

Trimethoprim

A selective bacterial dihydrofolate reductase inhibitor used alone in uncomplicated urinary infection and paired with sulfamethoxazole for sequential folate blockade - memorable for hyperkalaemia, a false creatinine rise and folate antagonism.

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

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Quick revision

One Liner: Trimethoprim competitively inhibits bacterial dihydrofolate reductase, binding the bacterial enzyme thousands of times more tightly than the human one; add sulfamethoxazole and you block two sequential steps of the same pathway.

1. Mechanism: competitive inhibition of dihydrofolate reductase, blocking conversion of dihydrofolate to tetrahydrofolate, the active folate needed for purine, DNA and protein synthesis. [3]
2. Selectivity is the whole point: binding affinity for bacterial dihydrofolate reductase is substantially greater than for the human enzyme. [5]
3. Alone each agent is bacteriostatic; sulfamethoxazole plus trimethoprim blocks two sequential steps and is bactericidal in certain settings such as the urinary tract. [3]
4. Trimethoprim alone is used for uncomplicated urinary tract infection, with activity against aerobic gram-negatives including *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Enterobacter* species. Resistance is common. [4]
5. Hyperkalaemia: trimethoprim blocks the epithelial sodium channel in the distal nephron in the same way as amiloride, reducing potassium excretion. [6]
6. The hyperkalaemia risk rises with renal impairment and with ACE inhibitors, angiotensin receptor blockers, spironolactone and other potassium-sparing agents. [3][6]
7. Serum creatinine rises without any fall in glomerular filtration rate, because trimethoprim inhibits tubular creatinine secretion - a reversible, artefactual change. [7]
8. Folate antagonism causes folate deficiency and megaloblastic anaemia; folinic acid (leucovorin) is the rescue when marrow suppression appears. [3]
9. First-trimester exposure to co-trimoxazole increases congenital malformations, including cardiac defects, cleft lip or palate and neural tube defects. [3]

Overview

1. Trimethoprim is a diaminopyrimidine antifolate that competitively inhibits dihydrofolate reductase, the enzyme that converts dihydrofolate to tetrahydrofolate. Tetrahydrofolate is required for purine synthesis and therefore for DNA and protein production, so blocking the reductase halts bacterial replication. Its usefulness rests on selectivity: the binding affinity for bacterial dihydrofolate reductase is substantially greater than for the human enzyme, and the two active sites differ. [3][5]
2. Used alone, trimethoprim is a urinary agent with activity against aerobic gram-negative organisms such as *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Enterobacter* species, and resistance is common. Its more familiar form is the fixed combination with sulfamethoxazole, approved in the United States in 1973 and still heavily prescribed, in which the sulfonamide blocks the step before it. Individually each drug is bacteriostatic; together they block two sequential steps of the same pathway and become bactericidal in certain settings such as the urinary tract. [4][3]
3. What makes trimethoprim examinable is that its off-target pharmacology is more distinctive than its antibacterial one.

It blocks the epithelial sodium channel of the distal nephron in the same manner as amiloride, causing hyperkalaemia; it inhibits tubular creatinine secretion, producing a creatinine rise with no true fall in glomerular filtration rate; and it antagonises folate, producing megaloblastic change in the patient and teratogenic risk in the first trimester. This page covers trimethoprim itself and the combination viewpoint. The sulfonamide half - sulfonamide hypersensitivity, Stevens-Johnson syndrome, sulfonamide hepatotoxicity - is covered on the sulfonamides page. [6][7][3]

Classification and drug examples

Intro: A single-drug class in practice, best organised by whether trimethoprim is used alone or as the reductase-inhibiting half of a sequential-blockade combination.

1. Name: Trimethoprim as monotherapy

1. Note: Used as a urinary antibacterial, including where a sulfonamide is unsuitable.

Name: Trimethoprim

TMP

Route: Oral

Note: Approved in the United States in 1980 and used much less often than the fixed combination; active against many aerobic gram-negative organisms, with common resistance. [4] [4]

2. Name: Sequential folate blockade combinations

2. Note: Trimethoprim paired with a dihydropteroate synthase inhibitor so that two consecutive steps of folate synthesis are blocked.

Name: Trimethoprim-sulfamethoxazole

1. Co-trimoxazole

2. TMP-SMX

3. TMP-SMZ

Route: Oral/IV

Note: Fixed-dose combination approved in the United States in 1973; the sulfonamide half is covered on the sulfonamides page. [4][3] [3]

3. Name: Related antifolates encountered alongside it

3. Note: Not trimethoprim, but they act on the same pathway and their interactions with it are examinable.

1. Name: Methotrexate

1. Route: Oral/IV/SC

1. Note: Also a dihydrofolate reductase inhibitor; combined use adds enzyme blockade, displaces protein binding and reduces renal tubular secretion, raising toxicity risk. [3]

2. Name: Pyrimethamine

2. Route: Oral

2. Note: Another diaminopyrimidine; doses above 25 mg weekly with TMP-SMX may cause megaloblastic anaemia. [3] [3]

Mechanism of action

Summary: Trimethoprim competitively inhibits bacterial dihydrofolate reductase, preventing formation of tetrahydrofolate and so of the purines needed for DNA and protein synthesis; with sulfamethoxazole blocking the preceding step, the pathway is interrupted twice.

Target: Bacterial dihydrofolate reductase (DHFR)

Cidal Static: bacteriostatic alone; bactericidal in certain settings when combined with sulfamethoxazole

Kill Kinetics: time-dependent

1. Step: 1

1. Title: It reaches a selective target

1. Detail: Trimethoprim binds bacterial dihydrofolate reductase far more tightly than the human enzyme, and the

bacterial and human active sites differ. [5]

2. Step: 2

2. Title: The reductase is competitively inhibited

2. Detail: As a competitive inhibitor it occupies the enzyme and prevents the reduction of dihydrofolate to tetrahydrofolate, the active form of folate. [3]

3. Step: 3

3. Title: Tetrahydrofolate runs out

3. Detail: Tetrahydrofolate is essential for purine synthesis and in turn for DNA and protein production, so replication stalls. [3]

4. Step: 4

4. Title: Sulfamethoxazole blocks the step before

4. Detail: Sulfamethoxazole competes with para-aminobenzoic acid to inhibit dihydropteroate synthase, so dihydrofolate is not made in the first place. Blocking substrate supply and the enzyme that consumes it is what produces synergy. [3][4]

5. Step: 5

5. Title: Two blocks change the endpoint

5. Detail: Each agent alone is bacteriostatic; together they block two sequential steps in bacterial nucleic acid and protein synthesis and produce bactericidal activity in certain settings, such as the urinary tract. [3]

6. Step: 6

6. Title: The human folate pathway is only relatively spared

6. Detail: Human cells depend on the same reductase, so the selectivity margin is quantitative rather than absolute - the reason folate deficiency, megaloblastic anaemia and first-trimester teratogenicity appear at all. [5][3]

Spectrum of activity

Intro: Trimethoprim alone is essentially a gram-negative urinary agent; the combination with sulfamethoxazole widens cover to organisms and opportunistic pathogens the single agent does not reliably reach.

1. Subclass Id: trimethoprim-alone

Limited as monotherapy

1. Escherichia coli

2. Klebsiella pneumoniae

3. Proteus mirabilis

4. Enterobacter species

Common acquired resistance among urinary gram-negatives [4]

2. Subclass Id: sequential-blockade-combination

1. Susceptible Streptococcus pneumoniae

2. Methicillin-resistant Staphylococcus aureus (off-label use)

1. Urinary gram-negatives

2. Susceptible Haemophilus influenzae

3. Shigella species

1. Pneumocystis jirovecii

2. Toxoplasma gondii

Resistance from plasmid-borne variant dihydropteroate synthase and dihydrofolate reductase genes [3]

Major clinical uses

1. Drug: Trimethoprim

1. Organism: Aerobic urinary gram-negative organisms

1. Indication: Uncomplicated urinary tract infection

1. Line: first-line

1. Note: Used as a single agent; local resistance is common and should guide the choice. [4]

2. Drug: Trimethoprim-sulfamethoxazole

2. Organism: Susceptible urinary pathogens

2. Indication: Urinary tract infection

2. Line: first-line

2. Note: An FDA-approved indication for the combination; the urinary tract is one of the settings where the pairing behaves bactericidally. [3]

3. Drug: Trimethoprim-sulfamethoxazole

3. Organism: *Pneumocystis jirovecii*

3. Indication: Treatment and prophylaxis of *Pneumocystis jirovecii* pneumonia

3. Line: first-line

3. Note: Also used chronically to prevent opportunistic infection in immune-deficient individuals. [3][4]

4. Drug: Trimethoprim-sulfamethoxazole

4. Organism: *Toxoplasma gondii*

4. Indication: Treatment and prophylaxis of toxoplasmosis

4. Line: targeted

4. Note: An approved indication for the combination rather than for trimethoprim alone. [3]

5. Drug: Trimethoprim-sulfamethoxazole

5. Organism: Susceptible *Streptococcus pneumoniae* or *Haemophilus influenzae*

5. Indication: Acute exacerbation of chronic bronchitis; acute otitis media in children

5. Line: targeted

5. Note: Approved indications restricted to susceptible strains. [3]

6. Drug: Trimethoprim-sulfamethoxazole

6. Organism: *Shigella* species and enteric pathogens

6. Indication: Shigellosis; traveller's diarrhoea, treatment and prophylaxis

6. Line: targeted

6. Note: Approved indications for the combination. [3]

7. Drug: Trimethoprim-sulfamethoxazole

7. Organism: Methicillin-resistant *Staphylococcus aureus*

7. Indication: Skin and soft-tissue infection

7. Line: targeted

7. Note: Off-label use, alongside off-label roles in acne vulgaris, community-acquired pneumonia and prophylaxis in people with HIV. [3]

Pharmacokinetics

1. Drug: Trimethoprim

1. Route: Oral

1. Absorption: Well absorbed orally; peak levels within 1 to 4 hours, steady state in about 3 days for the combination

1. Csf Penetration: Distributes widely, including into bronchial secretions; crosses the placenta and enters breast milk

1. Metabolism: Minimal hepatic metabolism; substrate of P-glycoprotein, OCT1 and OCT2

1. Elimination: Renal, largely unchanged, by glomerular filtration and tubular secretion

1. Half Life: 8 to 10 hours

1. Dose Adjust: Reduced renal function; see prescribing reference [3]

2. Drug: Sulfamethoxazole (combination partner)

2. Route: Oral/IV

2. Absorption: Peak levels within 1 to 4 hours after oral dosing

- 2. Csf Penetration: Distributes into sputum, vaginal fluid and middle ear fluid; crosses the placenta
- 2. Metabolism: Hepatic via cytochrome P450; inhibits CYP2C9
- 2. Elimination: Renal, by filtration and tubular secretion
- 2. Half Life: 6 to 12 hours, rising to 20 to 50 hours in renal impairment
- 2. Dose Adjust: Reduced renal function; see prescribing reference [3]
- 1. Protein binding differs between the two components - roughly 70% for sulfamethoxazole and 44% for trimethoprim - which matters when a third protein-bound drug such as methotrexate or warfarin is added. [3]
- 2. Trimethoprim inhibits renal organic cation transporter 2, so it raises plasma concentrations of OCT2 substrates and of drugs that rely on tubular secretion for clearance. The same tubular action explains the creatinine rise. [3][7]
- 3. Because clearance is predominantly renal, both hyperkalaemia and haematological toxicity become more likely as renal function falls. [3][6]
- 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
 - 1. Detail: Loss of appetite, nausea, vomiting, dyspepsia, and with trimethoprim alone abdominal upset. [3][4]
- 2. Effect: Rash and photosensitivity
 - 2. Detail: Rash, urticaria and photosensitivity are among the primary adverse effects of the combination; trimethoprim alone can cause rash and pruritus. [3][4]
- 3. Effect: Folate deficiency
 - 3. Detail: Folate deficiency is listed among the primary adverse effects, the direct consequence of inhibiting dihydrofolate reductase in the patient as well as the organism. [3]
- 4. Effect: Rise in serum creatinine
 - 4. Detail: Inhibition of tubular creatinine secretion raises serum creatinine and lowers creatinine-based estimated GFR without any change in measured glomerular filtration rate; the effect is reversible. Co-trimoxazole may separately overestimate creatinine by about 10% through interference with the Jaff alkaline picrate assay. [7][3]
- 1. Effect: Hyperkalaemia
 - 1. Detail: Trimethoprim blocks the epithelial sodium channel of the distal nephron in the same way as amiloride, reducing renal potassium excretion. Risk is greatest in renal impairment, in older adults and with drugs that already retain potassium.
 - 1. Action: Monitor serum potassium periodically in patients with renal impairment or on interacting drugs, and review the regimen if potassium rises. [6][3]
- 2. Effect: Megaloblastic anaemia and bone marrow suppression
 - 2. Detail: Folate antagonism can produce megaloblastic anaemia; the combination is contraindicated in patients who already have megaloblastic anaemia due to folate deficiency.
 - 2. Action: Where marrow suppression is present, folic acid (leucovorin) is used until haematopoietic function normalises, on specialist direction. [3]
- 3. Effect: Embryo-fetal toxicity
 - 3. Detail: First-trimester exposure to co-trimoxazole increases congenital malformations including cardiac defects, cleft lip or palate and neural tube defects.
 - 3. Action: Use requires a documented risk-benefit assessment, with folic acid supplementation recommended if therapy proceeds. [3][4]
- 4. Effect: Acute kidney injury and renal tubular acidosis
 - 4. Detail: Genuine renal injury occurs, particularly in older adults with chronic kidney disease or on renin-angiotensin blockade; co-trimoxazole may rarely cause renal tubular acidosis.
 - 4. Action: Monitor renal function and potassium closely in these groups rather than assuming every creatinine change

is artefactual. [3]

5. Effect: Severe cutaneous and systemic hypersensitivity

5. Detail: Rare but potentially severe reactions to the combination include Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS, anaphylaxis and shock, along with aplastic anaemia, agranulocytosis and thrombocytopenia.

5. Action: Stop the drug and seek urgent assessment. The sulfonamide component is the usual driver - see the sulfonamides page. [4]

1. Drug: Trimethoprim alone

1. Effect: Idiosyncratic clinically apparent acute liver injury, typically after 2 to 12 weeks, with a mixed or cholestatic enzyme pattern and few immunoallergic features - a different signature from the sulfonamide half. [4]

2. Drug: Trimethoprim-sulfamethoxazole

2. Effect: Clinically apparent acute liver injury that can be severe and even fatal; the sulfonamide component is implicated in most cases, and the combination is contraindicated in hepatic impairment. [4][3]

Contraindications, precautions and interactions

1. Known hypersensitivity to trimethoprim or sulfamethoxazole, or a history of sulfonamide allergy (for the combination). [3]

2. Megaloblastic anaemia due to folate deficiency. [3]

3. Marked hepatic damage is a contraindication to the trimethoprim-sulfamethoxazole combination, driven by the sulfonamide component. It is not a contraindication to trimethoprim used alone: that label restricts use only in hypersensitivity and in documented megaloblastic anaemia due to folate deficiency. [3][1][2]

4. For the combination: severe renal insufficiency where renal function cannot be monitored, neonates younger than 6 weeks, concurrent dofetilide, and a history of drug-induced immune thrombocytopenia with trimethoprim or a sulfonamide. The combination is also contraindicated in pregnancy and in nursing mothers because sulfonamides cross the placenta and enter milk. [3][2]

1. First trimester of pregnancy, where folate antagonism carries embryo-fetal risk and any use needs an explicit risk-benefit decision with folic acid supplementation. [3]

2. Older adults, particularly with chronic kidney disease or on renin-angiotensin blockade or potassium-sparing diuretics, where the 2023 American Geriatrics Society Beers Criteria advise cautious use with close monitoring of renal function and potassium. [3]

3. Any degree of renal impairment, which amplifies both hyperkalaemia and haematological toxicity. [3][6]

1. With: ACE inhibitors and angiotensin receptor blockers

1. Effect: Clinically significant hyperkalaemia, especially in older adults or renal impairment; monitor potassium closely. [3]

2. With: Spironolactone and other potassium-sparing agents

2. Effect: Severe, potentially fatal hyperkalaemia - the same distal-nephron defect from two directions. [3][6]

3. With: Methotrexate

3. Effect: Additive dihydrofolate reductase inhibition plus displacement from protein binding and reduced renal tubular secretion, raising the risk of methotrexate toxicity and megaloblastic anaemia. [3]

4. With: Pyrimethamine

4. Effect: Doses above 25 mg weekly with TMP-SMX may cause megaloblastic anaemia. [3]

5. With: OCT2 substrates and renally secreted antiretrovirals (zidovudine, lamivudine, zalcitabine)

5. Effect: Trimethoprim inhibits renal OCT2 and tubular secretion, raising their plasma concentrations; zidovudine also adds haematological toxicity and neutropenia risk. [3]

6. With: Warfarin, sulfonylureas and other CYP2C9 or CYP2C8 substrates

6. Effect: Prothrombin time may be prolonged and hypoglycaemic effects enhanced through the sulfamethoxazole component's CYP inhibition; monitor INR and blood glucose. [3]

7. With: Rifampin

7. Effect: Reduces plasma concentrations of both trimethoprim and sulfamethoxazole, potentially lowering efficacy. [3]

Resistance mechanisms

1. Mechanism: Plasmid-borne resistant target enzymes

1. Detail: Resistance arises mainly from plasmid-encoded variants of dihydrofolate reductase and dihydropteroate synthase that the drugs no longer inhibit - the target is replaced rather than the drug destroyed.

1. Enterobacterales carrying dfr genes

2. Enterobacterales carrying sul genes

1. Countermeasure: Susceptibility-guided prescribing and attention to local urinary resistance rates. [3]

2. Mechanism: Efflux and reduced permeability

2. Detail: Active efflux pumps and decreased membrane permeability lower intracellular drug concentration.

Gram-negative urinary isolates

2. Countermeasure: Culture-directed therapy when empiric treatment fails. [3]

3. Mechanism: Widespread background resistance in urinary isolates

3. Detail: Resistance to trimethoprim used alone is described as common, which limits confident empiric monotherapy.

1. Escherichia coli

2. Klebsiella pneumoniae

3. Countermeasure: Check local antibiogram data before choosing trimethoprim empirically. [4]

Stewardship Note: Trimethoprim's appeal is a narrow, cheap oral option for urinary infection, but common resistance means the empiric decision depends on local antibiogram data, and the combination's broader roles - Pneumocystis and toxoplasmosis prophylaxis in particular - are worth protecting from casual use.

Comparison tables

1. Title: Which half of co-trimoxazole does what

1. Caption: The split that answers most exam questions about this combination. Therapy decisions follow local susceptibility data and a prescribing reference.

1. Key: feature

1. Label: Feature

1. Is Row Header: true

2. Key: tmp

2. Label: Trimethoprim

3. Key: smx

3. Label: Sulfamethoxazole

1. Feature: Enzyme inhibited

1. Tmp: Dihydrofolate reductase

1. Smx: Dihydropteroate synthase [3]

2. Feature: Step in the pathway

2. Tmp: Dihydrofolate to tetrahydrofolate

2. Smx: Para-aminobenzoic acid to dihydrofolate [3][4]

3. Feature: Effect alone

3. Tmp: Bacteriostatic

3. Smx: Bacteriostatic [3]

4. Feature: Signature adverse effect

4. Tmp: Hyperkalaemia and a false creatinine rise

4. Smx: Sulfonamide hypersensitivity and hepatic injury [6][7][4]

5. Feature: Half-life

5. Tmp: 8 to 10 hours

5. Smx: 6 to 12 hours; 20 to 50 hours in renal impairment [3]
6. Feature: Protein binding
6. Tmp: About 44%
6. Smx: About 70% [3]
2. Title: Two renal effects that look alike and are not
2. Caption: Distinguishing the artefactual creatinine rise from true injury and from the potassium effect.
1. Key: effect
1. Label: Effect
1. Is Row Header: true
2. Key: mechanism
2. Label: Mechanism
3. Key: gfr
3. Label: True GFR
4. Key: response
4. Label: What it means
1. Effect: Rise in serum creatinine
1. Mechanism: Inhibition of tubular creatinine secretion
1. Gfr: Unchanged
1. Response: Reversible and artefactual; estimated GFR is falsely low [7]
2. Effect: Assay overestimation
2. Mechanism: Interference with the Jaff alkaline picrate assay
2. Gfr: Unchanged
2. Response: Adds roughly 10% within the normal range [3]
3. Effect: Hyperkalaemia
3. Mechanism: Amiloride-like blockade of the distal nephron epithelial sodium channel
3. Gfr: Unchanged by this mechanism
3. Response: Real and potentially dangerous; monitor potassium [6]
4. Effect: Acute kidney injury
4. Mechanism: True renal injury, notably in older adults with chronic kidney disease or on renin-angiotensin blockade
4. Gfr: Reduced
4. Response: Requires clinical assessment, not reassurance [3]

High-yield exam pearls

1. Pearl: Trimethoprim inhibits dihydrofolate reductase; sulfamethoxazole inhibits dihydropteroate synthase. One pathway, two steps.
1. Why: Sulfamethoxazole competes with para-aminobenzoic acid to block dihydrofolate production, and trimethoprim blocks the next step to tetrahydrofolate. Sequential blockade of the same pathway is what produces synergy. [3][4]
2. Pearl: Humans have dihydrofolate reductase too - selectivity, not absence of the target, is what protects the patient.
2. Why: Trimethoprim's affinity for bacterial dihydrofolate reductase is substantially greater than for the human enzyme, and the active sites differ. That margin is finite, which is exactly why folate deficiency still occurs. [5][3]
3. Pearl: A rising creatinine on trimethoprim is not automatically kidney injury.
3. Why: Trimethoprim inhibits tubular creatinine secretion, so serum creatinine rises and estimated GFR falls while measured glomerular filtration rate is unchanged. The effect is reversible on stopping. [7]
4. Pearl: Think amiloride when you see the potassium rise.
4. Why: Trimethoprim blocks the epithelial sodium channel of the distal nephron exactly as amiloride does, cutting the electrochemical driving force for potassium secretion. [6]
5. Pearl: The dangerous combination is trimethoprim plus a drug that already retains potassium.

5. Why: ACE inhibitors, angiotensin receptor blockers and spironolactone stack on the same defect; with spironolactone the resulting hyperkalaemia can be severe and potentially fatal. [3]
6. Pearl: Trimethoprim is an organic cation transporter inhibitor as well as an antifolate.
6. Why: It inhibits renal OCT2, raising plasma concentrations of OCT2 substrates and of drugs cleared by tubular secretion such as zidovudine, lamivudine and zalcitabine. [3]
7. Pearl: Methotrexate and trimethoprim are the same insult twice.
7. Why: Both inhibit dihydrofolate reductase, so co-administration gives additive enzyme blockade plus displacement from protein binding and reduced renal tubular secretion, raising the risk of methotrexate toxicity and megaloblastic anaemia. [3]

Common exam traps

1. Trap: "Creatinine went up, so trimethoprim caused acute kidney injury."
1. Correction: Trimethoprim inhibits tubular creatinine secretion, raising serum creatinine and lowering creatinine-based estimated GFR without any change in measured glomerular filtration rate. The rise is reversible. Co-trimoxazole can additionally overestimate creatinine by about 10% through interference with the Jaff alkaline picrate assay. Genuine renal injury is a separate possibility that must still be excluded clinically. [7][3]
2. Trap: "The sulfa component is responsible for the hyperkalaemia."
2. Correction: It is the trimethoprim component that raises potassium, by blocking the distal nephron epithelial sodium channel. Sulfamethoxazole is the component classically implicated in hypersensitivity and hepatic injury. [3][6]
3. Trap: "Trimethoprim cannot affect human folate because it targets a bacterial enzyme."
3. Correction: Humans have dihydrofolate reductase as well. Selectivity is quantitative - markedly higher affinity for the bacterial enzyme - not absolute, and folate deficiency with megaloblastic anaemia is a recognised adverse effect. [5][3]
4. Trap: "Give folic acid to correct trimethoprim-induced marrow suppression."
4. Correction: The block is downstream of dihydrofolate, so the rescue agent is folinic acid (leucovorin), which bypasses the inhibited reductase step. Folic acid supplementation is what is recommended alongside exposure in pregnancy, a different indication. [3]
5. Trap: "Trimethoprim is a safe choice in early pregnancy because it is only an antibiotic."
5. Correction: First-trimester co-trimoxazole exposure increases congenital malformations including cardiac defects, cleft lip or palate and neural tube defects - the expected consequence of folate antagonism during organogenesis. Use requires a risk-benefit decision with folic acid supplementation. [3]
6. Trap: "Trimethoprim alone and TMP-SMX are interchangeable."
6. Correction: Trimethoprim alone is a urinary agent; the combination adds the sulfonamide half and with it *Pneumocystis jirovecii*, toxoplasmosis and other indications, plus the sulfonamide hypersensitivity and hepatotoxicity profile. See the sulfonamides page for that half. [3][4]

Self-test questions

1. Question: Which enzyme does trimethoprim inhibit, and what is the immediate consequence?
1. Dihydropteroate synthase, so para-aminobenzoic acid can no longer be incorporated into dihydrofolate
2. Dihydrofolate reductase, so dihydrofolate is not reduced to tetrahydrofolate
3. Bacterial DNA gyrase, so the chromosome cannot be supercoiled
4. The 50S ribosomal subunit, so peptide bonds cannot be formed
1. Explanation: Trimethoprim occupies bacterial dihydrofolate reductase as a competitive inhibitor, halting the reduction of dihydrofolate to its active tetrahydrofolate form. Without tetrahydrofolate the organism cannot assemble purines, so DNA and protein production stall. The step before this one, from para-aminobenzoic acid to dihydrofolate, belongs to sulfamethoxazole and dihydropteroate synthase. [3]
2. Question: Trimethoprim and sulfamethoxazole are each bacteriostatic when used alone. What changes when they are given together?

1. The pair becomes bacteriostatic against a broader range of organisms but never cidal
2. Sulfamethoxazole raises trimethoprim plasma levels, so a smaller amount of trimethoprim suffices
3. The two drugs bind opposite faces of the same enzyme, doubling the rate of inhibition
4. Two consecutive steps of one pathway are blocked, which yields bactericidal activity in certain settings such as the urinary tract
2. Explanation: The synergy is positional rather than pharmacokinetic. Sulfamethoxazole starves the pathway of dihydrofolate by inhibiting dihydropteroate synthase, and trimethoprim shuts down the reductase that would consume whatever dihydrofolate remains. Interrupting the pathway at two consecutive points converts two bacteriostatic drugs into a combination that kills in certain settings, the urinary tract among them. [3]
3. Question: By what mechanism does trimethoprim raise serum potassium?
 1. Competitive antagonism at the mineralocorticoid receptor of the collecting duct
 2. Inhibition of the sodium-potassium-chloride cotransporter in the thick ascending limb
 3. Direct inhibition of skeletal muscle Na/K-ATPase, driving potassium out of cells
 4. Blockade of the epithelial sodium channel in the distal nephron, exactly as amiloride does
3. Explanation: The drug behaves like a potassium-sparing diuretic at the distal nephron, closing the epithelial sodium channel and so removing the electrochemical gradient that drives potassium into the urine. Renal impairment, older age, and co-prescription of ACE inhibitors, angiotensin receptor blockers or spironolactone all magnify the resulting rise in potassium. [6][3]
4. Question: A patient taking trimethoprim shows a rising serum creatinine, yet measured glomerular filtration rate is unchanged. What best accounts for this?
 1. Early acute tubular necrosis that has not yet reduced filtration
 2. Muscle breakdown releasing creatine and creatinine into the plasma
 3. Inhibition of tubular creatinine secretion, giving a reversible and artefactual rise
 4. Accelerated hepatic creatinine synthesis driven by folate blockade
4. Explanation: Creatinine is cleared partly by tubular secretion, and trimethoprim blocks that secretion. Serum creatinine therefore climbs and any creatinine-based estimate of filtration falls, while true filtration is untouched; the change reverses once the drug stops. The combination product can add roughly a further tenth through interference with the Jaffe alkaline picrate assay. None of this excludes genuine kidney injury, which still has to be assessed on its own merits. [7][3]
5. Question: Bone marrow suppression from folate antagonism has developed during co-trimoxazole therapy. Which rescue agent is appropriate, and why?
 1. Folic acid, because it supplies the substrate that the inhibited enzyme requires
 2. Folinic acid (leucovorin), because it enters the pathway beyond the blocked reductase step
 3. Vitamin B12, because the anaemia has a megaloblastic blood film
 4. Ferrous sulfate, because recovering marrow has a high iron requirement
5. Explanation: The blockade sits at the reduction of dihydrofolate, so supplying more of the substrate upstream achieves nothing. Folinic acid bypasses the inhibited enzyme and is what is used, under specialist direction, until haematopoiesis recovers. Folic acid has a separate role as supplementation alongside exposure during pregnancy, which is a different question altogether. [3]
6. Question: Human cells possess dihydrofolate reductase. Why is trimethoprim nonetheless usable as an antibacterial?
 1. Because its affinity for the bacterial enzyme is far greater than for the human one, a margin that is large but quantitative rather than absolute
 2. Because human cells lack dihydrofolate reductase in the cytoplasm, expressing it only in mitochondria
 3. Because human cells take up preformed tetrahydrofolate from the diet and never need the reductase
 4. Because the drug cannot cross mammalian cell membranes at all
6. Explanation: Selectivity here is a matter of degree, not of a target that humans lack. The bacterial and human active

sites differ and the drug binds the bacterial version much more tightly, but the margin has limits - which is precisely why folate deficiency, megaloblastic anaemia and first-trimester teratogenic risk remain real adverse outcomes. [5][3]

7. Question: Which fetal outcome is associated with first-trimester exposure to co-trimoxazole?

1. Irreversible sensorineural deafness
2. Grey baby syndrome from immature glucuronidation
3. Congenital malformations including cardiac defects, cleft lip or palate and neural tube defects
4. Fetal tooth discoloration and impaired bone growth

7. Explanation: Antagonising folate during organogenesis produces exactly the pattern of defects one would predict, and an excess of cardiac, orofacial cleft and neural tube anomalies is reported after exposure in the first trimester. Any use in that window is therefore an explicit risk-benefit judgement by the treating clinician, with folic acid supplementation recommended if treatment goes ahead. [3]

8. Question: What is the principal mechanism of acquired resistance to trimethoprim and to trimethoprim-sulfamethoxazole?

1. Plasmid-encoded variant forms of dihydrofolate reductase and dihydropteroate synthase that the drugs no longer inhibit
2. Plasmid-encoded beta-lactamases that hydrolyse both components
3. Methylation of the ribosomal binding site so the drugs cannot attach
4. Point mutation in the A subunit of DNA gyrase

8. Explanation: Resistance is achieved by swapping the target rather than by destroying the drug: plasmids carry genes for altered versions of both enzymes that the antifolates cannot inhibit, with efflux and reduced permeability contributing as well. Background resistance among urinary gram-negatives such as *Escherichia coli* and *Klebsiella pneumoniae* is common enough that local antibiogram data, not habit, should govern empiric choice. [3][4]

Frequently asked questions

1. Question: Why does adding sulfamethoxazole make trimethoprim more effective?

1. Answer: Because the two drugs block consecutive steps of one pathway. Sulfamethoxazole stops dihydrofolate being made from para-aminobenzoic acid, and trimethoprim stops dihydrofolate being converted to tetrahydrofolate. Individually each is bacteriostatic; together they are bactericidal in certain settings such as the urinary tract. [3]

2. Question: If humans also have dihydrofolate reductase, why does trimethoprim not poison the patient?

2. Answer: Selectivity. Trimethoprim binds the bacterial enzyme far more tightly than the human one, and the active sites differ. That margin is large but not infinite, which is why folate deficiency, megaloblastic anaemia and first-trimester teratogenic risk are still real. [5][3]

3. Question: Why does trimethoprim raise potassium?

3. Answer: It blocks the epithelial sodium channel in the distal nephron in the same manner as amiloride, which reduces renal potassium excretion. The effect matters most in renal impairment, in older adults, and alongside ACE inhibitors, angiotensin receptor blockers or spironolactone. [6][3]

4. Question: Does a rising creatinine on trimethoprim mean the kidneys are failing?

4. Answer: Not necessarily. Trimethoprim inhibits tubular creatinine secretion, so serum creatinine rises and creatinine-based estimated GFR falls while measured glomerular filtration rate is unchanged, and the change reverses on stopping. Genuine acute kidney injury still occurs, particularly in older adults with chronic kidney disease, so this is a reason to assess rather than to ignore. [7][3]

5. Question: Folic acid or folinic acid?

5. Answer: Folinic acid (leucovorin) is what bypasses the inhibited reductase step and is used when bone marrow suppression has developed, on specialist direction. Folic acid supplementation is what is recommended alongside exposure in pregnancy. They are not interchangeable answers. [3]

6. Question: Is trimethoprim safe in pregnancy?

6. Answer: First-trimester exposure to co-trimoxazole increases congenital malformations including cardiac defects,

cleft lip or palate and neural tube defects, which is what folate antagonism during organogenesis would predict. Any use needs an explicit risk-benefit decision by the treating clinician, with folic acid supplementation if therapy proceeds.

[3]

7. Question: What does trimethoprim alone still get used for?

7. Answer: Uncomplicated urinary tract infection, using its activity against aerobic gram-negatives such as *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Enterobacter* species. Resistance is common, so local susceptibility data matter. [4]

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