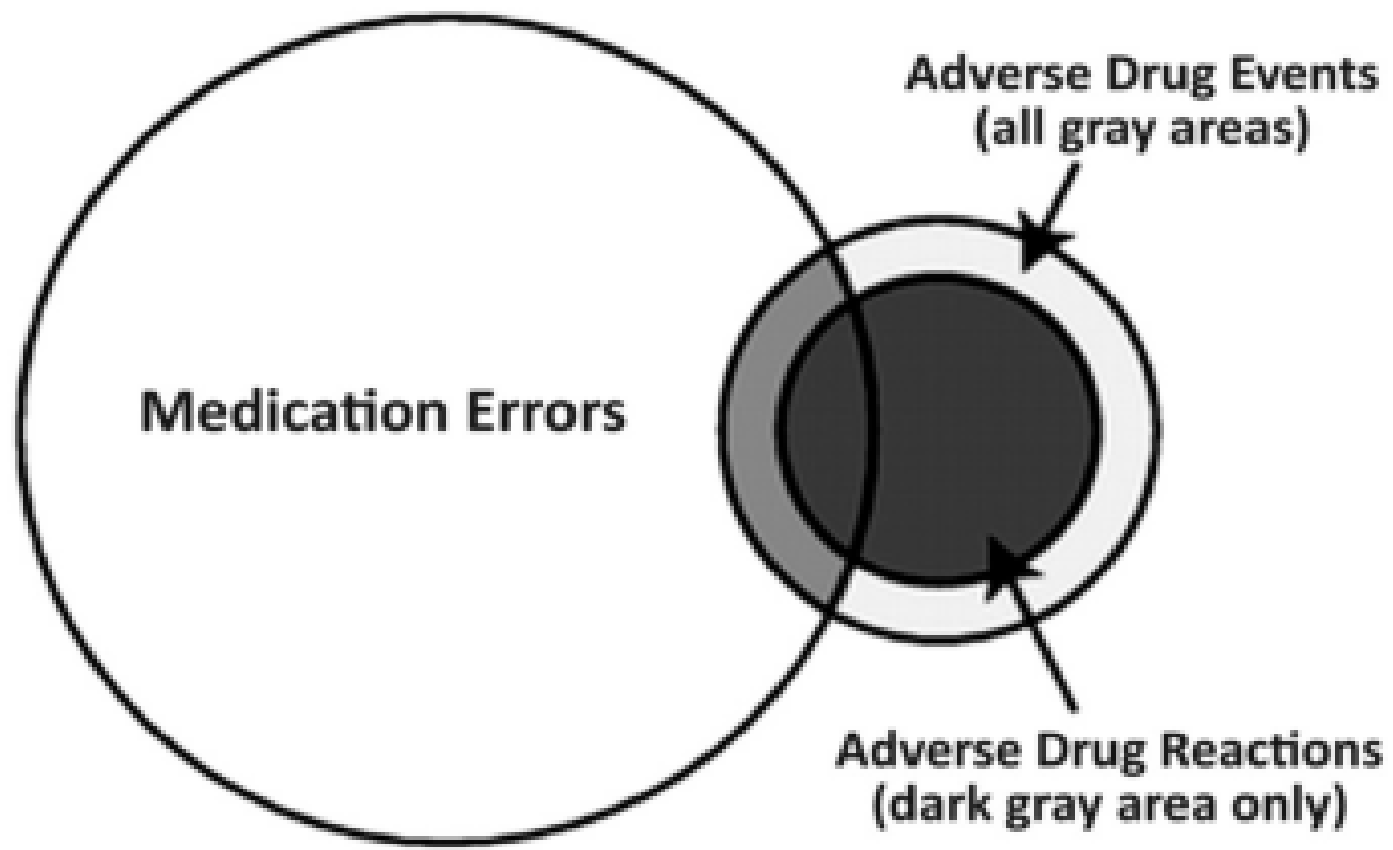


Adverse drug reactions (Side,
unwanted, Adverse event or
untoward effects)

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A harmful or significantly unpleasant effect caused by a drug at doses intended for therapeutic effect (or prophylaxis or diagnosis) which warrants reduction of dose or withdrawal of the drug and/or foretells hazard from future administration



Medication Errors

**Adverse Drug Events
(all gray areas)**

**Adverse Drug Reactions
(dark gray area only)**

Types of Adverse Drug Reactions

| Type of ADRs | Characteristics | Examples |
|--------------|---|--|
| Type A | <ul style="list-style-type: none"> -Dose-related -Related to a pharmacological action of drug -Predictable from known pharmacology | <ul style="list-style-type: none"> -Nephrotoxicity caused by aminoglycosides -Anticholinergic effects of tricyclic antidepressants |
| Type B | <ul style="list-style-type: none"> -Not dose-related -Uncommon -No relation to a pharmacological action of the drug | <ul style="list-style-type: none"> -Penicillin- induced urticaria -Anticonvulsant hypersensitivity syndrome reaction |
| Type C | <ul style="list-style-type: none"> -Uncommon -Long term exposure of drugs | <ul style="list-style-type: none"> -Hypothalamic-pituitary-adrenal axis suppression by corticosteroids |
| Type D | <ul style="list-style-type: none"> -Prolonged exposure to a drug | <ul style="list-style-type: none"> -Tardive dyskinesia caused by antipsychotic medication |
| Type E | <ul style="list-style-type: none"> -Termination of treatment | <ul style="list-style-type: none"> -Tachyphylaxia |

Conclusion

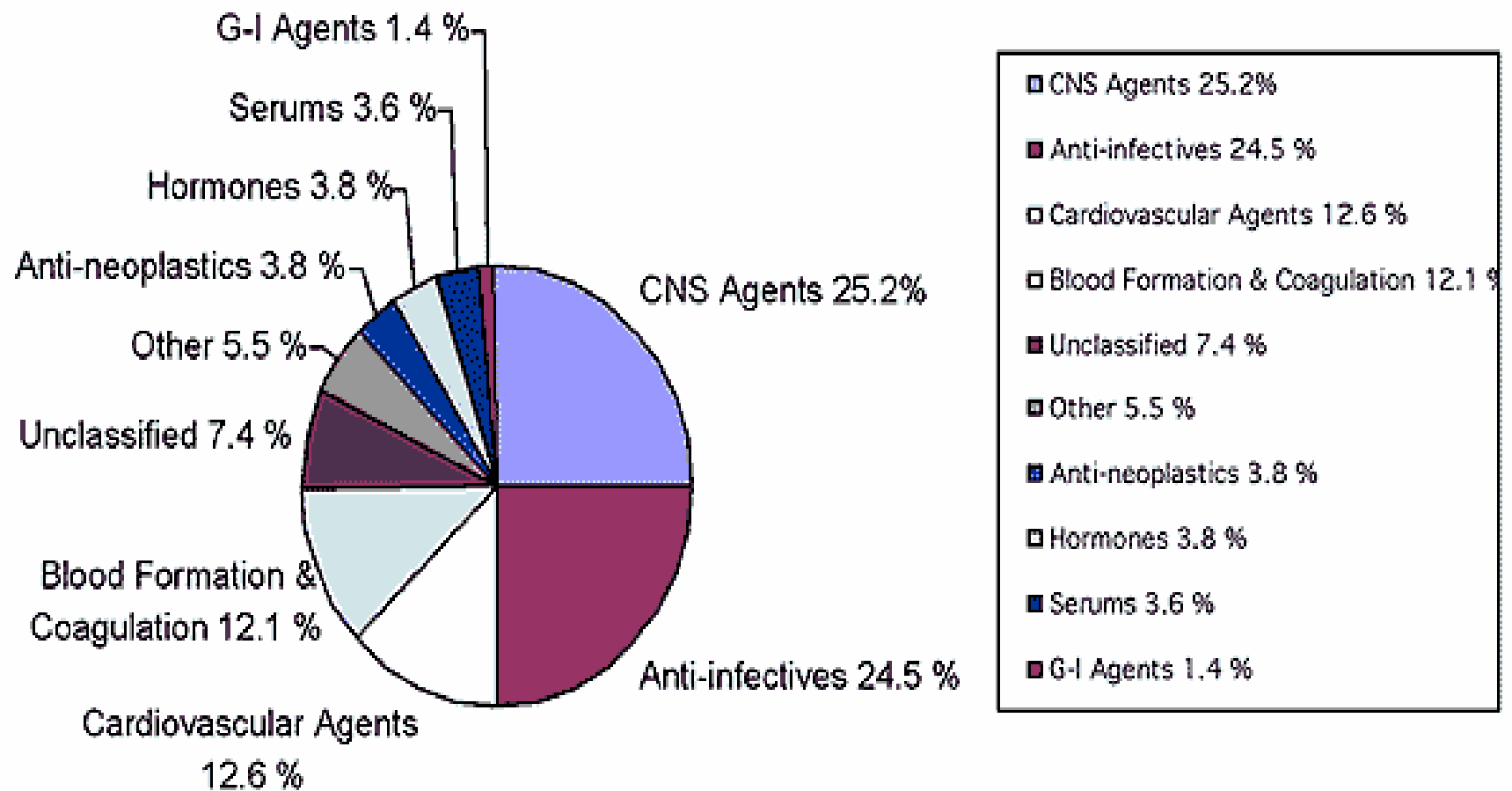
Types of allergic reactions

- **Type I – immediate**
- **Type II - cytotoxic antibody (IgG, IgM)**
- **Type III - serum sickness**
- **Type IV - delayed hypersensitivity**

GRADING OF SEVERITY OF ADVERSE DRUG REACTIONS :

- ❑ **Mild** : No therapy, antidote or prolongation of hospitalization is required.
- ❑ **Moderate**: Requires change in drug therapy, specific treatment or prolongs hospital stay.
- ❑ **Severe**: **Potentially** life-threatening, causes permanent damage or requires intensive medical treatment.
- ❑ **Lethal** : Directly or indirectly contributes to death of the patient.

Figure 1: ADRs by Drug Class



■ Incidence of ADR more

- Polypharmacy
- Elderly
- Children
- Patient with multiple diseases
- Drug Abusers and addicts

Diagnosis and attribution of causality

- ❑ If a patient is taking medicines, the differential diagnosis should include the possibility of an adverse drug reaction(OTC or OCP)
- ❑ 1- Timing
- 2-Pattern recognition(digoxin) and background frequency of the event (headache and aplastic anemia)
- ❑ 3- Investigations (TDM, biopsy, allergy test , organ function)

- Management : (the severity of the reaction, dose reduction, The waiting period and cross-sensitivity)

Beta-blockers

■ Adverse effects:

Fatigue, cold hands and feet, exacerbation of intermittent claudication and raynaud phenomenon, bronchospasm, bradycardia, heart failure, sleep disturbances including nightmares, depression, confusion, hypoglycaemia or hyperglycaemia, exacerbation of psoriasis

□ Drug interaction:

Indral+lidocaine

Indral+ergotamine C

Beta-blockers+CCB

Beta-blockers+ antiarrhythmic class I

ACE inhibitors and ARBs

- Hypotension(first dose phenomenon), angioedema, dry cough(20%), hyperkalemia: **Patients with renal failure,**
- **Drug interaction**
 - K sparing diuretics
 - NSAIDs
- Renal failure, Sexual dysfunction
- Cough (20 %) } **Kinin-related (?)**
- Angioedema }
- With captopril especially: neutropenia, nephrotic syndrome, skin rash, taste disturbances (SH group-related).

ARB: Less decrease in GFR in volume depleted states

ARB: Less side effects especially cough, angioedema

Diuretics

■ **Thiazides:**

Hypokalemia

Dehydration

Hyperglycemia

Hyperuricemia

Impotence

Hyponatremia

Metabolic alkalosis

Hypercalcemia

□ **Loop diuretics : Hypocalcemia and ototoxicity and Orthostatic hypotension**

Furosemide + alluporinol: skin reaction

Furosemide + AMGs: ototoxicity

Furosemide + ACEinhibitors or manitol: renal insufficiency

Furosemide + Li

Furosemide + Dig

Acetazolamide

■ Hyperchloremic metabolic acidosis

Kidney stone formation

Hypokalemia

Anaphylactic shock (sensitivity to sulfanamids)

■ Spironolactone:

Hyperkalemia: ↑ risk by NSAIDs, beta-blockers, ACE inhibitors

Gynecomastia

□ **Triamterene:** Kidney stone

Triamterene + Indomethacin: ARF

□ **Mannitol:** Edema, Hypernatremia and hyperkalemia

□ Verapamil

Constipation, gingival hyperplasia, flushing, headache, ankle edema, hyperprolactinemia and with high doses: hypotension. Bradycardia , AV block and CHF

■ Diltiazem

has the best properties of the nifedipine- and verapamil-relatives can be used for hypertension, angina and arrhythmias with fewer side effects than the others

Dis: ↑ Cyclosporin concentration, ↑ Dig concentration

■ AMIODARONE

Pulmonary fibrosis, Altered thyroid tests, Hypo- & Hyperthyroidism, Photosensitivity, Constipation, Hepatic dysfunction, Corneal deposits

Torsade de points:

Abs, TCAs, Antifungals, Antipsychotics

Dis:

Amiodarone + Dig

Amiodarone + warfarin

■ QUINIDINE

GI disturbances, Cinchonism, Quinidine syncope (due to torsade de pointes) , Hypotension (iv administration)

■ PROCAINAMIDE

Lupus-like syndrome, Agranulocytosis, Nausea & diarrhea
Torsade de pointes, Hypotension & QRS widening

■ LIDOCAINE

Seizure , Paresthesia, Nausea, Tremor and Nystagmus

Digoxin

- پاسخ اولیه: (تغییرات زودرس در ECG)
- افزایش PR interval به دلیل کاهش سرعت هدایت گره دهلیزی- بطنی
- مسطح شدن موج T
- افزایش دوره تحریک ناپذیری AV
- کاهش سرعت ضربان بطنی
- QT کوتاه - T معکوس - افت قطعه ST (اثر پاراسمپاتیکی بر قلب)
- افزایش فعالیت قلب به دلیل تجمع کلسیم داخل سلول که می تواند در قلب extrasystole، Tachycardia و یا Fibrillation ایجاد کند

■ درمان مسمومیت:

- ❖ قطع مصرف دیگوکسین و دیورتیکهای دفع کننده پتاسیم
- ❖ تجویز کلرور پتاسیم در صورت بروز هیپوکالمی
- ❖ تجویز داروهای ضد آریتمی (لیدوکائین، فنی توئین یا پروپرانولول)
- ❖ آنتی بادی اختصاصی دیگوکسین (Digibind)

DIIs : Amiodarone, clarithromycine, itraconazole, verapamil

Interactions with WARFARIN

- Reduced absorption
- Reduced protein binding
- Altered clearance – P450 *induction* by rifampicin, barbiturate or phenytoin; P450 *inhibition* by amiodarone, metronidazole and cimetidine.

- Altered vit K intake
- Altered levels of clotting factors –
- Augmented bleeding tendency –

LMWH vs. Unfractionated HEPARIN

- **less likely to cause thrombocytopenia or osteoporosis long-term**

- **Cannot be monitored by APTT**

- specific anti-Xa assay needed

- **Not fully reversed by protamine**

ANTIPLATELET DRUGS

- **ASPIRIN**(GI effects)
- **CLOPIDOGREL AND TICLOPIDINE** (neutropenia 2 %)
, thrombotic thrombocytopenic purpura.
- **Abciximab , Eptifibatide , Tirofiban**
(Thrombocytopenia and, of course, bleeding)
- **DIPYRIDAMOLE**

جدول ۳- مقایسه شدت برخی از شایع ترین واکنش های ناخواسته TCA

| افزایش وزن | اختلال جنسی | ناراحتی گوارشی | افت فشار خون وضعیتی | اثرات آنتی کولینرژیک | بی خوابی یا تحریک پذیری | اثرات آرام بخشی | دارو |
|------------|-------------|----------------|---------------------|----------------------|-------------------------|-----------------|---------------|
| ++ | + | -/+ | +++ | ++ | + | ++ | Desipramine |
| ++ | + | -/+ | ++ | ++ | + | ++ | Nortriptyline |
| +++ | ++ | -/+ | ++++ | ++++ | +/- | ++++ | Amitriptyline |
| ++ | ++ | -/+ | +++ | +++ | -/+ | +++ | Imipramine |
| ++ | ++ | -/+ | ++++ | ++++ | -/+ | ++++ | Doxepin |
| +++ | ++ | + | +++ | +++ | + | +++ | Clomipramine |

Serotonin Syndrome

| Neuromuscular Effects | Autonomic Effects | Mental Status Changes |
|--|---|------------------------------|
| Ataxia – loss of co-ordination | Tachycardia | |
| Hyperreflexia – heightened reflexes | Labile blood pressure | Confusion |
| Myoclonus – Muscle twitching (spontaneous or inducible) | Hyperthermia: Mild < 38.5°C, severe ≥ 38.5°C | Agitation - restlessness |
| Ocular Clonus | Hypertension | Memory loss |
| Weakness | Diaphoresis | Dizziness |
| Trembling, shivering or shaking | Mydriasis | Hallucinations |
| Akathisia – restlessness | Diarrhoea | Hypomania |
| Hypertonia – rigidity | Fever | Anxiety |
| Bradykinesia – slow movements | Seizures Weakness | Coma |

NMS

| | |
|--|---------------------------|
| High temperature | Sweating |
| Unstable blood pressure: high & low | Pale skin |
| Irregular heart beat: Arrhythmia | Tremor |
| Rapid heartbeat: Tachycardia | Muscle Rigidity/stiffness |
| Incontinence | Kidney failure |
| Elevated creatinine phosphokinase (CPK) - a sign of muscle breakdown | Respiratory failure |
| | Drooling |
| Increased White Blood Cell Count | Difficulty in speaking |
| Agitation | Seizures |

Receptor Affinities of 2nd Generation Antipsychotics

| Drug | Dopamine (D2) | Serotonin | | Alpha 1 adrenergic | Histamine (H1) |
|-------------|---------------|-----------|-------|--------------------|----------------|
| | | 5HT2A | 5HT2C | | |
| Clozapine | + | +++++ | +++ | +++ | ++ |
| Olanzapine | ++ | +++++ | +++++ | - | ++ |
| Quetiapine | + | + | + | +++ | ++ |
| Risperidone | +++++ | +++++ | ++ | + | ++++ |
| Ziprasidone | +++++ | +++++ | + | - | ++ |

| Antipsychotic agent | Decreased Incidence of EPS | ↑ Effects on Prolactin Release | Treating Positive Symptoms | Treating Negative Symptoms |
|---------------------|----------------------------|--------------------------------|----------------------------|----------------------------|
| Clozapine | Yes | No | Yes? | Yes |
| Risperidone | Maybe | Yes | Maybe | No |
| Olanzapine | Probably | No | Maybe | Probably |
| Quetiapine | Maybe | No | No | No |

Table 4. Side effects of established antiepileptic drugs.

| CARBAMAZEPINE | CLOBAZAM | CLONAZEPAM | ETHOSUXIMIDE | GABAPENTIN |
|----------------------|-----------------|-------------------------|--------------|--------------|
| * Diplopia | * Fatigue | * Fatigue | * Nausea | * Somnolence |
| * Dizziness | * Drowsiness | * Sedation | Anorexia | * Dizziness |
| * Headache | Dizziness | * Drowsiness | Vomiting | * Ataxia |
| * Nausea | Ataxia | Dizziness | Agitation | * Fatigue |
| Drowsiness | Irritability | Ataxia | Drowsiness | * Diplopia |
| Neutropenia | Aggression | Irritability | Headache | Paraesthesia |
| Hyponatraemia | Hypersalivation | Aggression (children) | Lethargy | Amnesia |
| Hypocalcaemia | Bronchorrhoea | Hyperkinesia (children) | | |
| Orofacial dyskinesia | Weight gain | Hypersalivation | | |
| Cardiac arrhythmia | Muscle weakness | Bronchorrhoea | | |
| | Psychosis | Psychosis | | |

Table 4 (contd). Side effects of established antiepileptic drugs.

| LAMOTRIGINE | PHENOBARBITAL | PHENYTOIN | PIRACETAM | PRIMIDONE |
|--------------|------------------------------|-------------|---------------|---------------------------|
| * Drowsiness | * Fatigue | * Nystagmus | * Diarrhoea | * Fatigue |
| * Diplopia | * Listlessness | * Ataxia | * Weight gain | * Listlessness |
| * Headache | * Tiredness | Anorexia | Insomnia | * Tiredness |
| * Ataxia | * Depression | Dyspepsia | Depression | * Depression |
| * Insomnia | * Insomnia (children) | Nausea | Hyperkinesia | * Psychosis |
| * Tremor | * Distractibility (children) | Vomiting | | * Decreased libido |
| Nausea | * Hyperkinesia (children) | Aggression | | * Impotence |
| Vomiting | * Irritability (children) | Depression | | * Hyperkinesia (children) |
| Aggression | Aggression | Drowsiness | | * Irritability (children) |
| Irritability | Poor memory | Headache | | Nausea |

Table 4 (contd). Side effects of established antiepileptic drugs.

| SODIUM VALPROATE | TIAGABINE | TOPIRAMATE | VIGABATRIN |
|-------------------|----------------------------|--------------------------|----------------|
| * Tremor | * Dizziness | * Anorexia | * Drowsiness |
| * Weight gain | * Headache | * Weight loss | * Fatigue |
| * Hair loss | * Tremor | * Impaired concentration | * Headache |
| Anorexia | * Difficulty concentrating | * Impaired speech | * Ataxia |
| Dyspepsia | Light-headedness | * Paraesthesias | * Nystagmus |
| Nausea | * Nervousness | Kidney stones | * Diplopia |
| Vomiting | Asthenia | Impaired memory | * Irritability |
| Alopecia | Abnormal thinking | Ataxia | * Depression |
| Peripheral oedema | | | Psychosis |

Adverse Reactions of Penicillins

Maculopapular rash & urticaria



Exfoliative dermatitis



Figura 3: Dermatite
esfoliativa. Eritema
de base difuso e esca-
mas lamelares

*Figure 3 : Exfoliative
Dermatitis.
Erythema with a dif-
fuse base and lamel-
lar scales*

Erythema multiform



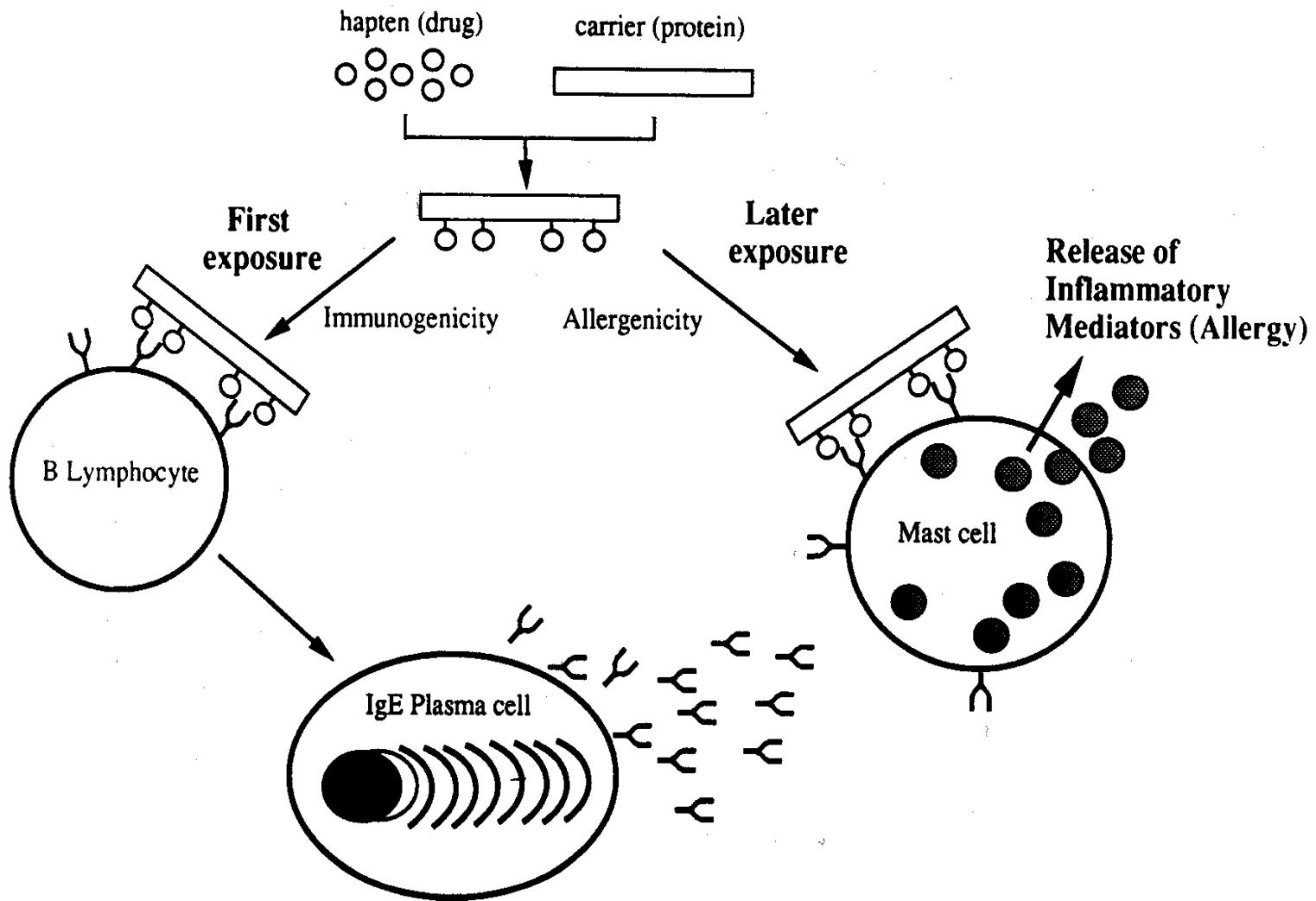
Stevens-Johnson syndrome

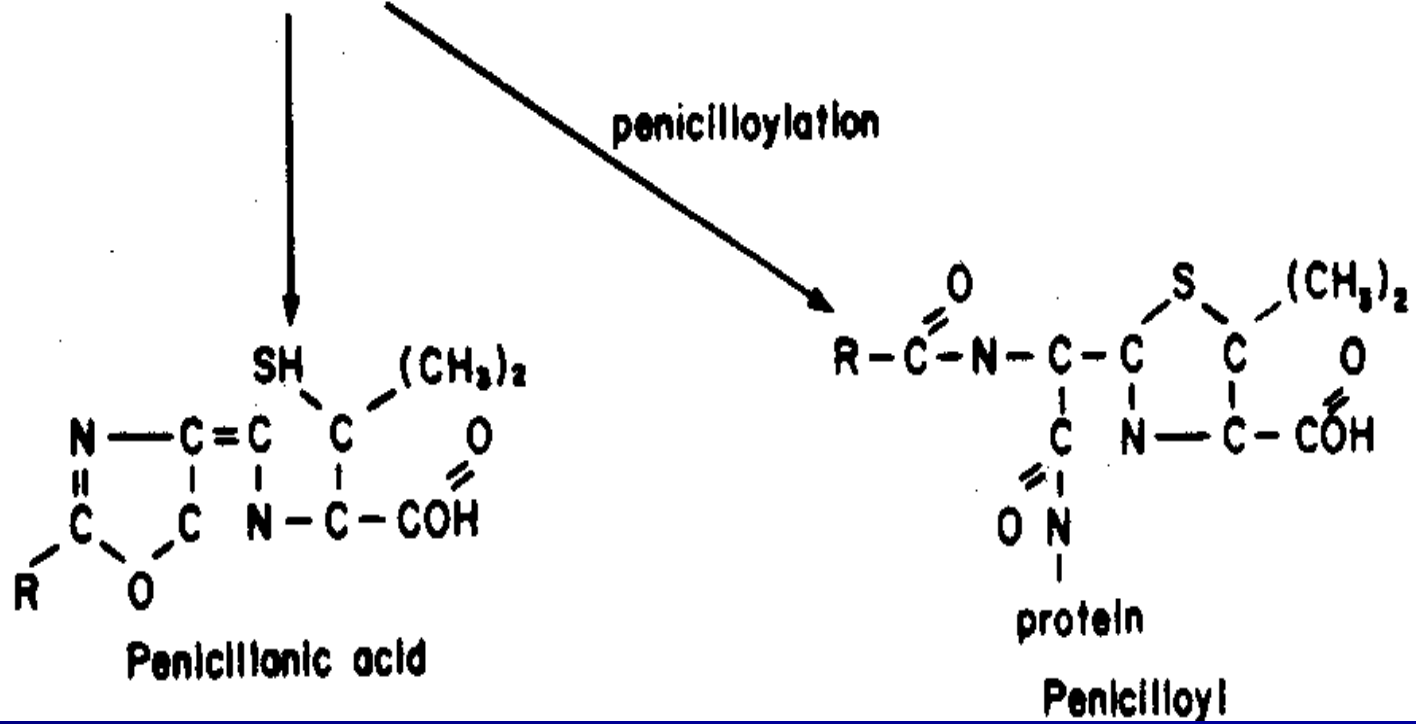
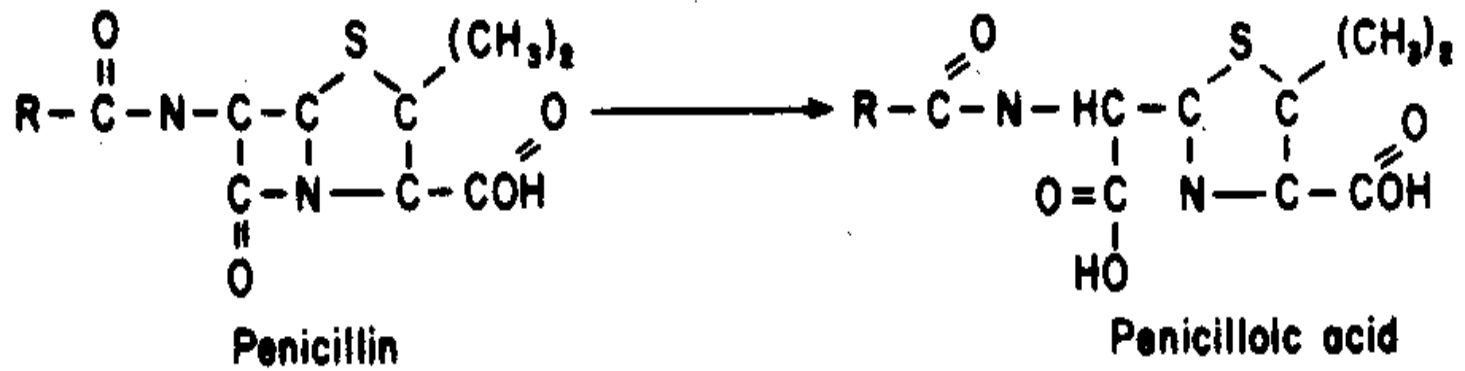
Angioedema



Stevens-Johnson syndrome after penicillin





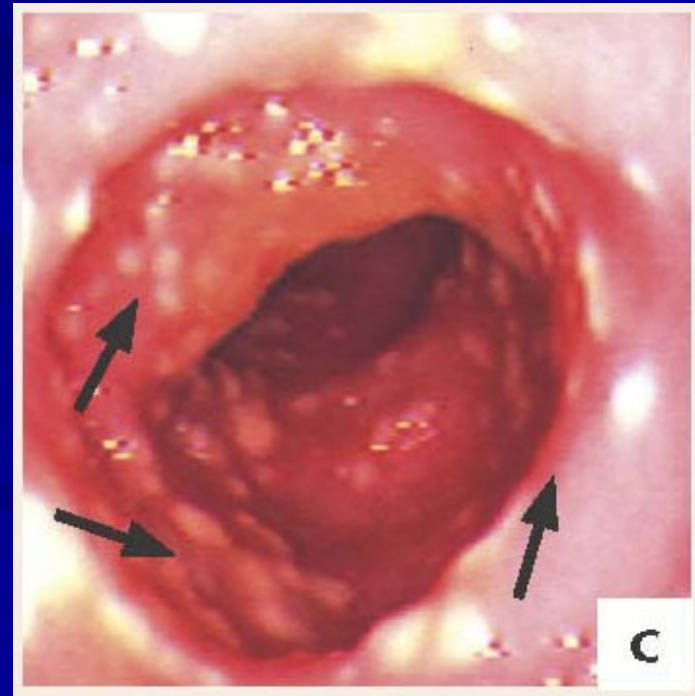


Superinfections

Oral candidiasis



Pseudomembranous colitis



AMINOGLYCOSIDES



Adverse Drug Reactions:

1. Ototoxicity (auditory & vestibular)
2. Nephrotoxicity

Ototoxicity  Neo > Strep > Amik=Genta=Tobra  Nephrotoxicity

Vestibular  Genta=Strep > Tobra > Amik=Neo  Auditory

3. Neuromuscular Blockade
4. Neurologic Disorder (with Streptomycin)
5. Allergic Reactions (rarely)

Tetracyclines

Adverse Effects:

Esophagitis

GI irritation

Nausea & vomiting

Diarrhea

Hepatotoxicity

Teeth discoloration

Photosensitivity

Teeth discoloration



Photosensitivity



Macrolides

1. GI disturbances (lesser for clarythromycin & least for azithromycin)
2. Important drug interactions due to enzyme inhibition: phenytoin, carbamazepine, valproate, theophylline, warfarin, terfenadine, cyclosporine, cisapride, lovastatin (azithromycin is much safer in this regard)
3. Hepatitis
4. QT prolongation
5. Skin rash and fever

CLINDAMYCIN

Adverse effects

- **Diarrhea**
- **Pseudomembranous colitis (abdominal pain & tenderness, fever, severe diarrhea, mucus and blood in stool)**
- **Skin rashes**
- **Neutropenia**

Metronidazole

ADRs:

- Common: nausea, headache, dry mouth, metallic taste
- Uncommon: vomiting, diarrhea, insomnia, weakness, oral thrush, paresthesia and other neurotoxicities
- Others: disulfiram-like syndrome, teratogenicity(?)