

Aspirin (Acetylsalicylic Acid)

Mechanisms of toxicity, gastric injury and platelet dysfunction

Clinicopathologic lecture

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Explain how aspirin suppresses cyclooxygenase-dependent mediators.
- Trace respiratory and metabolic derangements in acute salicylate toxicity.
- Recognize chronic salicylism, gastric injury and platelet dysfunction.
- Integrate symptoms, morphology and mechanisms in clinical scenarios.

A useful drug can also produce characteristic injury

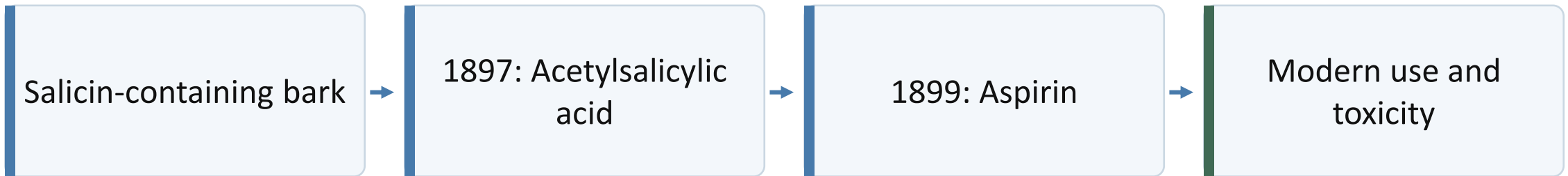
Therapeutic effects

- Pain and fever control
- Anti-inflammatory action
- Antiplatelet effect

Potential injury

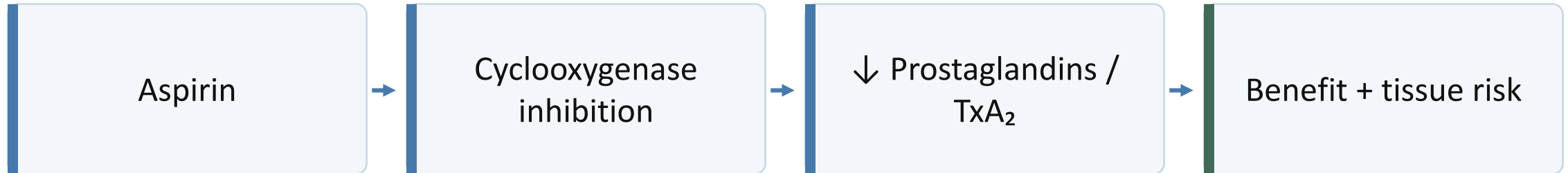
- Acute metabolic toxicity
- Gastric mucosal damage
- Bleeding tendency

Salicylates: A long clinical history



Sequence is schematic; Individual clinical courses vary.

Therapeutic actions and adverse consequences



- Cyclooxygenase inhibition reduces prostaglandin synthesis.
- Prostaglandins have inflammatory and protective roles.
- Platelet thromboxane A₂ production is also inhibited.

Where aspirin fits among therapeutic drug injuries

Direct drug action

- COX acetylation
- Prostaglandin depletion
- Reduced platelet TxA₂

Systemic toxicity

- Respiratory center stimulation
- Mitochondrial disruption
- Acid–base disturbance

Two clinically distinct patterns

Feature	Acute toxicity	Chronic salicylism
Exposure	Overdose / toxic ingestion	Prolonged high daily intake
Core pathology	Acid–base and energy failure	CNS, gastric and platelet injury
Major concern	Neurologic deterioration	Erosion, hemorrhage, bleeding

Exposure context matters

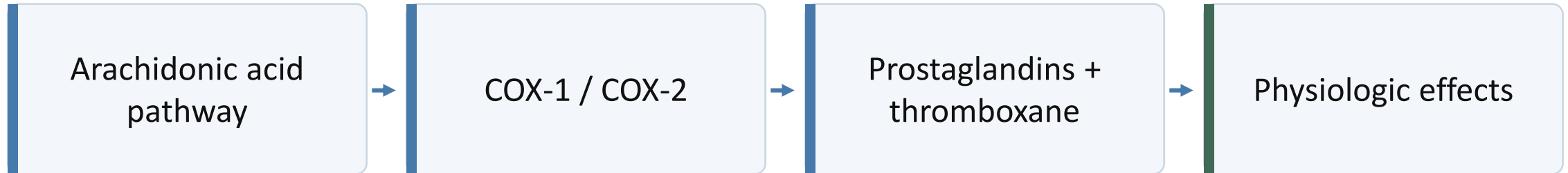
Children

- Accidental ingestion highlighted
- Potential for severe poisoning

Adults

- Intentional overdose highlighted
- Chronic pain/inflammation exposure also relevant

Cyclooxygenase: The shared molecular target



- Aspirin irreversibly acetylates and inactivates cyclooxygenases.
- COX-1 participates in homeostatic prostaglandin generation.
- COX-2 is especially active in inflammatory responses, but the division is not absolute.

COX inhibition has more than one consequence

Inflammation

↓ Pain- and fever-related
PGs

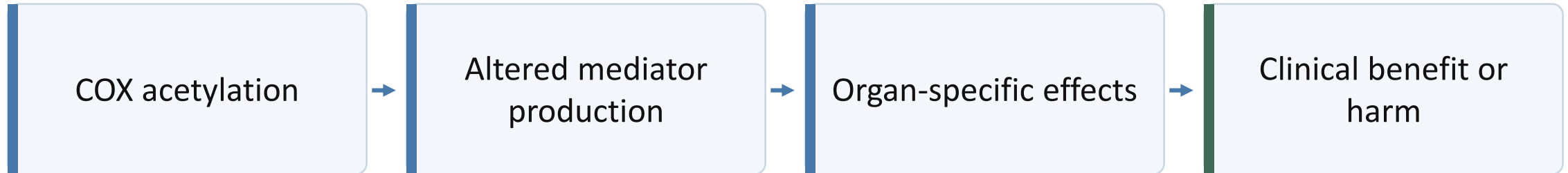
Gastric mucosa

↓ Protective PGs

Platelets

↓ TxA₂ activation

The therapeutic–toxic trade-off is mechanistic



- One enzyme system generates mediators serving different organs.
- A single inhibitor can therefore modify inflammation, gastric defense and hemostasis.
- Clinical evaluation should not treat these organ effects as unrelated events.

Aspirin-associated toxicity pathways

Aspirin exposure

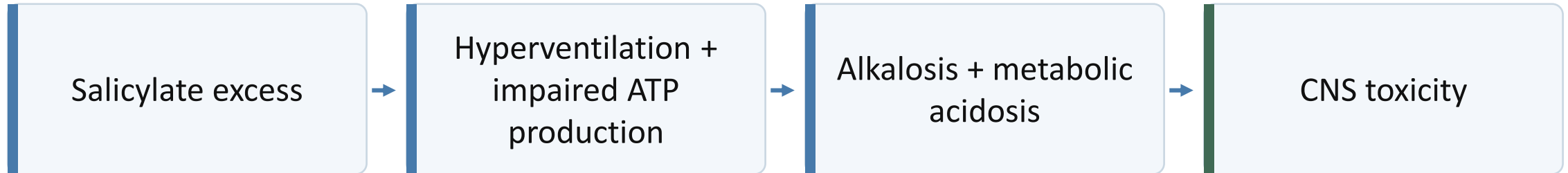
```
graph TD; A[Aspirin exposure] --> B[Acute: Acid-base effects]; A --> C[Gastric: Mucosal injury]; A --> D[Platelets: ↓ aggregation];
```

Acute: Acid-base effects

Gastric: Mucosal injury

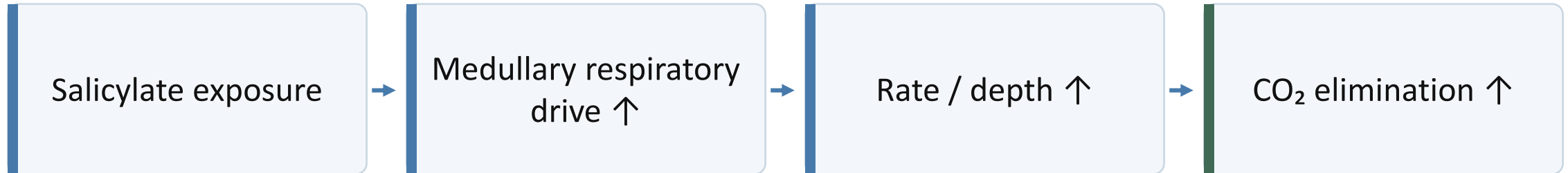
Platelets: ↓ aggregation

Acute salicylate poisoning: Mechanistic overview



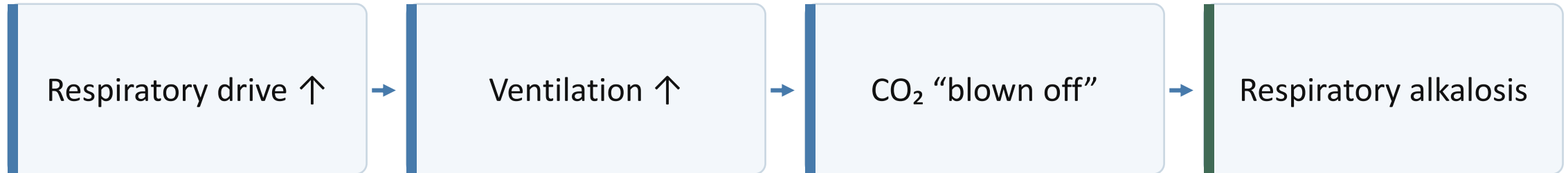
- Early stimulation of the medullary respiratory center causes hypocapnia.
- Mitochondrial uncoupling and Krebs-cycle inhibition disrupt energy metabolism.
- Acidosis increases the nonionized salicylate fraction reaching the CNS.

Medullary stimulation occurs early



- Salicylate toxicity stimulates the respiratory center in the medulla.
- Respirations increase in both rate and depth.
- This effect precedes or coexists with later metabolic abnormalities.

Hyperventilation reduces carbon dioxide



- Increased alveolar ventilation expels CO₂ more rapidly.
- A fall in CO₂ shifts the blood acid–base system toward alkalinity.
- The source describes this initial consequence as respiratory alkalosis.

Respiratory alkalosis is not the complete disorder

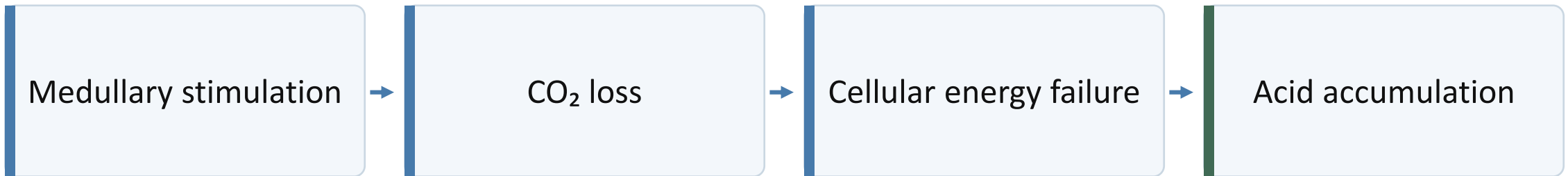
Respiratory component

- Increased rate and depth
- Excess CO₂ loss
- Alkalinizing effect

Metabolic component

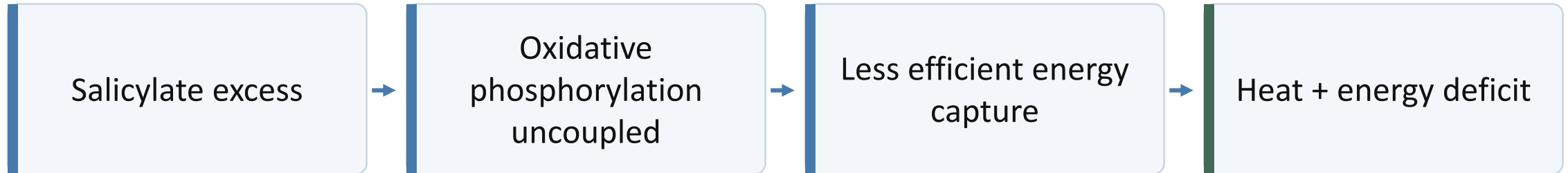
- Impaired oxidative metabolism
- Lactate accumulation
- Acidifying effect

A changing acid–base profile is expected



Sequence is schematic; Individual clinical courses vary.

Mitochondrial uncoupling is central to toxicity



- Salicylates uncouple oxidative phosphorylation.
- Energy capture from oxidative metabolism becomes inefficient.
- This change helps explain increased heat generation and metabolic stress.

Why uncoupling is a systemic problem

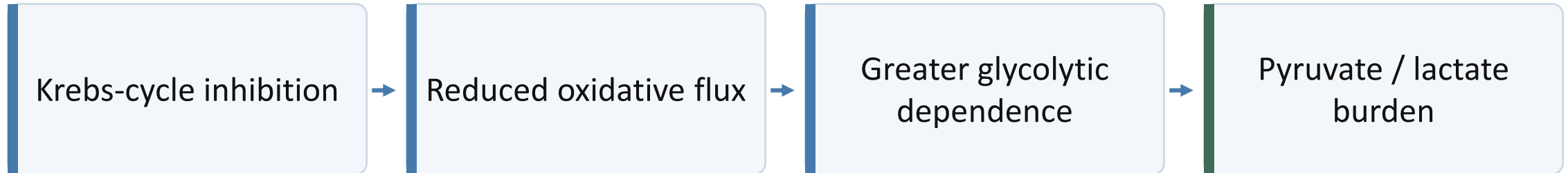
Coupled state

- Oxidation
- ATP generation
- Efficient energy transfer

Uncoupled state

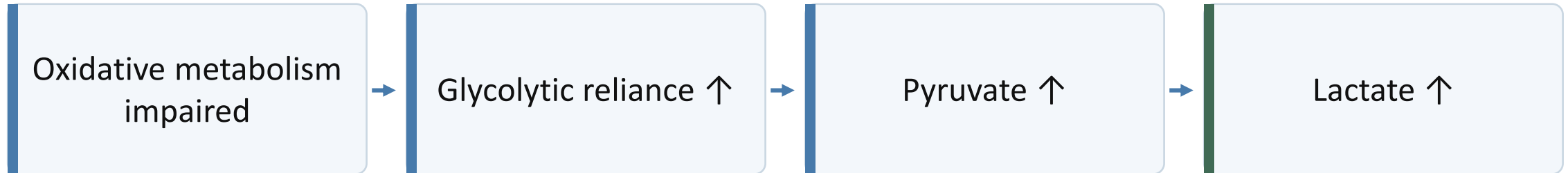
- Oxidation persists
- ATP generation inefficient
- Heat / metabolic strain

The Krebs cycle is also inhibited



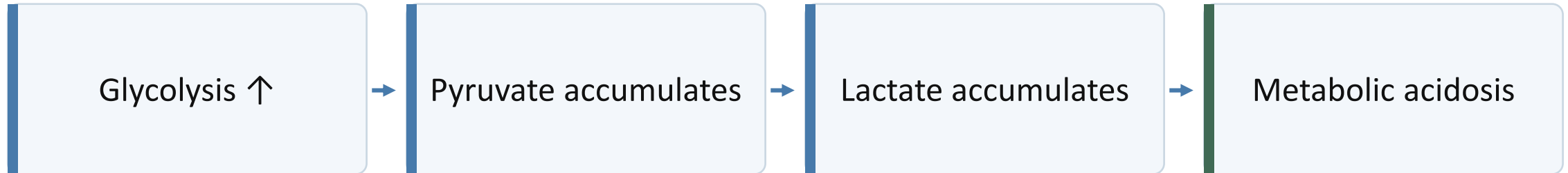
- The source identifies Krebs-cycle inhibition during toxicity.
- This further compromises aerobic energy metabolism.
- The metabolic shift favors dependence on glycolytic pathways.

Glycolysis becomes more important



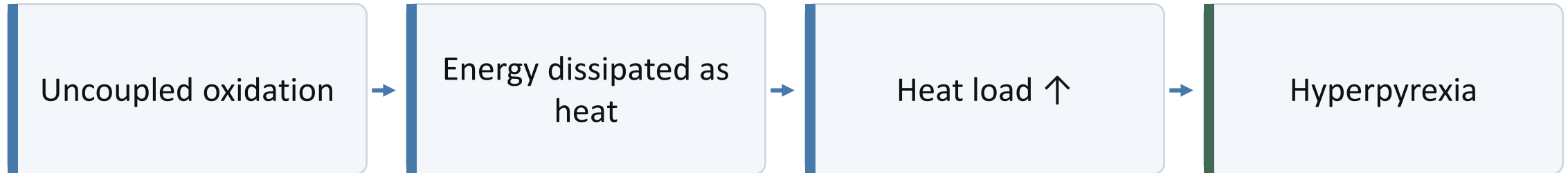
- With oxidative pathways disrupted, cells rely more heavily on glycolysis.
- Pyruvate production and subsequent lactate accumulation increase.
- This explains why metabolic acidosis is linked to energy derangement.

Pyruvate and lactate accumulation



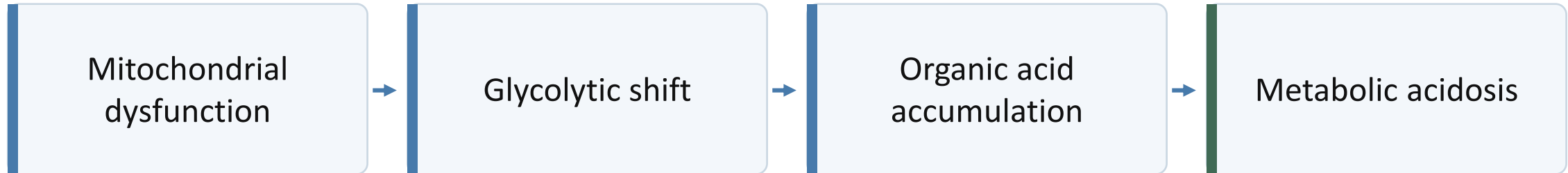
- Accumulation of pyruvate and lactate.
- These metabolites mark a shift away from efficient oxidative energy production.
- The rising acid burden contributes to systemic metabolic acidosis.

Hyperpyrexia follows disturbed energy coupling



- Mitochondrial uncoupling changes how energy is released.
- Heat generation increases rather than being efficiently conserved as ATP.
- Severe temperature elevation is a pathophysiologic consequence in the source.

Metabolic acidosis emerges from energy failure

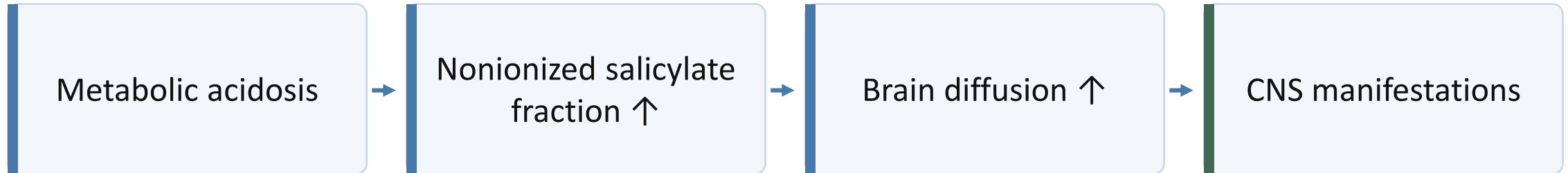


- Oxidative phosphorylation is uncoupled.
- Krebs-cycle activity is inhibited.
- Greater glycolytic reliance and lactate accumulation produce an acidifying burden.

Two mechanisms point in opposite pH directions

Mechanism	Primary event	Acid–base direction
Respiratory	Excess CO ₂ elimination	Alkalinizing
Metabolic	Pyruvate / lactate accumulation	Acidifying

Acidemia alters salicylate distribution



- Metabolic acidosis increases the nonionized salicylate fraction.
- Nonionized salicylate can diffuse into the brain more readily.
- This directly links systemic acid–base derangement to neurologic toxicity.

Why ionization matters for the brain

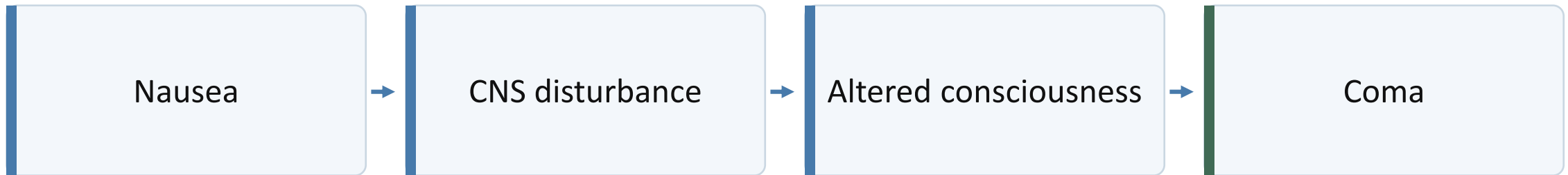
More ionized

- Less lipid-permeant fraction
- Less favored brain diffusion

More nonionized

- Favored during acidosis
- Greater brain entry

Neurologic toxicity has a clinical spectrum



Sequence is schematic; Individual clinical courses vary.

Acute intoxication links organs through physiology

Respiratory

Hyperventilation / CO₂
loss

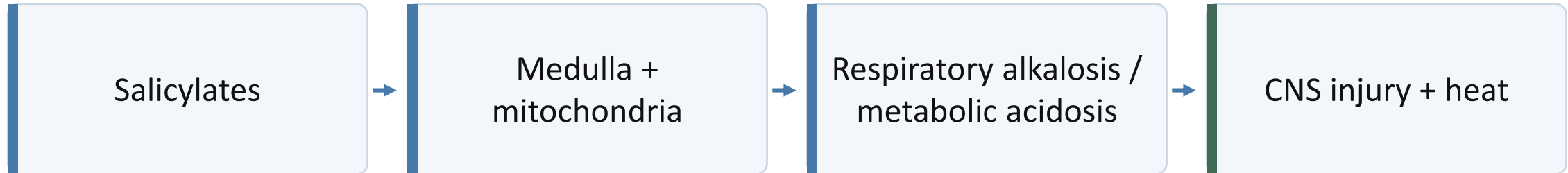
Metabolic

Heat + lactate generation

Neurologic

Nonionized drug enters
CNS

Acute toxicity: Integrated causal map



- The alkalinizing and acidifying mechanisms arise from different targets.
- The CNS effect is promoted by the acidifying component.
- Uncoupling also explains hyperpyrexia, not merely acid production.

Ingested mass does not equal a triage threshold

- Potentially fatal ingestion of 2–4 g in children and 10–30 g in adults.
- Survival after substantially larger amounts is also described.
- These historical textbook ranges are not safe doses or stand-alone prognostic thresholds.

Case: Early acute intoxication

- Hypothetical patient with aspirin overdose develops rapid, deep breathing.
- Which organ target explains the respiratory pattern?
- What acid–base tendency follows increased CO₂ elimination?

Explain the mechanism before revealing the answer

Case: Later metabolic deterioration

- The same hypothetical patient develops severe temperature elevation and neurologic decline.
- What two mitochondrial pathways are disrupted?
- Why does acidosis worsen cerebral exposure to salicylate?

Explain the mechanism before revealing the answer

Chronic salicylism is a prolonged-exposure syndrome

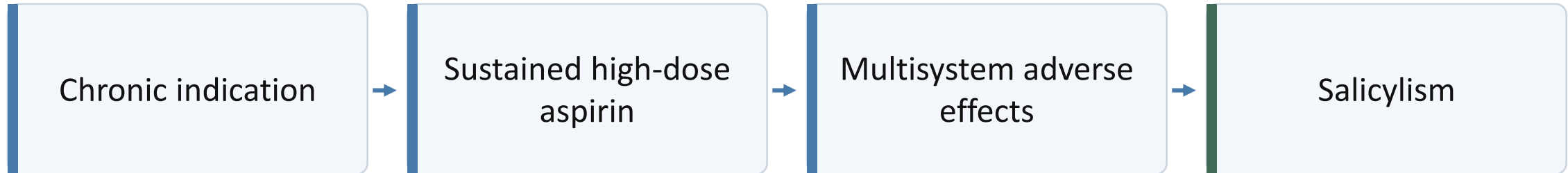
Exposure pattern

- Repeated daily use
- Long time course
- High-dose setting

Affected systems

- Central nervous system
- Gastrointestinal tract
- Platelet function

Prolonged high-dose use shapes the risk



- Unlike single acute overdose, chronic salicylism reflects cumulative exposure.
- The source associates the syndrome with daily ingestion of 3 g or more over long periods.
- This is a descriptive source association—not a recommendation or safety cutoff.

Headache and dizziness may be early clues

- Headache is included in the reported chronic syndrome.
- Dizziness adds a nonspecific neurologic symptom.
- The exposure history gives these common symptoms diagnostic meaning.

Tinnitus is a characteristic sensory clue

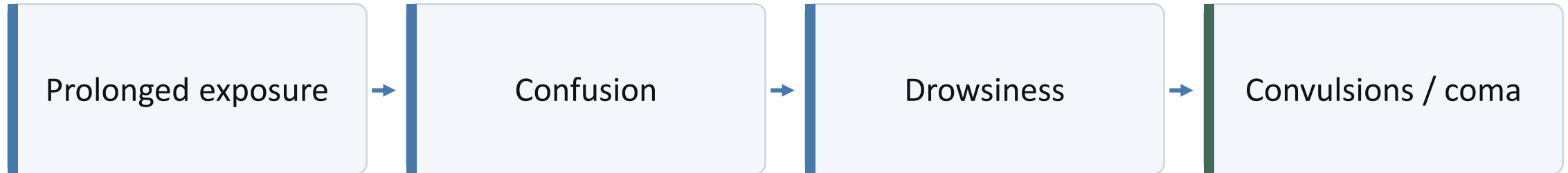
Subjective auditory symptom

- Tinnitus
- Ringing in the ears

Functional effect

- Hearing impairment
- May coexist with neurologic complaints

Mental-status changes are part of salicylism



- Mental confusion and drowsiness are described manifestations.
- These signify clinically important CNS involvement.
- Progression to convulsions or coma marks severe deterioration.

Gastrointestinal symptoms may precede hemorrhage

- Nausea, vomiting and diarrhea are included in chronic toxicity.
- Aspirin-related gastric injury adds a structural source of morbidity.
- Symptoms alone cannot establish the depth of mucosal injury.

Chronic toxicity: Symptom clusters

Auditory

Tinnitus; Hearing change

Neurologic

Headache to altered
consciousness

Gastrointestinal

Nausea; Vomiting;
Diarrhea

The gastric mucosa normally resists a hostile lumen

Intact mucosal defense

Mucus / bicarbonate shield

Surface epithelium intact

Mucosal blood flow + repair

Aspirin-impaired defense

Reduced mucus / HCO_3^-

Surface erosion risk

Reduced repair and protection

Prostaglandins sustain gastric protection

Gastric PGE₂ / PGI₂

```
graph TD; A[Gastric PGE2 / PGI2] --> B[Mucus + bicarbonate]; A --> C[Mucosal blood flow]; A --> D[Epithelial restitution];
```

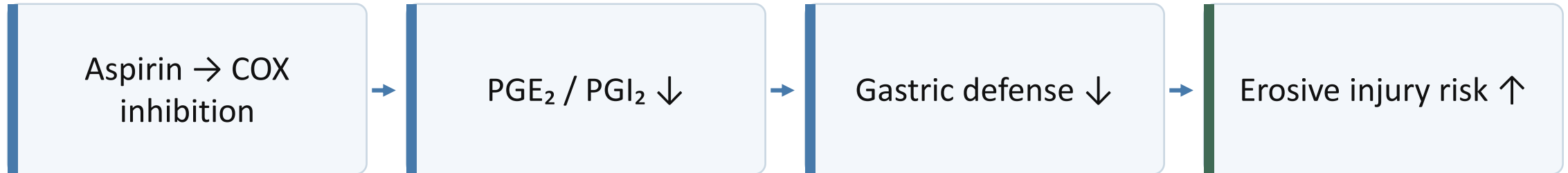
The diagram is a flowchart illustrating the role of gastric prostaglandins in maintaining gastric protection. At the top, a light blue box with rounded corners and a dark blue vertical bar on its left side contains the text 'Gastric PGE₂ / PGI₂'. A blue arrow points down from this box to a horizontal line. From this line, three separate blue arrows point down to three separate light blue boxes with rounded corners and dark blue vertical bars on their left sides. The first box on the left contains the text 'Mucus + bicarbonate', the middle box contains 'Mucosal blood flow', and the third box on the right contains 'Epithelial restitution'.

Mucus + bicarbonate

Mucosal blood flow

Epithelial restitution

Aspirin inhibits COX-dependent mucosal defense

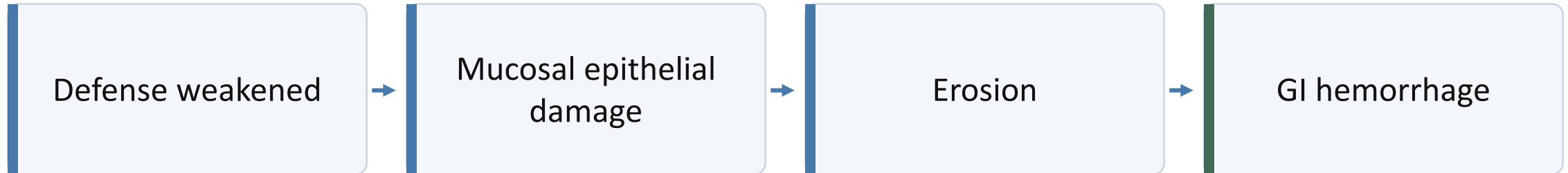


- Nonselective cyclooxygenase inhibition lowers gastroprotective prostaglandins.
- Reduced prostaglandin action weakens mucus, bicarbonate and epithelial repair.
- The result is increased vulnerability to acid and peptic injury.

Gastropathy, gastritis and erosion are not synonymous

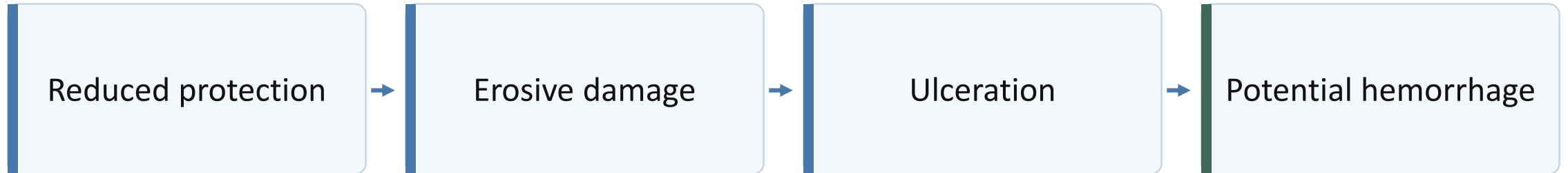
Term	Key tissue finding
Gastropathy	Epithelial injury; few inflammatory cells
Acute gastritis	Neutrophilic inflammation
Erosion	Superficial mucosal defect

A superficial erosion can become clinically important



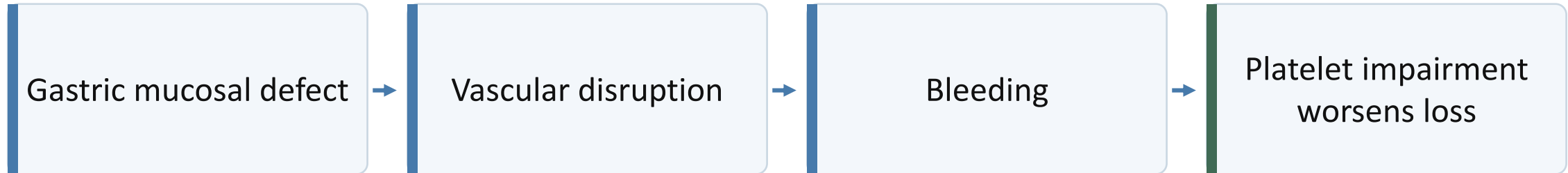
- The aspirin section emphasizes acute erosive gastritis as a common morphologic consequence.
- Erosion exposes fragile tissue to luminal injury.
- Bleeding can occur even before deep ulceration is present.

Gastric ulceration represents deeper injury



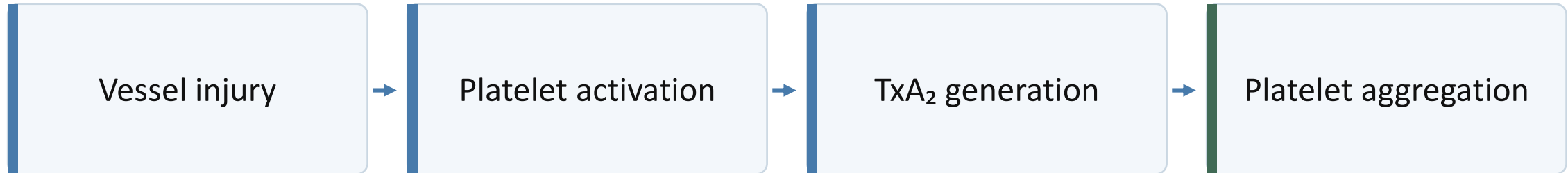
- Sustained or severe mucosal injury may progress to gastric ulceration.
- The Robbins aspirin section identifies ulceration as a possible consequence.
- Depth of injury and bleeding risk are not captured by symptom intensity alone.

GI bleeding is a major morbidity mechanism



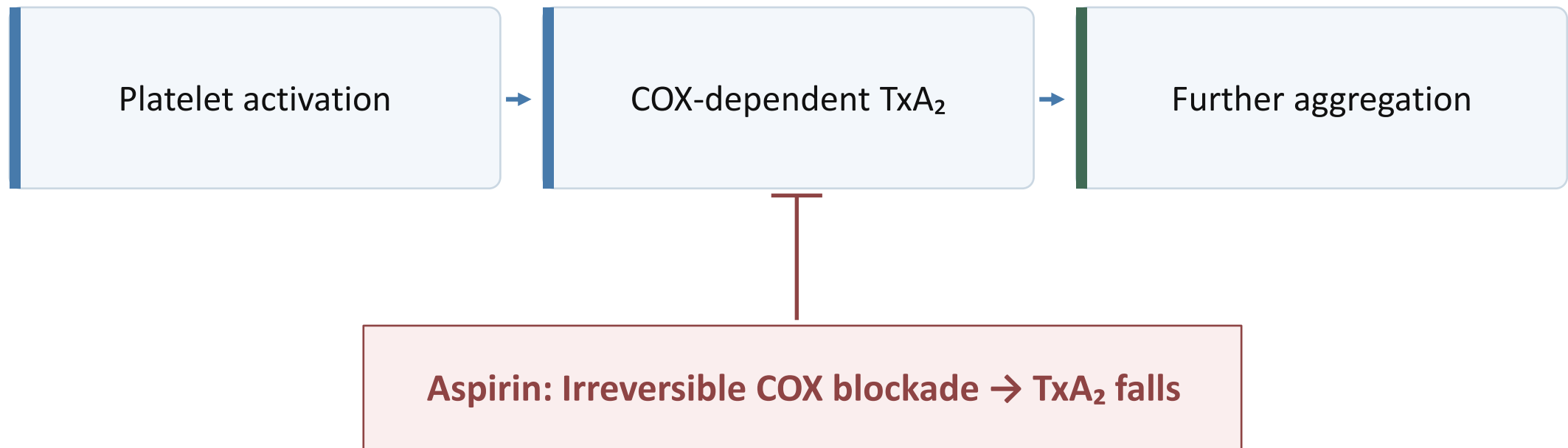
- Erosive gastritis can produce gastrointestinal bleeding.
- Gastric ulceration may compound blood loss.
- Aspirin-associated platelet dysfunction can further aggravate hemorrhage.

Primary hemostasis depends on platelet recruitment

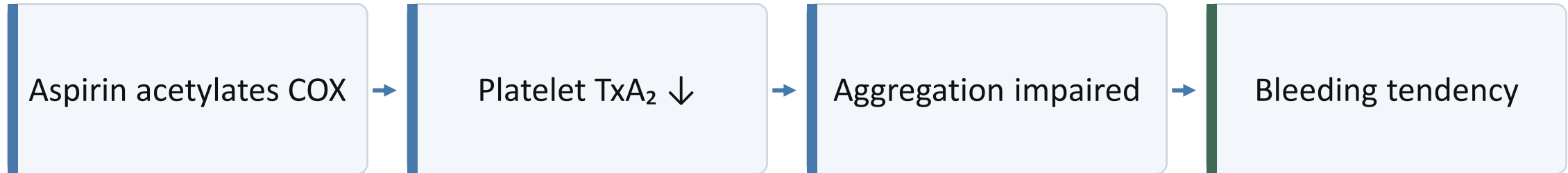


- Platelets adhere and become activated at sites of vascular injury.
- Activated platelets release and generate mediators that recruit more platelets.
- Thromboxane A₂ is a potent amplifier of platelet aggregation.

TxA₂ depends on platelet cyclooxygenase



Irreversible inhibition differentiates aspirin



- Aspirin irreversibly inactivates platelet cyclooxygenase.
- Platelet thromboxane A₂ synthesis is therefore persistently impaired.
- This produces a platelet-function defect rather than direct deficiency of clotting factors.

Petechiae reflect impaired primary hemostasis

Mechanism

- TxA_2 production blocked
- Platelet aggregation impaired

Clinical morphology

- Petechial hemorrhages
- Skin and visceral sites

Why gastric hemorrhage can be disproportionately severe

Gastrointestinal hemorrhage

```
graph TD; A[Gastrointestinal hemorrhage] --> B[Erosion / ulcer: Injured surface]; A --> C[Platelet COX block: Poor aggregation];
```

The diagram is a flowchart with a light blue background. At the top, a light blue box with a dark blue border contains the text 'Gastrointestinal hemorrhage'. A vertical blue arrow points down from this box to a horizontal blue line. From this line, two vertical blue arrows point down to two separate light blue boxes with dark blue borders. The left box contains the text 'Erosion / ulcer: Injured surface' and has a dark red vertical bar on its left side. The right box contains the text 'Platelet COX block: Poor aggregation' and has a dark blue vertical bar on its left side.

Erosion / ulcer: Injured surface

Platelet COX block: Poor aggregation

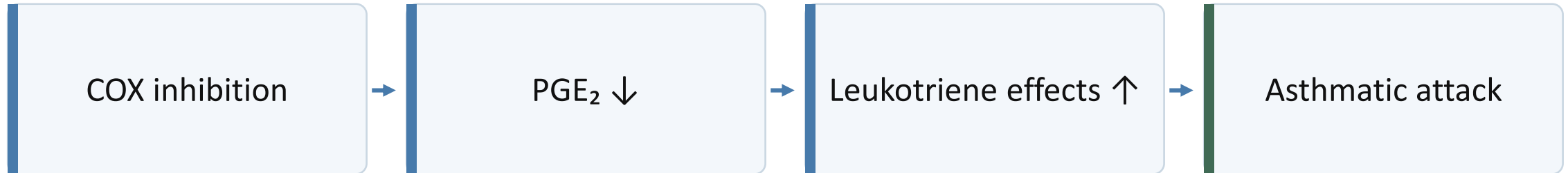
Aspirin-related bleeding is an acquired platelet defect

Category	Dominant mechanism	Illustrative pattern
Aspirin-associated	Platelet function impaired	Petechiae / mucosal bleeding
Clotting-factor deficiency	Coagulation activity deficient	Deep bleeding / hematomas

Aspirin and other COX inhibitors share gastric risk

Drug class	COX inhibition	Gastric protection
Aspirin / nonselective NSAIDs	COX-1 and COX-2	Risk of mucosal injury
Selective COX-2 inhibitors	Predominantly COX-2	Risk reduced in some settings, not abolished

Aspirin sensitivity may present with respiratory symptoms



- Uncommon aspirin-sensitive asthma with recurrent rhinitis and nasal polyps.
- Even small amounts may provoke urticaria and asthmatic attacks in affected patients.
- The implicated pathway involves COX inhibition, reduced PGE₂ and enhanced leukotriene-mediated effects.

Additional adverse drug findings

Respiratory association

- Salicylate-sensitive asthma
- Distinct from medullary hyperventilation

Renal association

- Tubulointerstitial injury
- Papillary necrosis in ADR table

Acute toxicity and chronic salicylism: A comparison

Domain	Acute toxicity	Chronic salicylism
Metabolism	Acid–base disturbance	Not defining in supplied section
Neuro	CNS entry with acidosis	Tinnitus, confusion, seizures
Stomach	Not the central focus	Erosions and ulcers
Hemostasis	Not the central focus	TxA ₂ -related bleeding

Case: Chronic exposure with tinnitus

- Hypothetical patient with persistent aspirin use for inflammatory pain develops tinnitus and dizziness.
- Later they report dark gastrointestinal bleeding symptoms.
- What two independent aspirin effects should be suspected?

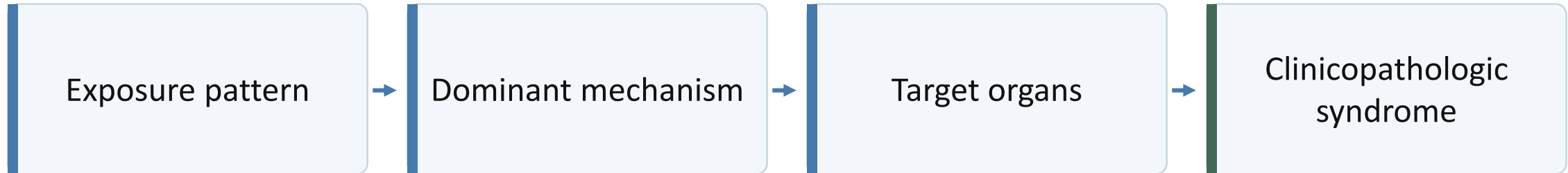
Explain the mechanism before revealing the answer

Case: Interpreting petechiae

- A hypothetical aspirin-exposed patient develops petechiae without a documented coagulation-factor deficiency.
- Which arm of hemostasis is most directly affected?
- Which platelet mediator is decreased?

Explain the mechanism before revealing the answer

A mechanism-first framework prevents missed connections



- Recognize exposure pattern before attaching a syndrome label.
- Identify respiratory and metabolic disturbances as separate acute mechanisms.
- In chronic exposure, assess auditory, neurologic, gastric and bleeding findings together.

Review: Five relationships worth retaining

- Aspirin irreversibly acetylates cyclooxygenase.
- Medullary stimulation causes respiratory alkalosis.
- Mitochondrial disruption causes hyperpyrexia and metabolic acidosis.
- Acidosis favors nonionized salicylate brain entry.
- Gastric injury and TxA₂ inhibition cooperate to increase bleeding.

References and source scope

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026).
- Primary: Ch. 9, “Aspirin (Acetylsalicylic Acid),” pp. 385–386.
- Context: Ch. 3 (eicosanoids); Ch. 4 (primary hemostasis); Ch. 13 (platelet dysfunction); Ch. 17 (gastric injury); asthma section.