

Sulfonamides

PABA analogues that block dihydropteroate synthase - bacteriostatic alone, bactericidal with trimethoprim as co-trimoxazole, and defined by hypersensitivity, kernicterus and folate-pathway toxicity.

Online guide: <https://www.medguideglobal.com/pharmacology/antibiotics/sulfonamides>

Content updated: 2026-08-17

Quick revision

One Liner: Sulfonamides are structural analogues of PABA that competitively inhibit dihydropteroate synthase; add trimethoprim's DHFR block and the sequential hit on folate synthesis turns a bacteriostatic drug into a bactericidal combination.

1. Mechanism: structural analogues of para-aminobenzoic acid (PABA) that competitively inhibit dihydropteroate synthase, blocking bacterial folate synthesis. [1]
2. Bacteriostatic alone; bactericidal when combined with trimethoprim, which inhibits dihydrofolate reductase - sequential blockade of the same pathway. [1]
3. Selective toxicity: humans do not synthesise folate from PABA - we absorb dietary folate - so the target pathway is bacterial, not human. [1]
4. TMP-SMX (co-trimoxazole) covers urinary tract infection, Pneumocystis jirovecii pneumonia prophylaxis and treatment, community MRSA skin infection, and nocardiosis. [1]
5. Sulfadiazine with pyrimethamine is the classic regimen for toxoplasmosis. [1]
6. Hypersensitivity ranges from rash to Stevens-Johnson syndrome and toxic epidermal necrolysis - sulfonamide antibiotics are among the classic drug causes. [2][1]
7. Avoid in neonates and near term: sulfonamides displace bilirubin from albumin and risk kernicterus. [1]
8. G6PD deficiency risks hemolysis; poorly soluble metabolites risk crystalluria; trimethoprim causes hyperkalemia by an amiloride-like block of the distal sodium channel. [1]

Overview

1. Sulfonamides were the first widely used antibacterial class, and their pharmacology is still core exam material because it demonstrates two ideas cleanly: selective toxicity through a pathway humans lack, and synergy through sequential blockade. As structural analogues of para-aminobenzoic acid they competitively inhibit dihydropteroate synthase, the enzyme bacteria use to begin folate synthesis. Humans absorb dietary folate rather than making it, so the target is genuinely bacterial. [1]
2. Alone, a sulfonamide is bacteriostatic. Paired with trimethoprim, which inhibits dihydrofolate reductase one step further down the same pathway, the combination - co-trimoxazole, TMP-SMX - becomes bactericidal. That combination is where the class earns its modern keep: urinary tract infection, Pneumocystis jirovecii pneumonia prophylaxis and treatment in immunocompromised patients, community-acquired MRSA skin and soft-tissue infection, nocardiosis, and, as sulfadiazine with pyrimethamine, toxoplasmosis. [1]
3. What limits the class is its adverse-effect signature rather than its spectrum: hypersensitivity up to Stevens-Johnson syndrome and toxic epidermal necrolysis, kernicterus in neonates and near term, hemolysis in G6PD deficiency, crystalluria from poorly soluble metabolites, trimethoprim-driven hyperkalemia, folate-related marrow suppression, and a two-mechanism interaction with warfarin. The family also stretches beyond antibacterials - sulfasalazine in inflammatory bowel disease and rheumatoid arthritis, and topical silver sulfadiazine in burns - and the shared hypersensitivity risk travels with the sulfa structure. [1][2][3][4]

Classification and drug examples

Intro: Best learned by role: the systemic antibacterials that matter almost entirely as combinations, the anti-inflammatory sulfonamide used outside infection, and the topical burn agent.

1. Name: Systemic antibacterial sulfonamides

1. Note: Used in combination regimens that produce sequential folate-pathway blockade.

1. Name: Sulfamethoxazole

SMX; combined with trimethoprim as co-trimoxazole (TMP-SMX)

1. Route: Oral/IV

1. Note: Almost always given with trimethoprim in a fixed combination; the workhorse sulfonamide for UTI, PCP, MRSA skin infection and nocardiosis. [1]

2. Name: Sulfadiazine

2. Route: Oral

2. Note: Partnered with pyrimethamine for toxoplasmosis; among the sulfonamides more associated with crystalluria; adequate hydration is therefore relevant during therapy. [1][2]

3. Name: Sulfadoxine

Combined with pyrimethamine (Fansidar)

3. Route: Oral

3. Note: A long-acting sulfonamide used with pyrimethamine in malaria programs - the same sequential-blockade logic applied to plasmodial folate synthesis. [2] [1]

2. Name: Anti-inflammatory sulfonamide (context)

2. Note: A sulfonamide by structure but prescribed for inflammation, not infection; the sulfa hypersensitivity risk still applies.

Name: Sulfasalazine

Salazopyrin

Route: Oral

Note: Cleaved by colonic bacteria into sulfapyridine and 5-aminosalicylate; used in ulcerative colitis and as a DMARD in rheumatoid arthritis. [3] [3]

3. Name: Topical sulfonamide

3. Note: Local application to burn wounds; systemic absorption across large areas is enough to reproduce class toxicities.

Name: Silver sulfadiazine

SSD cream

Route: Topical

Note: Prevents infection in second- and third-degree burns; the silver moiety adds membrane and cell-wall effects to the sulfonamide action. [4] [4]

Mechanism of action

Summary: Sulfonamides are PABA analogues that competitively inhibit dihydropteroate synthase, halting bacterial folate synthesis; combined with trimethoprim's inhibition of dihydrofolate reductase, the sequential blockade stops nucleotide synthesis and becomes bactericidal.

Target: Dihydropteroate synthase (sulfonamide) and dihydrofolate reductase (trimethoprim) in the bacterial folate pathway

Cidal Static: bacteriostatic alone; bactericidal in combination with trimethoprim

Kill Kinetics: not the defining feature of this class; synergy of the sequential blockade is

1. Step: 1

1. Title: The drug impersonates PABA

1. Detail: Sulfonamides are structural analogues of para-aminobenzoic acid, the substrate bacteria use to build dihydropteroate. [1]
2. Step: 2
2. Title: Dihydropteroate synthase is competitively inhibited
2. Detail: The false substrate blocks the enzyme, so dihydropteroic acid - and downstream dihydrofolate - cannot be made. [1]
3. Step: 3
3. Title: Growth stops but the organism survives
3. Detail: With folate reserves intact the bacterium is inhibited rather than killed - this is the bacteriostatic phase. [1]
4. Step: 4
4. Title: Trimethoprim blocks the next enzyme
4. Detail: Trimethoprim inhibits dihydrofolate reductase, preventing conversion of dihydrofolate to tetrahydrofolate - the second, sequential hit on the same pathway. [1]
5. Step: 5
5. Title: Nucleotide synthesis collapses and the combination kills
5. Detail: Without tetrahydrofolate the organism cannot make purines, thymidylate or key amino acids; DNA synthesis fails and the double blockade is bactericidal. [1]

Spectrum of activity

Intro: The clinically relevant spectrum is that of TMP-SMX: gram-positive cover that includes community MRSA, enteric gram-negatives, and a distinctive set of opportunists - Pneumocystis, Nocardia and, with sulfadiazine, Toxoplasma.

Subclass Id: systemic-antibacterial

1. Staphylococcus aureus, including community-acquired MRSA
2. Some streptococci, with variable reliability
1. Escherichia coli and other enteric gram-negatives causing UTI
2. Haemophilus influenzae
3. Stenotrophomonas maltophilia
1. Pneumocystis jirovecii
2. Nocardia species
3. Toxoplasma gondii (sulfadiazine with pyrimethamine)
1. Pseudomonas aeruginosa
2. Anaerobes
3. Organisms that salvage exogenous folate or thymidine, which bypass the blockade [1]

Major clinical uses

1. Drug: Trimethoprim-sulfamethoxazole
1. Organism: Enteric gram-negatives, principally Escherichia coli
1. Indication: Urinary tract infection
1. Line: targeted
1. Note: Choice depends on local resistance patterns among urinary isolates. [1]
2. Drug: Trimethoprim-sulfamethoxazole
2. Organism: Pneumocystis jirovecii
2. Indication: Prophylaxis and treatment of Pneumocystis pneumonia in immunocompromised patients, including HIV with low CD4 counts
2. Line: targeted
2. Note: The signature indication of the combination - both prevention and treatment. [1]
3. Drug: Trimethoprim-sulfamethoxazole

3. Organism: Community-acquired MRSA
3. Indication: Skin and soft-tissue infection
3. Line: targeted
3. Note: An oral option for purulent skin infection where community MRSA is the concern. [1]
4. Drug: Trimethoprim-sulfamethoxazole
4. Organism: Nocardia species
4. Indication: Nocardiosis
4. Line: targeted
4. Note: First-line therapy for this immunocompromised-host pathogen. [1]
5. Drug: Sulfadiazine
5. Organism: Toxoplasma gondii
5. Indication: Toxoplasmosis, in combination with pyrimethamine
5. Line: targeted
5. Note: Folinic acid is co-administered in practice to protect host cells from the antifolate effect; specifics belong to the treating clinician. [1]
6. Drug: Silver sulfadiazine
6. Organism: Burn-wound flora, gram-positive and gram-negative
6. Indication: Prevention of wound infection in second- and third-degree burns
6. Line: adjunct
6. Note: Topical use; avoid near term, in neonates, and in sulfonamide hypersensitivity. It has long been the agent other burn treatments are tested against, but that position rests on convention more than on comparative evidence: a Cochrane review of 56 randomised trials found silver-based antiseptics may shorten average healing time relative to it, on low-certainty evidence. [4][5]
7. Drug: Sulfasalazine
7. Organism: Not an antimicrobial indication
7. Indication: Ulcerative colitis; disease-modifying therapy in rheumatoid arthritis
7. Line: adjunct
7. Note: Included for context: a sulfonamide prescribed for inflammation, whose sulfa moiety still carries class hypersensitivity risk. [3]

Pharmacokinetics

1. Drug: Sulfamethoxazole (with trimethoprim)
1. Route: Oral/IV
1. Absorption: Well absorbed orally
1. Csf Penetration: Penetrates tissues and CSF well enough for use against Nocardia and Toxoplasma under specialist direction
1. Metabolism: Hepatic, principally N-acetylation and glucuronidation; acetylated metabolites are poorly soluble in acidic urine
1. Elimination: Renal
1. Half Life: See prescribing reference; the fixed combination is designed so the two components' exposures align
1. Dose Adjust: Renal impairment; avoid near term and in neonates [1]
2. Drug: Sulfadiazine
2. Route: Oral
2. Absorption: Well absorbed orally
2. Csf Penetration: Adequate for CNS toxoplasmosis regimens under specialist direction
2. Metabolism: Hepatic acetylation to poorly soluble metabolites
2. Elimination: Renal

2. Half Life: See prescribing reference
2. Dose Adjust: Renal impairment; adequate hydration is maintained because crystalluria is the characteristic renal hazard [1][2]
3. Drug: Sulfasalazine
3. Route: Oral
3. Absorption: Poorly absorbed as the parent drug - by design, so it reaches the colon intact
3. Csf Penetration: Not applicable
3. Metabolism: Azo bond cleaved by colonic bacteria into sulfapyridine (absorbed, acetylated) and 5-aminosalicylate (acts locally)
3. Elimination: Renal for sulfapyridine metabolites; faecal for much of the 5-ASA
3. Half Life: See prescribing reference; acetylator status influences sulfapyridine exposure
3. Dose Adjust: See prescribing reference [3]
4. Drug: Silver sulfadiazine
4. Route: Topical
4. Absorption: Partial absorption of the sulfadiazine moiety across burned skin, greater with larger treated areas
4. Csf Penetration: Not applicable
4. Metabolism: As for systemic sulfadiazine once absorbed
4. Elimination: Renal for absorbed drug
4. Half Life: Not clinically relevant by this route
4. Dose Adjust: Caution with extensive burns, where systemic sulfonamide effects become possible [4]
1. The characteristic pharmacokinetic hazard of the class is solubility: acetylated sulfonamide metabolites precipitate in acidic urine as crystals, so adequate hydration accompanies systemic therapy. [1][2]
2. High plasma protein binding drives two exam-level problems - bilirubin displacement in the neonate (kernicterus) and warfarin displacement in the anticoagulated adult. [1]
3. Trimethoprim inhibits tubular secretion of creatinine, so serum creatinine can rise on TMP-SMX without a true fall in glomerular filtration. [1]
4. This page gives no dose regimens by design. Doses depend on indication, organism, renal function, age and weight, and belong in a prescribing reference used by the treating clinician.

Adverse effects

1. Effect: Gastrointestinal upset and rash
1. Detail: Nausea, vomiting, anorexia and maculopapular rash are the most frequent reactions; rash is the usual reason a course is stopped. [1][2]
2. Effect: Hyperkalemia
2. Detail: Trimethoprim blocks the distal-nephron epithelial sodium channel in amiloride-like fashion, reducing potassium secretion; most relevant with renal impairment or interacting drugs. [1]
3. Effect: Photosensitivity
3. Detail: Sulfonamides are among the classic photosensitising antibacterials. [2]
1. Effect: Stevens-Johnson syndrome, toxic epidermal necrolysis and DRESS
1. Detail: Sulfonamide antibiotics are among the archetypal drug causes of severe cutaneous adverse reactions and systemic hypersensitivity with fever, rash and organ involvement.
1. Action: A blistering or mucosal rash is a medical emergency requiring immediate assessment; the drug is stopped at the first sign and the class is then avoided lifelong. [2][1]
2. Effect: Kernicterus
2. Detail: Bilirubin displaced from albumin crosses the immature blood-brain barrier and deposits in the basal ganglia of the neonate.
2. Action: Sulfonamides are contraindicated in neonates, young infants, and women near term or breastfeeding a

vulnerable infant. [1]

3. Effect: Hemolysis in G6PD deficiency

3. Detail: Oxidant stress from sulfonamides precipitates acute hemolytic anemia in glucose-6-phosphate dehydrogenase deficiency.

3. Action: G6PD status is screened or asked about where deficiency is prevalent, and the drug is withdrawn if hemolysis develops. [1]

4. Effect: Crystalluria and renal injury

4. Detail: Poorly soluble acetylated metabolites precipitate in acidic urine, causing crystalluria, hematuria and obstructive renal injury - classically with sulfadiazine.

4. Action: Adequate hydration is maintained during therapy; interstitial nephritis is the other renal pattern to consider. [1][2]

5. Effect: Bone-marrow suppression and megaloblastic anemia

5. Detail: The antifolate effect can produce megaloblastic anemia, leukopenia and thrombocytopenia, particularly with prolonged therapy or pre-existing folate deficiency; agranulocytosis is a rarer idiosyncratic event.

5. Action: Blood counts are monitored on prolonged therapy and in folate-deficient patients. [1][2]

6. Effect: Hepatotoxicity

6. Detail: Sulfonamides are well-documented causes of idiosyncratic, often hypersensitivity-associated liver injury, ranging from hepatocellular to cholestatic patterns.

6. Action: The drug is withdrawn if hepatitis develops during therapy, and rechallenge is avoided. [2]

1. Drug: Sulfadiazine

1. Effect: The member most associated with crystalluria and crystal-induced renal injury. [2]

2. Drug: Sulfasalazine

2. Effect: Reversible oligospermia, orange discolouration of body fluids, and hypersensitivity attributable to the sulfapyridine moiety. [3]

3. Drug: Silver sulfadiazine

3. Effect: Transient leukopenia, and sulfonamide-type systemic reactions when applied over large burn areas, including hemolysis in G6PD deficiency. [4]

Contraindications, precautions and interactions

1. Previous severe hypersensitivity to a sulfonamide, including Stevens-Johnson syndrome or toxic epidermal necrolysis. [1][2]

2. Neonates and young infants, and pregnancy near term, because of the kernicterus risk from bilirubin displacement. [1]

1. G6PD deficiency, where oxidant hemolysis is the risk. [1]

2. Renal impairment and folate deficiency, which amplify crystalluria, hyperkalemia and marrow toxicity respectively. [1]

3. Early pregnancy: the antifolate effect of the trimethoprim component is the concern, distinct from the near-term kernicterus problem. [1]

1. With: Warfarin

1. Effect: Sulfamethoxazole inhibits CYP2C9 and displaces warfarin from protein binding - both raise the INR and bleeding risk. [1]

2. With: ACE inhibitors, ARBs, potassium-sparing diuretics

2. Effect: Additive hyperkalemia with trimethoprim's amiloride-like distal-nephron block. [1]

3. With: Methotrexate

3. Effect: Additive antifolate toxicity and displacement from protein binding raise the risk of severe myelosuppression. [1]

4. With: Sulfonylureas and phenytoin

4. Effect: CYP2C9 inhibition and protein-binding displacement can cause hypoglycemia and phenytoin toxicity

respectively. [1]

Resistance mechanisms

1. Mechanism: Altered or bypass dihydropteroate synthase

1. Detail: Plasmid-borne sul genes encode enzyme variants with low sulfonamide affinity, letting folate synthesis continue in the drug's presence - the dominant acquired mechanism.

Enteric gram-negatives carrying sul1/sul2

1. Countermeasure: Susceptibility testing and local resistance data guide whether TMP-SMX remains a sensible empiric UTI choice. [1]

2. Mechanism: PABA overproduction

2. Detail: Because inhibition is competitive, overproducing the natural substrate outcompetes the drug at the enzyme. Staphylococci

2. Countermeasure: The trimethoprim component's independent target keeps the combination useful when only the sulfonamide step is compromised. [1]

3. Mechanism: Folate or thymidine salvage

3. Detail: Organisms able to take up exogenous folate or thymidine bypass the blocked synthetic pathway entirely, which is why the combination is unreliable against them.

Enterococci in thymidine-rich environments

3. Countermeasure: Choose a class with a different target where salvage is possible. [1]

Stewardship Note: Resistance among urinary Escherichia coli varies widely by region, so the decision to use TMP-SMX empirically for UTI is a local-data decision; where resistance is high the combination is reserved for susceptibility-confirmed infection and for the indications where it remains first-line, such as Pneumocystis and Nocardia.

Comparison tables

Title: The sulfonamides worth knowing, by role

Caption: One shared mechanism and hypersensitivity risk; very different jobs. Local susceptibility data and a prescribing reference govern actual therapy.

1. Key: drug

1. Label: Drug

1. Is Row Header: true

2. Key: partner

2. Label: Usual partner

3. Key: role

3. Label: Typical role

4. Key: signature

4. Label: Signature point

1. Drug: Sulfamethoxazole

1. Partner: Trimethoprim (co-trimoxazole)

1. Role: UTI, PCP prophylaxis and treatment, MRSA skin infection, nocardiosis

1. Signature: Sequential blockade makes the combination bactericidal [1]

2. Drug: Sulfadiazine

2. Partner: Pyrimethamine

2. Role: Toxoplasmosis

2. Signature: The crystalluria sulfonamide - hydration matters [1][2]

3. Drug: Sulfadoxine

3. Partner: Pyrimethamine

3. Role: Malaria programs
3. Signature: Long-acting; same folate logic applied to Plasmodium [2]
4. Drug: Sulfasalazine
4. Partner: None - cleaved by gut bacteria
4. Role: Ulcerative colitis; DMARD in rheumatoid arthritis
4. Signature: Prodrug of sulfapyridine plus 5-ASA; not an antimicrobial use [3]
5. Drug: Silver sulfadiazine
5. Partner: Silver moiety
5. Role: Topical burn-wound infection prevention; the traditional comparator rather than an evidence-established first choice
5. Signature: Large-area use can reproduce systemic sulfa toxicity [4][5]

High-yield exam pearls

1. Pearl: Two drugs, one pathway - sequential blockade.
 1. Why: Sulfamethoxazole blocks dihydropteroate synthase and trimethoprim blocks dihydrofolate reductase, hitting bacterial folate synthesis at two consecutive steps. That is why the combination is bactericidal when each component alone is bacteriostatic. [1]
 2. Pearl: The kernicterus contraindication is about protein binding, not the folate pathway.
 2. Why: Sulfonamides compete with bilirubin for albumin binding sites. In neonates and near-term pregnancy the displaced unconjugated bilirubin can deposit in the basal ganglia - kernicterus - so the class is avoided in both settings. [1]
 3. Pearl: Trimethoprim behaves like amiloride at the distal nephron.
 3. Why: It blocks the epithelial sodium channel in the distal tubule, reducing potassium secretion. Hyperkalemia is the exam consequence, especially with ACE inhibitors, ARBs or potassium-sparing diuretics. [1]
 4. Pearl: The warfarin interaction has two mechanisms at once.
 4. Why: Sulfamethoxazole inhibits CYP2C9, the enzyme that clears the more potent S-warfarin, and also displaces warfarin from plasma protein binding. INR rises and bleeding risk with concurrent TMP-SMX is a classic scenario. [1]
 5. Pearl: Sulfasalazine is a sulfonamide used for inflammation, not infection.
 5. Why: Colonic bacteria cleave its azo bond into sulfapyridine and 5-aminosalicylate; the 5-ASA moiety treats ulcerative colitis and the parent drug is a DMARD in rheumatoid arthritis. Its sulfa component still carries sulfonamide hypersensitivity risk. [3]
 6. Pearl: Silver sulfadiazine is the sulfonamide used on burns, though its status as the default is contested.
 6. Why: It is applied topically to limit infection in second- and third-degree burns, and systemic sulfonamide toxicities such as hemolysis in G6PD deficiency and leukopenia can still follow large-area application. It is also the comparator most burn trials are designed around: pooled data credit silver-based antiseptics with roughly three days faster average healing against it on low-certainty evidence, while honey probably heals burns faster than topical antibiotics on moderate-certainty evidence. [4][5]

Common exam traps

1. Trap: "Sulfonamides are bactericidal."
 1. Correction: Alone they are bacteriostatic - organisms stop making folate but survive on reserves. Only the combination with trimethoprim, blocking the next enzyme in the pathway, is bactericidal. [1]
 2. Trap: "Sulfonamides poison human folate synthesis too."
 2. Correction: Humans do not synthesise folate from PABA; we absorb it from the diet. The marrow suppression seen with prolonged TMP-SMX comes from trimethoprim's weak inhibition of the human dihydrofolate reductase, not from the sulfonamide step. [1]
 3. Trap: "A rising creatinine on TMP-SMX always means kidney injury."

3. Correction: Trimethoprim competitively inhibits tubular creatinine secretion, so serum creatinine can rise without any fall in true glomerular filtration. Genuine injury - interstitial nephritis or sulfonamide crystalluria - must still be excluded.

[1]

4. Trap: "Topical means systemically safe."

4. Correction: Silver sulfadiazine applied over large burn areas is absorbed enough to cause sulfonamide-type reactions, including hemolysis in G6PD deficiency and transient leukopenia. [4]

5. Trap: "Sulfasalazine hypersensitivity is unrelated to sulfa allergy."

5. Correction: Sulfasalazine is cleaved to sulfapyridine, a sulfonamide, and hypersensitivity reactions to it are well documented - a prior severe sulfonamide reaction matters here too. [3]

Self-test questions

1. Question: Sulfonamides are structural analogues of para-aminobenzoic acid. What does that mimicry accomplish?

1. It allows an active PABA transporter to concentrate them inside the bacterial cell
2. It lets them be incorporated into bacterial DNA in place of a normal base
3. It lets them competitively inhibit dihydropteroate synthase, so bacterial folate synthesis stalls at its first step
4. It lets them occupy dihydrofolate reductase in place of the natural cofactor

1. Explanation: Because the drug looks like the natural substrate, it competes for the enzyme that begins folate manufacture, and the pathway stalls there. Selective toxicity follows from the fact that human cells never run that pathway, taking preformed folate from the diet instead of assembling it from PABA, so the target simply does not exist in the host. [1]

2. Question: Sulfamethoxazole alone is bacteriostatic, yet co-trimoxazole is bactericidal. What explains the change?

1. Trimethoprim blocks dihydrofolate reductase, the next enzyme in the same pathway, so the sequential double block collapses tetrahydrofolate supply
2. Trimethoprim raises sulfamethoxazole plasma concentrations by inhibiting its metabolism
3. Trimethoprim disrupts the bacterial cell membrane, adding an unrelated lethal mechanism
4. Trimethoprim blocks efflux pumps, letting sulfamethoxazole accumulate to lethal levels

2. Explanation: The two agents strike consecutive steps of a single pathway. With both the synthase and the reductase inhibited, the organism cannot generate tetrahydrofolate at all, and without it purines, thymidylate and several amino acids become unavailable. DNA synthesis fails, so the organism dies instead of merely pausing. [1]

3. Question: Which reaction is the archetypal reason a sulfonamide is avoided for the rest of a patient's life once it has occurred?

1. Photosensitivity rash
2. Nausea and anorexia
3. A modest rise in serum creatinine
4. Stevens-Johnson syndrome or toxic epidermal necrolysis

3. Explanation: These drugs sit among the classic causes of severe cutaneous reactions and of systemic hypersensitivity with fever, rash and organ involvement. A blistering or mucosal eruption is an emergency, the drug is stopped at once, and the whole class is then kept away from that patient permanently. Ordinary maculopapular rash is far commoner and is the usual reason a routine course is abandoned. [2][1]

4. Question: Which mechanism explains why sulfonamides are avoided in neonates and in late pregnancy?

1. Inhibition of fetal dihydropteroate synthase, causing neural tube defects
2. Competition with unconjugated bilirubin for albumin binding, so displaced bilirubin deposits in the basal ganglia
3. Direct oxidant injury to the neonatal cochlea
4. Accumulation in fetal bone, staining the developing teeth

4. Explanation: The hazard here is protein binding rather than the folate pathway. These drugs occupy albumin sites that unconjugated bilirubin would otherwise use, and the bilirubin set free can cross an immature blood-brain barrier and lodge in the basal ganglia, which is kernicterus. The antifolate worry in early pregnancy is a separate matter,

arising from the trimethoprim component. [1]

5. Question: Serum creatinine rises modestly in a patient taking TMP-SMX for a urinary tract infection. What should be considered first?

1. Glomerular filtration has definitely fallen and the drug has caused acute kidney injury
2. The result must be a laboratory error, because the combination has no renal effects at all
3. Trimethoprim competitively inhibits tubular secretion of creatinine, so the level can rise with filtration unchanged
4. Sulfamethoxazole increases creatinine production in skeletal muscle
5. Explanation: Blocking the tubular transporter that secretes creatinine lifts the measured serum level without any change in true glomerular filtration, a well-recognised artefact of this combination. It is not a licence to ignore the result, though, because genuine injury from interstitial nephritis or from sulfonamide crystals still has to be excluded when the rise is large. [1]

6. Question: Which resistance mechanism is the dominant acquired route to sulfonamide failure in enteric gram-negative organisms?

1. Ribosomal methylation that prevents the drug binding
2. Loss of the porin channel through which the drug enters
3. Beta-lactamase-mediated hydrolysis of the sulfonamide ring
4. Plasmid-carried sul genes encoding a dihydropteroate synthase variant with low affinity for the drug
6. Explanation: An enzyme the drug barely binds lets folate manufacture carry on regardless, and the genes encoding it travel on plasmids, which is what makes this the leading acquired route. Two other escapes exist: overproducing the natural substrate simply outcompetes a competitive inhibitor, and organisms able to scavenge ready-made folate or thymidine from their surroundings sidestep the blocked pathway altogether. [1]

7. Question: A patient stabilised on warfarin is prescribed TMP-SMX and the INR climbs. Which explanation fits this class?

1. Sulfamethoxazole inhibits CYP2C9 and also displaces warfarin from protein binding, so both routes push the INR upward
2. Trimethoprim induces CYP2C9, increasing conversion of warfarin to an active metabolite
3. Killing colonic flora depletes vitamin K, and that is the only mechanism involved
4. Sulfamethoxazole delays gastric emptying, increasing the fraction of warfarin absorbed
7. Explanation: Two mechanisms operate at once. The enzyme that clears the more potent S-isomer of warfarin is inhibited, and warfarin is simultaneously pushed off its plasma protein binding sites. A rising INR and a real bleeding hazard follow, which is why this pairing is a standing examination scenario. [1]

8. Question: Why can silver sulfadiazine applied to extensive burns produce systemic sulfonamide toxicity?

1. The silver component is itself metabolised into a sulfonamide
2. Enough of the sulfadiazine moiety crosses burned skin, and increasingly so as the treated area grows
3. Wound flora convert the topical drug into a systemically active prodrug
4. Small amounts of the cream are routinely swallowed during dressing changes
8. Explanation: Damaged skin is a poor barrier, and the larger the surface treated the more drug crosses it. That is sufficient to reproduce the reactions expected from systemic exposure, including haemolysis in glucose-6-phosphate dehydrogenase deficiency and transient leukopenia, so a topical route is not automatically a systemically safe one. [4]

Frequently asked questions

1. Question: Why is TMP-SMX bactericidal when each drug alone is bacteriostatic?

1. Answer: Each component blocks one enzyme in the bacterial folate pathway - sulfamethoxazole at dihydropteroate synthase, trimethoprim at dihydrofolate reductase. Blocking two sequential steps collapses tetrahydrofolate supply so completely that nucleotide synthesis fails and the organism dies rather than merely stalling. [1]

2. Question: Why don't sulfonamides poison human cells the same way?

2. Answer: Humans do not synthesise folate from PABA; we absorb preformed folate from the diet, so the sulfonamide

target does not exist in human cells. The human-relevant antifolate effect in the combination comes from trimethoprim's weak activity against human dihydrofolate reductase, seen mainly as marrow effects with prolonged use. [1]

3. Question: Why are sulfonamides avoided in neonates and late pregnancy?

3. Answer: They compete with unconjugated bilirubin for albumin binding. The displaced bilirubin can cross the immature blood-brain barrier and deposit in the basal ganglia, causing kernicterus. [1]

4. Question: Does a sulfa antibiotic allergy apply to sulfasalazine or silver sulfadiazine?

4. Answer: Yes in principle - sulfasalazine releases sulfapyridine, a sulfonamide, and silver sulfadiazine is absorbed across burned skin, so a previous severe sulfonamide reaction is a reason to avoid both. The overlap question is drug-specific and belongs to the treating clinician. [3][4]

5. Question: Why can creatinine rise on TMP-SMX without real kidney damage?

5. Answer: Trimethoprim competitively inhibits the tubular secretion of creatinine, so the serum level rises even though glomerular filtration is unchanged. True injury - crystalluria or interstitial nephritis - still has to be excluded when the rise is large or accompanied by other findings. [1]

References

[1] Trimethoprim-Sulfamethoxazole (StatPearls). StatPearls Publishing / NCBI Bookshelf 2023.

<https://www.ncbi.nlm.nih.gov/books/NBK513232/>

[2] Sulfonamides (LiverTox). LiverTox, NIDDK / NCBI Bookshelf 2020. <https://www.ncbi.nlm.nih.gov/books/NBK548382/>

[3] Sulfasalazine (StatPearls). StatPearls Publishing / NCBI Bookshelf 2023. <https://www.ncbi.nlm.nih.gov/books/NBK557809/>

[4] Silver Sulfadiazine (StatPearls). StatPearls Publishing / NCBI Bookshelf 2023.

<https://www.ncbi.nlm.nih.gov/books/NBK556054/>

[5] Antiseptics for burns (Cochrane Database of Systematic Reviews, 2017). Cochrane Wounds 2017.

<https://doi.org/10.1002/14651858.CD011821.pub2>

For education only. This guide does not replace professional medical advice. Do not use it to choose or change treatment.