

Injury by Therapeutic Drugs (Adverse Drug Reactions)

Pathologic patterns, mechanisms, and clinicopathologic correlations

General pathology • clinicopathologic interpretation

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What should you be able to explain?

- Define an adverse drug reaction and distinguish it from overdose toxicity.
- Contrast direct drug actions with immune-mediated hypersensitivity.
- Recognize organ injury patterns and representative causal drugs.
- Link a medication history to morphology without assuming causation.

ADRs occur at prescribed drug doses

UNWANTED EFFECT DURING THERAPEUTIC USE

- An adverse drug reaction is an undesired effect occurring when a medication is taken at its prescribed dose.
- This definition makes the exposure context essential to labeling an event an ADR.
- An intentional or accidental overdose can also cause drug injury, but is a distinct exposure circumstance.

Therapeutic benefit and injury coexist

Therapeutic intent	Undesired consequence
• Prevent disease or control symptoms • The same drug has a desired pharmacologic effect • Treatment benefit may justify some risk	• Unintended tissue or functional injury • Severity ranges from mild to life-threatening • Risk–benefit judgment depends on context

Adverse does not mean the medication was necessarily prescribed incorrectly.

Exposure context changes interpretation

Therapeutic dosing

Reaction arises during prescribed use

The event may be called an ADR

Example: minocycline pigmentation

Excessive dosing

Toxicity follows drug amounts beyond prescribed use

Classify as overdose / poisoning when appropriate

Example: acetaminophen overdose injury

The same drug can cause different injuries under different exposure conditions.

Most ADRs are not life-threatening

- ADRs are common in clinical practice.
- Most are not life-threatening; A minority lead to major organ injury or death.
- Drug-induced pathology spans skin, blood, heart, kidney, lung, liver, and nervous system.
- The severity of an outcome cannot be inferred from the drug name alone.

ADRs occur beyond the hospital

Ambulatory care

- Medication exposure occurs in outpatient settings
- New or persistent symptoms may represent a treatment effect

Long-term care

- Nursing-home settings
- Medication-related injury must remain in the differential

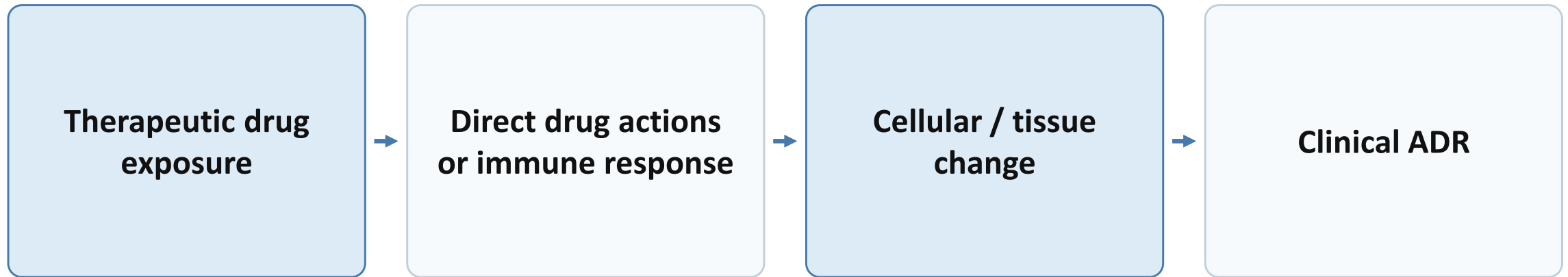
A medication review matters in every care setting.

Age over 65 increases ADR susceptibility

HOST SUSCEPTIBILITY

- People older than 65 years as more likely to experience ADRs.
- Age is a risk marker, not a diagnostic test for drug causation.
- The clinical implication is heightened attention to new findings after medication exposure.

Two major routes to drug injury



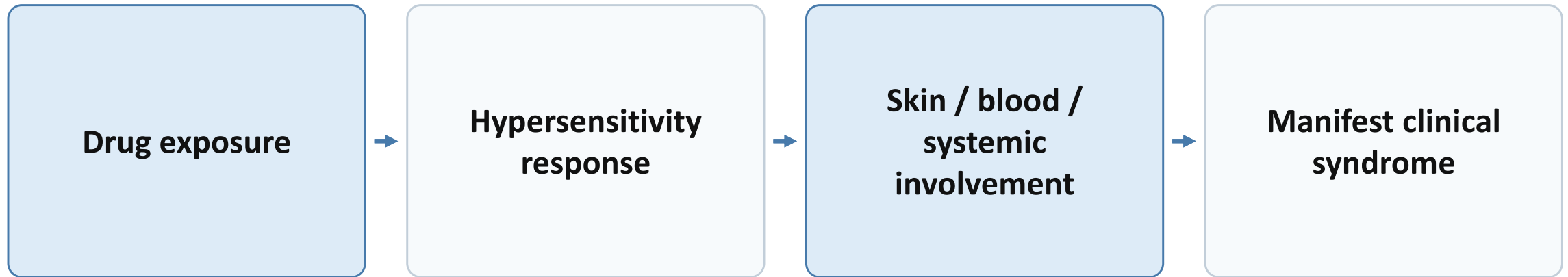
Conceptual model: Injury mechanism precedes the observed lesion.

Direct drug effects are organ-specific

Mechanism	Examples
• An effect of the medication or its metabolite • May manifest as functional disturbance or tissue injury	• Anticoagulants → bleeding • Anthracyclines → cardiomyopathy • Aminoglycosides → tubular necrosis

A plausible pharmacologic mechanism strengthens—but does not establish—attribution.

Immune-mediated reactions have varied targets



The immune pathway can resemble primary immunologic disease.

Direct injury versus hypersensitivity

Dimension	Direct drug action	Hypersensitivity
Dominant concept	Toxic or pharmacologic action	Immune-mediated response
Representative presentation	Drug-associated bleeding	Drug-associated rash
Other examples	Cardiac or renal toxicity	Drug-induced lupus-like disease
Pathology question	Which organ is directly injured?	Could an immune disorder be mimicked?

Potent treatments may carry accepted risks

RISK–BENEFIT CONTEXT

- Antineoplastic agents are cited as medications with substantial adverse effects.
- Such effects may be considered acceptable risks in the context of treatment benefit.
- The decision depends on the purpose of treatment and expected consequences—not on morphology alone.

Map adverse reactions by target tissue

Tissue compartment	Representative injury
Blood / marrow	Cytopenias; hemolytic anemia
Skin	Inflammatory eruption or pigment change
Heart / kidney	Arrhythmia; cardiomyopathy; nephritis
Lung / liver	Pneumonitis; fibrosis; hepatitis; cholestasis
Systemic / CNS	Anaphylaxis; lupus-like syndrome; neurologic effects

Blood-cell injury spans several lineages

White cells

Granulocytopenia

Red cells

Hemolytic anemia

Platelets

Thrombocytopenia

Distinguish lineage-specific destruction from broader marrow injury.

Granulocytopenia is a drug-associated pattern

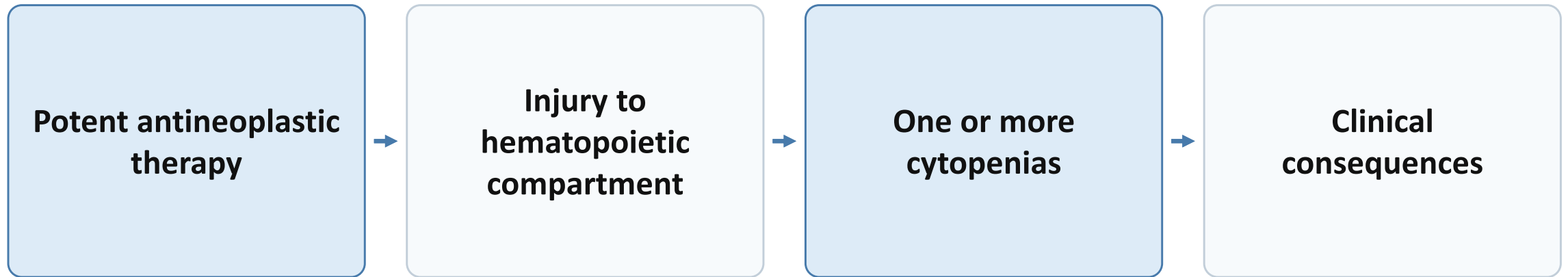
- Granulocytopenia appears among the marrow and blood-cell reactions listed by Robbins.
- It indicates a marked reduction in circulating granulocytes.
- Antineoplastic drugs and chloramphenicol are listed among the major agents for marrow suppression patterns.

Aplastic anemia and pancytopenia implicate marrow

Aplastic anemia	Pancytopenia
• A marrow-failure syndrome • The primary abnormality involves hematopoietic production	• Reduction across major blood-cell lineages • A descriptive peripheral-blood finding

These labels are related but not interchangeable.

Antineoplastic drugs can suppress hematopoiesis



Framework linking a potent treatment class to blood-cell deficits.

Hemolytic anemia reflects red-cell loss

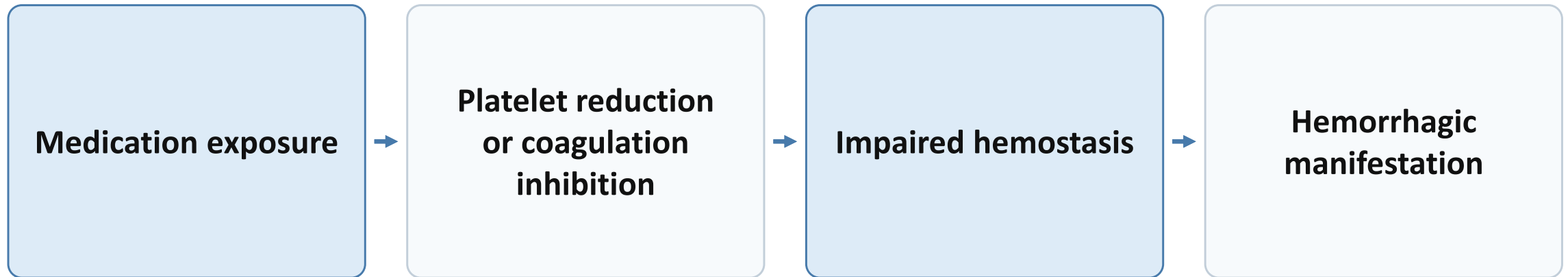
- Hemolytic anemia as a possible drug-related blood disorder.
- Penicillin, methyldopa, and quinidine appear among the associated drug examples.
- Drug-induced hemolysis is a different pathologic pathway from generalized marrow failure.

Immune thrombocytopenia may be drug-induced

Thrombocytopenia	Anticoagulant-associated bleeding
• Reduced platelet number • Drug-induced immune thrombocytopenia is identified • Heparin is among listed drug associations	• Impaired coagulation during intended therapy • Warfarin and dabigatran are listed • Platelet loss is not required

Low platelets and anticoagulant hemorrhage are distinct mechanisms.

Different mechanisms can produce bleeding



The observed event is the endpoint; Identify the relevant hemostatic defect.

Cutaneous ADRs have diverse morphologies

Cutaneous patterns	Additional skin findings
Urticaria	Petechiae
Macules and papules	Exfoliative dermatitis
Vesicles	Fixed drug eruptions
—	Abnormal pigmentation

Pattern recognition identifies the lesion; Medication linkage requires history.

Urticaria, macules, and papules are common clues

- Robbins specifically lists urticaria and maculopapular lesions among cutaneous ADRs.
- Such eruptions are compatible with—but not specific for—drug-related hypersensitivity.
- The key pathologic distinction is an inflammatory reaction rather than pigment accumulation.

Vesicles and exfoliation expand the skin spectrum

- The cutaneous list includes vesicular lesions and exfoliative dermatitis.
- Petechiae are another named manifestation; Not every drug eruption has the same underlying process.
- A description of the morphologic pattern should precede a claim about the culprit drug.

Pigmentation is not necessarily inflammation

Inflammatory eruption

- Urticaria, papules, or vesicles
- Often considered in hypersensitivity

Drug-pigment deposition

- Abnormal skin coloration
- May reflect retained drug-related material

The two mechanisms suggest different morphologic questions.

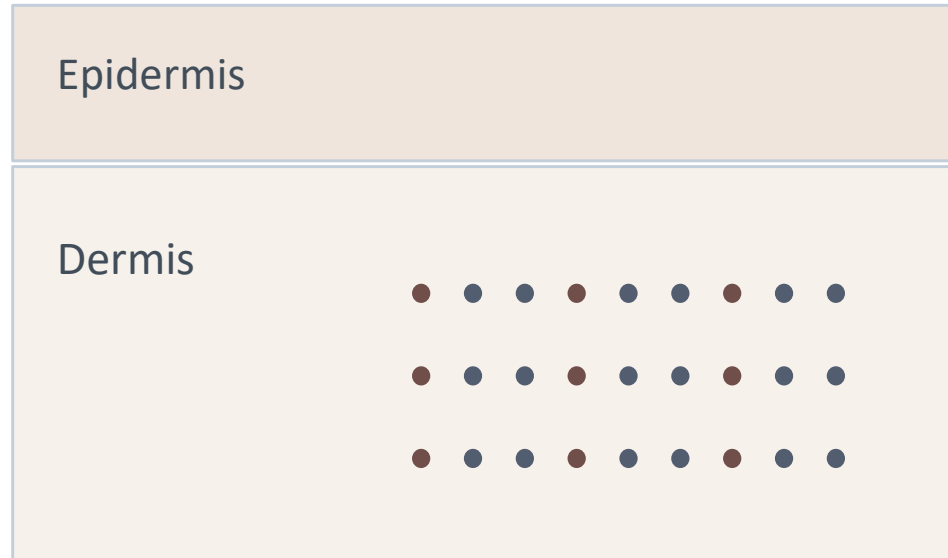
Minocycline can discolor the skin

MINOCYCLINE-ASSOCIATED PIGMENTATION

- Diffuse blue-gray forearm pigmentation following minocycline use.
- The pigment is associated with an oxidized metabolite of this antibiotic.
- The example shows that an ADR may be visible as a deposition process rather than an acute inflammatory lesion.

Minocycline pigmentation localizes to the dermis

Schematic skin cross-section



Deposited pigment particles

- The published example shows drug metabolite, iron, and melanin pigment particles within dermis.
- Dermal deposition explains why the clinical change appears as persistent skin coloration.
- The drawing is an original schematic, not the textbook photomicrograph.

The offender list for skin reactions is broad

Examples emphasized in Robbins	Relevant cutaneous outcome
Antineoplastic drugs	Multiple eruption patterns
Sulfonamides	Drug-related skin eruptions
Hydantoins	Drug-related skin eruptions
Various antibiotics	Drug-related skin eruptions

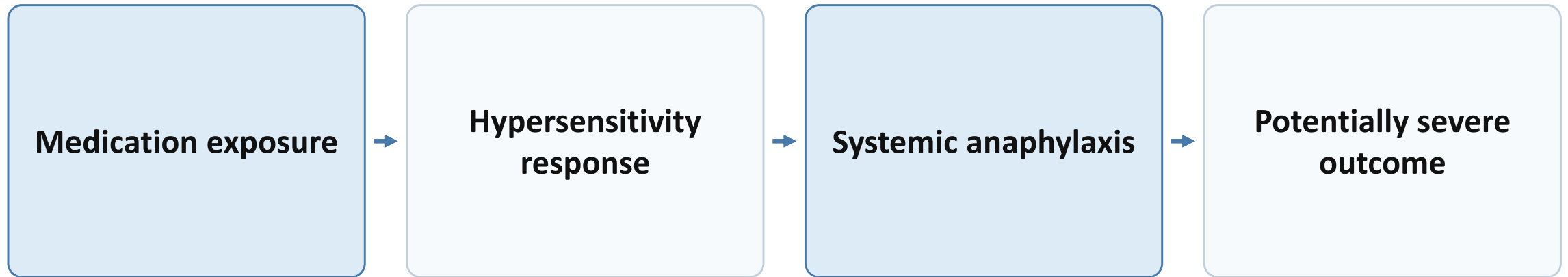
These offender lists show associations rather than establish individual causation.

Drug-induced lupus can imitate autoimmunity

Clinical-pathologic mimic	Associated agents
• Drug reaction resembling systemic lupus erythematosus • An immune-mediated pattern is possible	• Hydralazine • Procainamide

Consider drug exposure when a lupus-like syndrome is encountered.

Anaphylaxis is a systemic drug reaction



Penicillin is a representative drug listed for anaphylaxis.

Cardiac ADRs affect rhythm or muscle

Arrhythmia

- Electrical/rhythm disturbance
- Digoxin, theophylline, hydantoins

Cardiomyopathy

- Myocardial tissue dysfunction
- Doxorubicin, daunorubicin

Both are “cardiac” outcomes, but they are not the same lesion.

Drug-related arrhythmias

- Theophylline, hydantoins, and digoxin are listed as major examples.
- An arrhythmia is a functional electrical disturbance; It does not by itself prove structural myocardial injury.
- Medication association and the rhythm phenotype should be assessed separately.

Anthracyclines are associated with cardiomyopathy

MYOCARDIAL TOXICITY

- Doxorubicin and daunorubicin are listed as agents associated with cardiomyopathy.
- The affected structure is the myocardium rather than primarily the cardiac conduction pattern.
- This example illustrates a clinically important adverse effect of potent antineoplastic therapy.

Drug-induced renal injury has three patterns

Glomerulus

Glomerulonephritis

Tubules

Acute tubular necrosis

Tubulointerstitium / papilla

**Tubulointerstitial disease
with papillary necrosis**

Identify the compartment before selecting a likely drug association.

Penicillamine is associated with glomerulonephritis

- Penicillamine among agents associated with glomerulonephritis.
- The glomerular compartment is the named target of injury.
- Differentiate glomerular involvement from tubular necrosis or papillary disease.

Acute tubular necrosis has a drug differential

Renal lesion	Offending drugs listed
Acute tubular necrosis	Aminoglycoside antibiotics
Acute tubular necrosis	Cyclosporin
Acute tubular necrosis	Amphotericin B

Three distinct therapies converge on a tubular injury pattern.

Papillary necrosis is another renal drug lesion

Lesion	Representative agents
• Tubulointerstitial disease • Associated papillary necrosis	• Phenacetin • Salicylates

Papillary injury is not synonymous with acute tubular necrosis.

Pulmonary drug injury has three presentations

Airways

Asthma

Acute lung tissue

Pneumonitis

Interstitial compartment

Fibrosis

The respiratory presentation is not a single uniform toxic syndrome.

Salicylates can precipitate asthma

- Salicylates are listed as agents associated with asthma.
- The dominant manifestation is an airway disorder rather than fibrosis.
- A respiratory symptom during therapy cannot automatically be classified as an infectious pneumonitis.

Nitrofurantoin is linked to acute pneumonitis

Drug association	Diagnostic distinction
• Nitrofurantoin • Named as an acute pneumonitis offender	• Acute lung inflammation pattern • Different from the chronic interstitial fibrosis category

One drug appears in more than one respiratory injury category.

Several drugs are linked to pulmonary fibrosis

Pulmonary pattern	Drugs listed
Interstitial fibrosis	Busulfan
Interstitial fibrosis	Nitrofurantoin
Interstitial fibrosis	Bleomycin

A fibrotic interstitial lesion has a medication-related differential.

Hepatic ADRs show three injury categories

Fat accumulation

Fatty change

Hepatocytes

**Diffuse hepatocellular
damage**

Bile flow

Cholestasis

The dominant tissue reaction helps organize causal-drug possibilities.

Tetracycline can produce hepatic fatty change

- Fatty change is one of the hepatic morphologic responses listed by Robbins.
- Tetracycline is one drug associated with this hepatic pattern.
- Steatosis should not be equated with diffuse hepatocellular damage or cholestasis.

Diffuse hepatocellular damage has several causes

Pathologic pattern	Representative drug
Diffuse hepatocellular damage	Halothane
Diffuse hepatocellular damage	Isoniazid
Diffuse hepatocellular damage	Acetaminophen

A shared injury category does not imply identical mechanisms or exposure contexts.

Cholestasis is a distinct hepatic drug pattern

Drug associations	Named hepatic outcome
Chlorpromazine	Cholestasis
Estrogens	Cholestasis
Contraceptive agents	Cholestasis

A drug may disturb bile handling without the dominant morphology being steatosis.

The hepatic lesion directs the differential

Parenchymal injury

- Fatty change or hepatocellular damage
- Consider tetracycline, isoniazid, halothane, acetaminophen

Biliary-pattern injury

- Cholestasis
- Consider chlorpromazine or hormonal agents

Describe the lesion pattern before selecting the most plausible medication.

Neurologic effects can be sensory or motor

Neurologic manifestation	Medication example
Tinnitus; dizziness	Salicylates
Acute dystonic reactions	Phenothiazine antipsychotics
Parkinsonian syndrome	Phenothiazine antipsychotics
Respiratory depression	Sedatives

Phenothiazines can cause extrapyramidal syndromes

Acute dystonic reaction

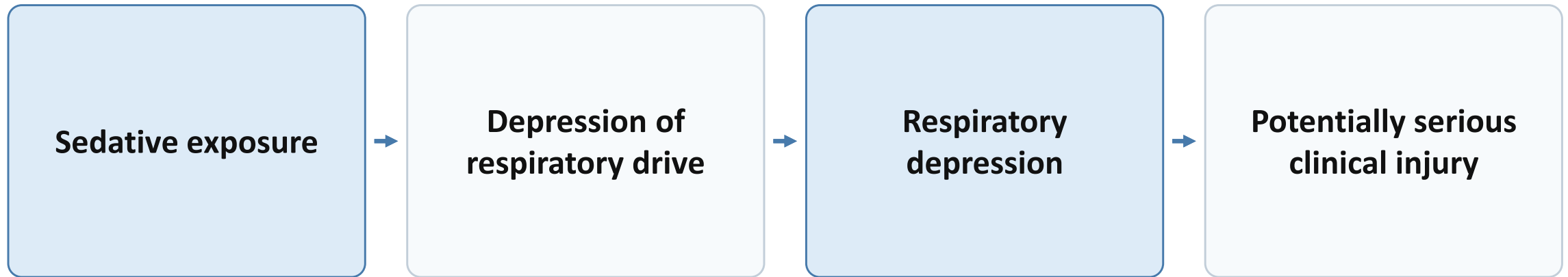
- Abnormal movement / sustained muscle contraction
- Named adverse reaction

Parkinsonian syndrome

- Drug-associated parkinsonian motor phenotype
- Named adverse reaction

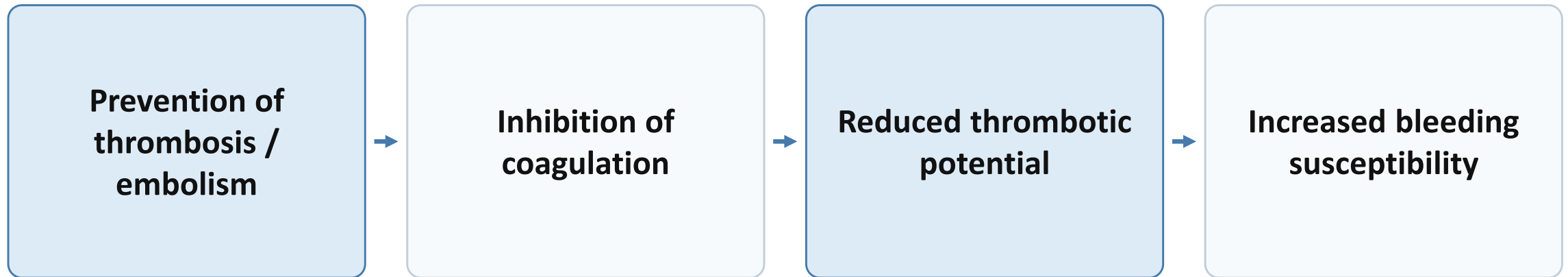
Neither clinical motor syndrome should be mistaken for a tissue-necrosis pattern.

Sedatives can depress respiration



A functional disturbance can be life-threatening without a specific biopsy lesion.

Anticoagulants expose a therapeutic trade-off



Anticoagulant-associated bleeding is explicitly discussed by Robbins.

Warfarin and dabigatran are bleeding examples

Warfarin

- Vitamin K antagonist
- Food and drug interactions complicate therapy
- Regular blood testing is described

Dabigatran

- Direct thrombin inhibitor
- Included among DOACs
- Bleeding remains a treatment-related risk

Both are therapies for thrombosis prevention; Both can produce serious bleeding.

Hormonal treatments illustrate population risk

Therapy group	Adverse effect emphasized in Robbins
Menopausal hormone therapy	Thromboembolism and stroke risk vary with regimen and clinical context
Oral contraceptives	Venous thromboembolism; association with hepatic adenoma
Hormonal agents generally	Some agents are associated with hepatic cholestasis

Risk varies by drug formulation and patient context; Avoid treating all formulations as identical.

Overdose toxicity is a useful contrast—not an ADR

Prescribed-dose ADR

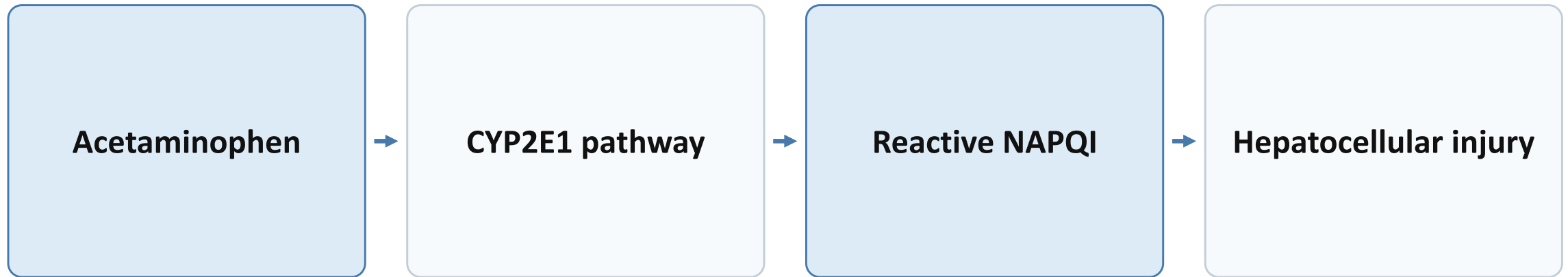
- By definition occurs at the prescribed dose
- Minocycline pigmentation and drug rashes illustrate the concept

Drug overdose injury

- Excessive exposure is the defining circumstance
- Acetaminophen and aspirin illustrate major toxic injury

Use exposure context precisely when teaching pharmacotoxicology.

Acetaminophen toxicity explains reactive metabolites

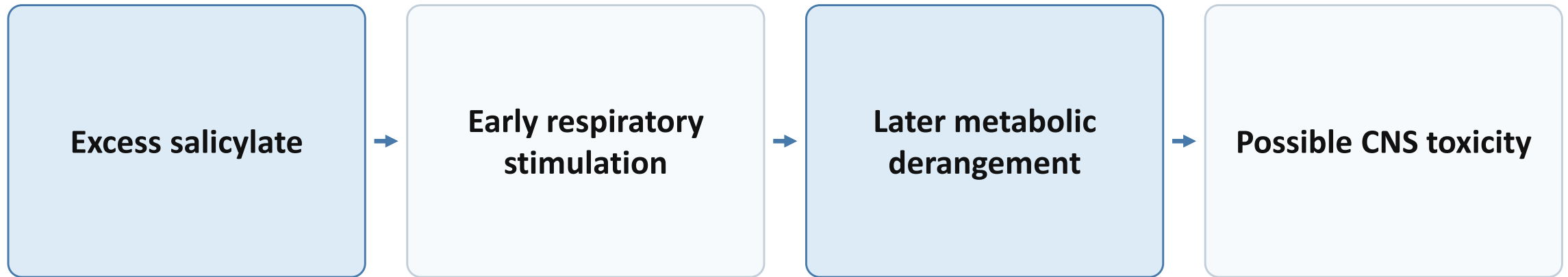


At ordinary doses, the larger share undergoes detoxification; Overdose increases reactive-metabolite burden.

Acetaminophen injury targets centrilobular hepatocytes

- Excess NAPQI causes covalent protein binding and mitochondrial injury.
- Glutathione depletion increases susceptibility to oxidant damage.
- The characteristic injury is centrilobular hepatocellular necrosis, which can progress to liver failure.
- This exemplifies overdose toxicology, not an automatically presumed prescribed-dose ADR.

Aspirin toxicity is a distinct exposure scenario



An early respiratory alkalosis followed by metabolic acidosis.

Chronic aspirin exposure can cause bleeding

Gastric injury

- Acute erosive gastritis
- Possible gastric ulceration and GI bleeding

Hemostatic effect

- Irreversible platelet cyclooxygenase inhibition
- Reduced thromboxane A₂–dependent aggregation

Mucosal injury and defective platelet function can amplify bleeding.

Case: Delayed blue-gray skin discoloration

A patient receiving prolonged minocycline therapy develops diffuse blue-gray pigmentation on the forearm.

Which tissue-level finding supports the medication association?

Interpretation

Pigment particles containing drug metabolite, iron, and melanin in the dermis; This is a deposition-type ADR.

Case: Cytopenias after potent treatment

A person undergoing antineoplastic therapy develops simultaneous reductions in multiple blood-cell lineages.

Which hematologic reaction category best explains this finding?

Interpretation

Pancytopenia / marrow suppression; Antineoplastic agents are major listed offenders.

Case: Drug-related acute kidney injury

A patient exposed to an aminoglycoside antibiotic develops a renal lesion reported as acute tubular necrosis.

Which renal compartment is primarily involved?

Interpretation

The renal tubular compartment. Robbins specifically links aminoglycosides with acute tubular necrosis.

Case: Two pulmonary drug syndromes

One exposed patient has acute pneumonitis; Another has interstitial pulmonary fibrosis.

Which medication is associated with both patterns?

Interpretation

Nitrofurantoin. The histopathologic pattern, not only the drug name, distinguishes the syndromes.

Case: Cholestasis rather than hepatocyte necrosis

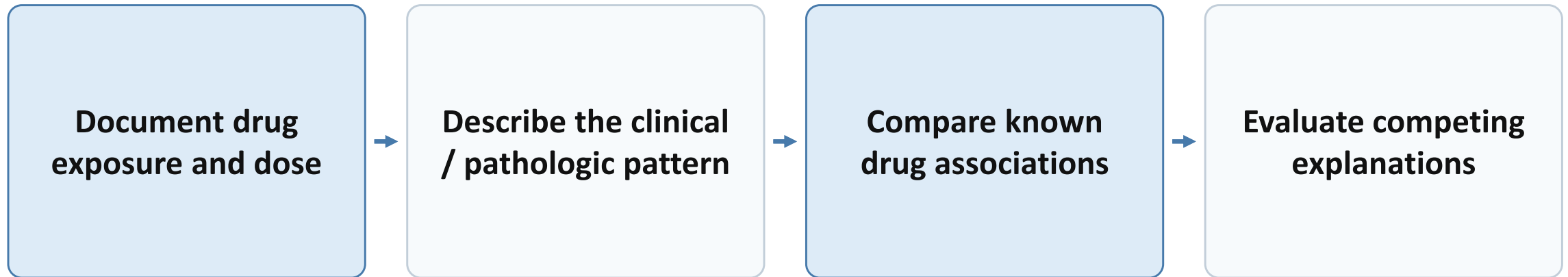
A patient taking chlorpromazine is evaluated for a hepatic adverse reaction characterized as cholestasis.

What hepatic injury category best describes this finding?

Interpretation

Drug-associated cholestasis—not the separate category of diffuse hepatocellular damage.

Integrate medication, lesion, and competing causes



This is an educational interpretation framework, not a formal causality-scoring tool.

High-yield injury pattern comparison

Target	Pathologic reaction	Representative drug
Marrow	Cytopenias	Antineoplastic therapy
Skin	Dermal pigmentation	Minocycline
Heart	Cardiomyopathy	Doxorubicin
Kidney	Acute tubular necrosis	Aminoglycosides
Lung	Interstitial fibrosis	Bleomycin
Liver	Cholestasis	Chlorpromazine

Summary: Five durable distinctions

- An ADR is an unwanted effect at the prescribed dose; Overdose is a separate exposure context.
- Both direct drug effects and immune hypersensitivity can injure organs.
- Anatomic site and lesion pattern organize the medication differential.
- One medication can produce different manifestations in different patients.
- A compatible drug history does not, by itself, prove causality.

Reference

Core reading

Robbins, Cotran & Kumar
Pathologic Basis of Disease, 11th edition (2026)

Environmental and Nutritional Diseases
Injury by Therapeutic Drugs (Adverse Drug Reactions)
Organ-specific toxicities and immune reactions