabolic Phase

Acetaminophen (APAP) → N-acetyl-p-benzoquinone imine (NAPQI)

Phase 2: Oxidative Stress Phase

Glutathione (GSH) Depletion → Covalent Binding to Cellular Proteins/Peptides → Increase Oxidative Stress → ↑ Mitochondrial Permeability (MPT) → Hepatocellular Necrosis

Acetaminophen (APA)

Phase 1: Metabolic Phase (Bioactivation) and
Phase 2: Oxidative Stress

Phase 1: Metabolic Phase

Reactive Metabolite

Acetaminophen (APAP) → CYP2E1 → Alcohol → N-acetyl-p-benzoquinone imine (NAPQI)

Phase 2: Oxidative Stress Phase

Glutathione (GSH) Depletion → Covalent Binding to Cellular Proteins/Peptides → Increase Oxidative Stress → Hepatocellular Necrosis

† Mitochondrial Permeability (MPT)


*Immune Response to APAP-induced Hepatocellular Necrosis*
Drug-induced Liver Injury (DILI)

Adverse Drug Reactions

- Diverse set of responses after exposure to manufactured or natural chemical compounds
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Idiosyncratic DILI

*Drug-induced Liver Injury (DILI)*

- Drug candidates that lead to intrinsic liver injury are usually eliminated during preclinical testing
  - Idiosyncratic DILI: account for large percent of postmarketing restrictions by FDA
- Hepatotoxicity not related to pharmacological action of drug
- Limited mechanistic understanding
- Wide range in the severity of toxic effects
- The liver is not the target organ but an acute stress can increase the sensitivity of the liver to injury
  - Example: Stress reduces cytochrome P450 metabolism
    - This reduces drug clearance, which leads to an increase in drug toxicity
- Mechanistic Theories for Idiosyncratic DILI (*animal models*)
  - Reactive Intermediate Hypothesis
  - Genetic Polymorphism Hypothesis
  - Hapten Hypothesis
  - The Danger Hypothesis
  - Mitochondrial Dysfunction Hypothesis
  - Failure-to-Adapt Hypothesis
  - Multiple Determinant Hypothesis
  - **Inflammatory Stress Hypothesis**

Factors that Affect Sensitivity to Hepatotoxicants

- Age
- Gender
- Metabolism
- Immunologic Reactions
- Pre-existing Condition
- Inflammation
- Environment
- Diet

Roth R.A. and Ganey P.E. J Pharmacology and Experimental Therapeutics. 2010; 332(3), 692-697

Shaw PJ, Ganey PE, and Roth RA. Toxicol Sci. 2010 Nov; 118(1): 7-18
Mechanism of Action Theories

Idiosyncratic DILI

- Reactive Intermediate Hypothesis

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Drug → Bioactivation Enzyme → Reactive Metabolites → Increase Oxidative Stress → Hepatocellular Necrosis → Mitochondrial Permeability (MPT) → Macromolecular-Drug Adducts → DILI

Shaw PJ, Ganey PE, and Roth RA. Toxicol Sci. 2010 Nov; 118(1): 7-18
Mechanism of Toxicity Theories

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Example: Isoniazid

Shaw PJ, Ganey PE, and Roth RA. Toxicol Sci. 2010 Nov; 118(1): 7-18
Isoniazid: Mechanism of Toxicity

**Idiosyncratic DILI**

- First-line agent in the treatment of active or latent tuberculosis
- **Mechanism of Action**
  - Bactericidal action: Block formation of mycolic acids
    - Mycolic acid: essential component of mycobacterial cell wall synthesis
    - Disruption of cell wall results in cell death
  - Animal model used to elucidate biochemical mechanism
    - ~20% of treated patients develop elevated liver enzymes and bilirubin *(small percentage develop hepatitis)*

![Chemical Diagram](https://via.placeholder.com/150)

- **NAT2: N-Acetyltransferase**
  - **Isoniazid** → **N-acetylisoniazid**
  - **Isonicotinic Acid** → **Acetyltihydrazine**
  - **Diacytltihydrazine**

**Chemical Reactions**

- **CYP2E1** → **Toxic Metabolite**
- **NAT2** → **↑ Mitochondrial Permeability (MPT)**
- **GSH Binding/Depletion** → **↑ Oxidative Stress**
- **Hepatocellular Apoptosis**

*Principles of Clinical Pharmacology, ed 3, ch.16, Fig. 16.6.*

*NAT2: N-Acetyltransferase 2*
Isoniazid: Mechanism of Toxicity

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![Chemical Diagram]

**Theories of Toxicity**
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NAT2: N-Acetyltransferase 2
Isoniazid: Mechanism of Toxicity

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**Theories of Toxicity**

- Reactive Intermediate Hypothesis
- Genetic Polymorphism Hypothesis
- Mitochondrial Dysfunction Hypothesis
Hapten Hypothesis

**Idiosyncratic DILI**

- Drug-induced hepatotoxic reaction mediated by an immune response
- Chemically reactive drug or reactive metabolite (hapten) binds endogenous protein that initiates an immune response
  - Macromolecule-drug adduct: neoantigen
- Example Drug: Halothane
  - Volatile general anesthetic
  - 2 types of hepatotoxicity of Halothane
    1. Subclinical increase in transaminase enzymes (in blood)
    2. Fatal hepatitis-like reaction (severe hepatocellular necrosis)

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Principles of Clinical Pharmacology, ed 3, ch. 16, Fig. 16.7.
Hapten Hypothesis

**Idiosyncratic DILI**

- Drug-induced hepatotoxic reaction mediated by an immune response
- Chemically reactive drug or reactive metabolite (hapten) binds endogenous protein that initiates an immune response
  - Macromolecule-drug adduct: neoantigen
- Example Drug: Tienilic Acid (Ticrynafen)
  - Uricosuric diuretic (marketed in 1979 and withdrawn within a few months)
  - Hepatitis-like adverse reaction (Immunologic response)

Principles of Clinical Pharmacology, ed 3, ch. 16, Fig. 16.8.
Inflammatory Stress Hypothesis
Idiosyncratic DILI

- Drug therapy coupled to inflammatory stress precipitates drug-induced liver injury
- Inflammatory stress induced by several factors
  - Infection, intestinal microbial disturbance, cell death, etc.
- Example Drug: Trovafloxacin (Trovan, Pfizer)
  - Broad-spectrum fluoroquinolone antibiotic
  - ~140 severe hepatic reactions reported/14 resulted in liver failure
  - Restrictions in 1999 and withdrawn in 2001--due to hepatotoxicity
  - Mode of action for hepatotoxicity identified via animal model
  - Mechanism of action:
    - Bactericidal activity exerted by parent compound (no reactive metabolite)
    - Inhibit bacterial DNA gyrase (topoisomerase II) and Topoisomerase IV

http://www.antibiotics-info.org/levofloxacin.html
Trofloxacin (TVX)

TVX and Inflammatory Stress via Animal Model

- **Mode of action for hepatotoxicity**: inflammation-drug interaction animal models

**Effect of TVX/LPS co-treatment on liver in mice model**

A: Vehicle (Veh)/Vehicle (Veh) (control)
B: TVX/Vehicle
C: LVX/Vehicle
D: Vehicle/LPS
E: TVX/LPS
F: LVX/LPS

Shaw PJ, Hopfensperger MJ, Ganey PE, and Roth RA. Toxicol Sci. 2007; 100(1): 259-266
Trofloxacin (TVX)

TVX and Inflammatory Stress via Animal Model

- Mode of action for hepatotoxicity: inflammation-drug interaction animal models

**Gene Expression after TVX/LPS co-treatment**

- Detectable liver injury

<table>
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<tr>
<th>Treatments</th>
<th>Δ Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVX/LPS</td>
<td>193↑ 580↓</td>
</tr>
<tr>
<td>Veh/LPS</td>
<td>534↑ 230↓</td>
</tr>
<tr>
<td>TVX/Veh</td>
<td>114↑ 105↓</td>
</tr>
<tr>
<td>Veh/Veh</td>
<td>197↑ 168↓</td>
</tr>
</tbody>
</table>

**Gene Profiling Results**

- Global Gene Profiling:
  - Genes involved in interferon signaling (IFN-γ) play a role in TVX/LPS co-exposure
  - Early Marker of Hepatotoxicity

Trovafloxacin (TVX)

TVX and Inflammatory Stress via Animal Model

- Mode of action for hepatotoxicity: inflammation-drug interaction animal models

Shaw PJ, Ganey PE, and Roth RA. Toxicol Sci. 2010 Nov; 118(1): 7-18
Mechanism of Toxicity Theories

Idiosyncratic DILI

- Inflammatory Stress Hypothesis: common link between the six theories

Shaw PJ, Ganey PE, and Roth RA. Toxicol Sci. 2010 Nov; 118(1): 7-18
Systemic Drug Reactions

*Drug-induced Adverse Effects (Drug Allergy)*

- Drug hypersensitivity
  - Immunologically mediated response to drug in a sensitized person (allergy or autoimmunity)
  - Reactions are classified into four groups

<table>
<thead>
<tr>
<th>Gell and Coombs Type</th>
<th>Mechanism</th>
<th>Clinical Manifestations</th>
<th>Time of Onset</th>
<th>Example Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (IgE-mediated)</td>
<td>Drug-IgE complex bind to mast cells and cause release of histamine, inflammatory mediators</td>
<td>Anaphylaxis, Urticaria</td>
<td>Minutes to hours after exposure (immediate)</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Type II (Cytotoxic, IgG or IgM)</td>
<td>Specific IgG or IgM antibodies directed at drug-hapten coated cells</td>
<td>Hemolytic anemia, Neutropenia, Thrombocytopenia</td>
<td>Hours to days (variable)</td>
<td>Cefotetan</td>
</tr>
<tr>
<td>Type III (Immune complex)</td>
<td>Tissue deposition of drug-antibody complexes with complement activation and inflammation</td>
<td>Arthralgias, Fever, Glomerulonephritis, Lymphadenopathy, Serum sickness, Rash, Urticaria, Vasculitis</td>
<td>1 to 3 weeks after exposure</td>
<td>Infliximab</td>
</tr>
<tr>
<td>Type IV (Delayed, cell-mediated)</td>
<td>MHC presentation of drug molecules to T cells with cytokine and inflammatory mediator release</td>
<td>Contact dermatitis, Maculopapular drug rash</td>
<td>2 to 7 days after exposure</td>
<td>Penicillin</td>
</tr>
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</table>
Hypersensitivity Reactions
Classification of Reactions - Gell and Coombs

Type I
- Hapten (chemical moiety too small to elicit an immune response)
- Protein
- Hapten-bound protein
- Mast cell

Type II
- Antigen
- Antigen-bound RBC
- Complement-mediated RBC lysis
- Antigen-antibody complexes
- Immune complex deposition in tissues

Type III
- Antigen
- Antibodies
- Antigen-antibody complexes
- Macrophage

Type IV
- Hapten
- Protein
- Hapten-bound protein

Hypersensitivity Reactions

Classification of Reactions - Gell and Coombs

- Type I, II and III Response
  - Humoral Antibodies
- Type IV Response
  - Sensitized Lymphocytes

A Textbook of Clinical Pharmacology and Therapeutics, ed 5, ch.12, Fig. 12.1.
Penicillin

Hypersensitivity Reactions (Type I and IV)

Principles of Clinical Pharmacology, ed 3, ch. 16, Fig. 16.10.
Penicillin

Hypersensitivity Reactions (Type I and IV)

Type I

Type IV

Penicillin

Haptenation Product

Penicillenic Acid

Penicillin

Penicillenyl Haptenation Product

Penicillamine Haptenation Product

Principles of Clinical Pharmacology, ed 3. ch. 16, Fig. 16.10.
Penicillin
Hypersensitivity Reactions (Type I and IV)

Clinical Decision for Penicillin Allergy

Allergy Evaluation

Type I Reaction (IgE-mediated)
Urticaria, Angioedema, Wheezing, Anaphylaxis
Penicillin skin test
Negative
Graded-dose Challenge
Positive
Avoid penicillin
Desensitization

Type IV Reaction (Cell-mediated)
Exfoliative dermatitis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Serum sickness, DRESS, Maculopapular rash
Skin test, challenge, and desensitization are contraindicated

Typical lesions of chronic urticaria
http://www.worldallergy.org/professional/allergic_diseases_center/urticaria/urticariasynopsis.php

Penicillin
Penicillenic Acid
Major
Minor
Minor
Penicilloyl-Protein
Penicillenyl Haptenation Product
Penicillamine Haptenation Product
Side Chain
Beta-lactam ring
Thiazolidine ring

Gonzalez-Estrada A and Radojicic C. Cleve clin J Med. 2015 May; 82(5): 295-300
Principles of Clinical Pharmacology, ed 3. ch.16, Fig. 16.10.
Infliximab (Remicad\textsuperscript{®})

Hypersensitivity Reactions (Type III)

- Infliximab
  - Chimeric monoclonal antibody (mAb) to human tumor necrosis factor (TNF-\(\alpha\))
  - Mouse (variable region)-human (IgG1 constant region)
  - Approved by FDA for treatment of Crohn's disease (1998) and Rheumatoid Arthritis (RA-1999)
    - Also used in Psoriasis, Ankylosing spondylitis (AS), and Behçet's disease

Type III

Infliximab (Remicad®)
Mechanism of Tumor Necrosis Factor (TNF-α)

**Infliximab (Remicad®)**

Mechanism of Drug Activity

Granuloma formation

- Crohn's disease
- Wegener's granulomatosis
- Sarcoidosis

Outside-to-inside signal (reverse signal)

Inhibition of effector function


Cell lysis

Granzyme B

Perforin

Infliximab

Fc receptor

Etanercept

C1

C3

Membrane attack complex (C5b-C9)

tmTNF

Target cell

Cell lysis

NK cell

Infliximab

Fc receptor

C1

C3

Membrane attack complex (C5b-C9)

tmTNF

Target cell

Cell lysis

Infliximab (Remicad®)

Mechanism of Drug Activity

Infliximab (Remicad®)

**Drug Toxicity**

  - Association with a 2- to 8-fold increase in risk for tuberculosis, listeriosis and histoplasmosis
  - Increased incidence in European countries as well
- Anti-TNF-α activity leads to increased risk of granulomatous infections
  - TNF: essential for host defenses against *Mycobacterium tuberculosis*
    - TNF is involved in the activation of specific macrophages enzymes (iNOS) which are vital for bacterial elimination

Infliximab (Remicad®) Drug Toxicity

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- Anti-TNF-α activity leads to increased risk of granulomatous infections
  - TNF: essential for host defenses against Mycobacterium tuberculosis
    - TNF is involved in the activation of specific macrophages enzymes (iNOS) which are vital for bacterial elimination

Distribution of Tuberculosis cases in relation to Anti-TNF therapy

Infliximab (Remicad®)

**Drug Toxicity**

  - Association with a 2- to 8-fold increase in risk for tuberculosis, listeriosis and histoplasmosis
  - Increased incidence in European countries as well

- Anti-TNF-α activity leads to increased risk of granulomatous infections
  - TNF: essential for host defenses against *Mycobacterium tuberculosis*
    - TNF is involved in the activation of specific macrophages enzymes (iNOS) which are vital for bacterial elimination

*Distribution of Tuberculosis cases in relation to Anti-TNF therapy*

*Effect of Anti-TNF therapy on M. tuberculosis Infection in Mice*


Adverse Effect of Chemotherapy

*Drug Toxicity*

- Basic principle: inhibit the mitotic and metabolic process of cancer cells
  - Cancer drugs either inhibit cellular proliferation or target specific proteins vital to the expansion of abnormal cells
- Normal cells and tissues are also affected, leading to various mild and severe adverse effects
- Chemotherapy has improved significantly but the applicability of the drugs are limited due to the risk of chemotherapy-induced cardiotoxicity
- Two types of chemotherapy-induced cardiotoxicity
  - **Type I**
    - *Irreversible myocyte destruction*
    - *Example: Anthracyclines (Doxorubicin)*
  - **Type II**
    - *Reversible myocyte damage (broad range of incidence and severity)*
    - *Example: Trastuzumab*
Type I Cardiotoxicity
Chemotherapy-induced Drug Toxicity

- Anthracyclines (Doxorubicin)
  - Well-studied class of cardiotoxic anti-cancer agents
  - Dose-dependent toxicity
  - Mechanism of action: target Topoisomerase II (Top 2) and form a Top 2-DNA complex that ultimately triggers cell death

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Three proposed mechanisms for cardiotoxicity
1. Formation of ROS to induce oxidative stress
2. Impaired Diastolic Relaxation
3. Inhibit prosurvival signaling pathways (NGRG-1 and ErbB inhibition)

Type II Cardiotoxicity
Chemotherapy-induced Drug Toxicity

- Trastuzumab (Herceptin)
  - New generation of targeted chemotherapy
  - Humanized monoclonal antibody (mAb)
  - Mechanism of action: Binds to extracellular domain of human epidermal growth factor 2 (HER2 or ErbB2)-inhibits proliferation of cancer cells
  - HER2-positive breast carcinoma treatment
  - Cardiotoxicity occurs in ~20-33% of patients treated with drug (mild and reversible)

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Teratogenic Reactions to Drugs

Drug Toxicity

• A teratogen is an agent that can disturb the development of the embryo or fetus
• Use of drugs in pregnancy is complicated due to potential for harmful effects on growing fetus

Pharmacokinetic changes in pregnancy.

Placental transfer of drugs from mother to fetus.

A Textbook of Clinical Pharmacology and Therapeutics, ed 5, ch.9, Fig. 9.1 and 9.2
Teratogenic Reactions to Drugs

**Drug Toxicity**

- A teratogen is an agent that can disturb the development of the embryo or fetus
- Use of drugs in pregnancy is complicated due to potential for harmful effects on growing fetus
- FDA established a system to classify drugs to indicate the potential of a drug to cause birth defects during pregnancy (based on human and animal data)

**A** - “Safe”, adequate data to demonstrate risk (1st trimester)
- Examples: Levothyroxine, Folic Acid, Magnesium Sulfate

**B** - Fetal risk confirmed in human studies but not animal study
- Examples: Metformin, Amoxicillin, Pantoprazole,

**C** - Fetal risk confirmed in animal studies but not human study
- Examples: Tramadol, Gabapentin, Amlodipine, Prednisone

**D** - Fetal risk shown in humans, use if benefit outweigh risk
- Examples: Lisinopril, Alprazolam, Losartan, Lorazepam

**X** - “Proven teratogen”, benefit does not outweigh risk
- Examples: ACE Inhibitors, Warfarin, Finasteride
Teratogenic Reactions to Drugs

**Drug Toxicity**

- A teratogen is an agent that can disturb the development of the embryo or fetus
- Use of drugs in pregnancy is complicated due to potential for harmful effects on growing fetus
- Angiotensin-converting enzyme (ACE)-inhibitors
  - Treatment of hypertension and congestive heart failure
  - Cause relaxation of blood vessels
  - Mechanism of action: reduce activity of renin-angiotensin-aldosterone system (RAAS)

![Diagram](https://www.mio-online.com/the-renin-angiotensin-aldosterone-system-increasingly-complex-and-prevalent.php)

Presentation Summary

Adverse Drug Reactions

I. Adverse Drug Reactions
   a. Methemoglobin-Benzocaine

II. Drug-induced Liver Injury (DILI)
   a. Intrinsinc
      1) Acetaminophen (APA)
   b. Idiosyncratic
      1) Mechanistic Theories (8)
      2) Isoniazid
      3) Halothane
      4) Trovafloxacin (TVX)

III. Systemic Drug Reactions
   a. Gell and Coombs Classification of Drug Reactions
   b. Penicillin
   c. Infliximab

IV. Chemotherapy Adverse Reactions
   a. Cardiotoxicity
   b. 2 Types
      1) Type I: Doxorubicin
      2) Type II: Trastuzumab

V. Teratogenic Reactions to Drugs
   a. FDA Classification of Drugs
   b. ACE Inhibitors