Co-trimoxazole use in adults
Information for prescribers

This information is provided to facilitate the safer prescribing of co-trimoxazole in adults in the acute care settings within NHS Lanarkshire (NHSL).

Co-trimoxazole

Co-trimoxazole is being introduced into the updated NHSL Acute Empirical Antibiotic Guidance. Co-trimoxazole is restricted by the Committee on Safety of Medicines for a limited range of indications, however it is being recommended empirically for some indications in NHSL. This use is off-label, but is supported by the evidence base, local sensitivities, and has been agreed by the AMC and ADTC. Co-trimoxazole has not been restricted in the same way in other countries. It has successfully been used in other Scottish Health Boards since 2009 to treat urinary, intra-abdominal and severe respiratory infections.

Drivers for change

1. Inclusion of co-trimoxazole as an empirical option will align prescribing practice with other Scottish Health Boards.
2. Co-trimoxazole has high oral bioavailability and can therefore promote the use of oral antibiotics instead of intravenous route where appropriate.
3. Co-trimoxazole has a lesser risk of *Clostridioides difficile* infection (CDI) compared to the antibiotics commonly associated with a high risk of CDI: cephalosporins, co-amoxiclav, clindamycin and quinolones (e.g. ciprofloxacin and levofloxacin). Antibiotics commonly associated with a high risk of CDI should be avoided where possible in frail elderly patients. Co-trimoxazole treatment may be an option where there is a greater risk of CDI, or as an alternative antibiotic in patients with true penicillin allergy.

Adverse effects

Antibiotics are extremely important in treating bacterial infections. However, it should be recognised that **all** antibiotics are associated with some adverse effects, for example:

- Risk of *Clostridioides difficile* infection
- Tendon damage (including rupture) – MHRA alert with quinolones
- Risk of convulsions – CSM alert with quinolones
- QTc prolongation – known risk with quinolones and macrolides

Co-trimoxazole has been associated with rare but serious skin and blood adverse effects. These are more common with higher doses (e.g. dose used for *Pneumocystis jirovecii* infections) and more prolonged courses than recommended in the empirical guidance.

Prescribers should be aware of the important safety information, cautions, side effects and monitoring associated with co-trimoxazole and should consider appropriateness on an individual patient basis.

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What is Co-trimoxazole?

Co-trimoxazole is an antibacterial drug composed of two active principles, sulfamethoxazole and trimethoprim. Sulfamethoxazole and trimethoprim are used in combination (as co-trimoxazole) because of their synergistic activity against bacterial folic acid synthesis. Previous brand name: Septrin®.

Therapeutic indications

Co-trimoxazole is recommended for use in NHS Lanarkshire if:

- listed as a treatment option on the Empirical Antibiotic Guidelines
- when recommended by an Infection Specialist
- or as indicated by positive culture and sensitivity report. Organisms that are reported as sensitive to trimethoprim on microbiology results will also be sensitive to co-trimoxazole.

Co-trimoxazole indications in the NHSL Empirical Antibiotic Guidance are considered off-label. Use of co-trimoxazole in NHS Lanarkshire has been agreed by the ADTC.

Dosing Advice

Co-trimoxazole has excellent bioavailability – consider the oral route. For treatment of susceptible infections:

Oral:	**Intravenous Infusion:**
960mg 12 hourly	**960mg 12 hourly**
NHS Indicative Price: £1.89 for 28 x 80mg/400mg tablets	**NHS Indicative Price:** £47.15 for 10 x 80mg/400mg/5ml solution for infusion ampoules

Please note: doses for the treatment of *Pneumocystis jirovecii* (*Pneumocystis carinii*) infections are much higher – consult BNF/SPC.

Dose adjustments in renal impairment

CrCl (ml/min)	Adult dosage recommendation
> 30	960mg 12 hourly
15-30	480mg 12 hourly
< 15	Not recommended

Monitor for hyperkalaemia and transient rises in serum creatinine in patients with renal impairment.

Contraindications / Cautions

For a full list see BNF/SPC.

Contraindications: Acute porphyrias; any history of hypersensitivity or allergy to co-trimoxazole, Septrin®, sulfamethoxazole or trimethoprim; drug-induced immune thrombocytopenia, previous Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS) with previous co-trimoxazole use.

Cautions: Asthma; avoid in patients with serious haematological disorders (unless under careful specialist supervision); elderly (increased risk of serious side-effects); avoid in severe liver disease; G6PD deficiency (risk of haemolytic anaemia); maintain adequate fluid intake; predisposition to folate deficiency; predisposition to hyperkalaemia. Avoid in Congenital Long QT Syndrome.

Pre-checks / Monitoring required

- U&Es – especially potassium, FBC, LFTs.
- Consider folate level if for long-term treatment or if predisposed to folate deficiency.
- Maintain adequate urinary output. Monitor and ensure adequate fluid intake.

Adverse Effects

For a full list see BNF/SPC.

Frequency:
Very common ≥ 1/10,
Common ≥ 1/100 and <1/10
Uncommon ≥ 1/1000 and <1/100
Rare ≥ 1/10,000 and <1/1000
Very rare <1/10,000
Not known

Most common adverse effects include headache, GI disturbances, rash, fungal overgrowth, and hyperkalaemia. May see a rise in serum creatinine levels, which may be due to competitive inhibition of tubular secretion of creatinine. Monitor U&Es during treatment.

Very rare / rare serious adverse reactions:
Discontinue co-trimoxazole immediately if any of the following develop:

- **Blood disorders** (including leucopenia, thrombocytopenia, megaloblastic anaemia, eosinophilia). Serious adverse effects are more common with high doses (e.g. dose used for *Pneumocystis jirovecii* infections) or prolonged courses. FBC should be monitored.
- **Serious skin reactions** (e.g. SJS, TEN, DRESS) have been very rarely reported. Monitor closely for progressive skin reaction or rash often with blisters or mucosal lesions, fever, eosinophilia present. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment. Best results come from early diagnosis and immediate discontinuation of suspect drug.

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	• **Respiratory toxicity** has been reported very rarely. Onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function may be preliminary signs of Acute Respiratory Distress Syndrome. • **Fulminant hepatic necrosis and cholestatic jaundice** has been very rarely reported. **Urinary output** should be maintained at all times to reduce the risk of crystalluria (rare occurrence). Risk increased in malnourished patients. Monitor and ensure adequate fluid intake. Report any suspected serious adverse reactions via the Yellow Card Scheme.
Interactions *Interactions with co-trimoxazole (trimethoprim/ sulfamethoxazole) include:*	*For a full list see BNF/SPC.* **Methotrexate** – co-trimoxazole may increase free plasma levels of methotrexate. Methotrexate and trimethoprim are both anti-folate drugs. Risk of bone marrow depression and/or pancytopenia. Avoid concurrent use with co-trimoxazole. **Drugs that can cause hyperkalaemia (e.g. angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers, and diuretics)** — concurrent use may result in clinically significant hyperkalaemia. Monitor potassium closely. **Diuretics —** in elderly people receiving diuretics, mainly thiazides, potential increased risk of thrombocytopenia with or without purpura. Manufacturer makes no specific recommendation. **Digoxin** — concurrent trimethoprim with digoxin can increase plasma digoxin levels in the elderly. Monitor for symptoms of digoxin toxicity (e.g. nausea, anorexia, or disturbance of colour vision) and check serum digoxin levels. **Phenytoin** — co-trimoxazole may prolong the half-life of phenytoin resulting in increased serum phenytoin levels. Monitor for symptoms of toxicity (e.g. confusion, blurred vision, nystagmus, ataxia, or drowsiness), check serum phenytoin levels and adjust the dose if necessary. **Warfarin** — concurrent treatment with co-trimoxazole may increase anticoagulant effects of warfarin. Monitor the international normalized ratio (INR), and adjust the warfarin dose accordingly. **Sulfonylureas (e.g. gliclazide)** - hypoglycaemia has been rarely reported however recommend increasing blood glucose monitoring and adjust antidiabetic drug doses if necessary.
Administration	**Oral** – Tablets of co-trimoxazole 480mg (consists of trimethoprim 80mg plus sulfamethoxazole 400mg). • Excellent bioavailability – consider the oral route. • Preferable to take tablets with some food or drink to minimise the possibility of gastrointestinal disturbances.
	IV – Ampoules of co-trimoxazole 480mg in 5mL (consists of trimethoprim 80mg plus sulfamethoxazole 400mg). *Full details available from Medusa monograph or SPC, including information for patients with a fluid restriction or prescribed lower/ higher doses.* • Co-Trimoxazole for Infusion must be diluted immediately before administration. • Using a 1 to 25 dilution, give over 60-90 minutes using an infusion pump. • Standard 1 to 25 dilution: Dilute each 5mL (480mg) ampoule with 125mL of glucose 5% or sodium chloride 0.9% e.g. 1 x 5mL ampoule added to 125mL 2 x 5mL ampoules added to 250mL IV co-trimoxazole may cause extravasation, administer via a large peripheral vein or central venous access device.
References	1. Joint Formulary Committee. *British National Formulary* (online) London: BMJ Group and Pharmaceutical Press. Accessed June 2022 via http://www.medicinescomplete.com 2. Accord-UK Ltd. Summary of Product Characteristics for Co-Trimoxazole Tablets 80/400mg. Last updated 23 Mar 2022. Accessed via www.medicines.org.uk 3. Aspen. Summary of Product Characteristics for Co-Trimoxazole 16 mg/ 80mg per ml for Infusion. Last updated 1 Sep 2021. Accessed via www.medicines.org.uk 4. BMJ. Co-trimozazole Use Restricted. Accessed June 2022 via https://dtb.bmj.com/content/33/12/92 5. NICE CKS. Co-trimoxazole Prescribing information. Accessed July 2022 via https://cks.nice.org.uk/topics/leg-ulcer-venous/prescribing-information/co-trimoxazole/ 6. With thanks to NHS Grampian – Empirical Guidance, Co-trimoxazole statement. 7. With thanks to NHS Greater Glasgow & Clyde – GGC Medicines: Co-trimoxazole: Reintroduction to GGC Acute Infection Management Guidelines for Adults. Last updated 23 Feb 2022. 8. CredibleMeds. Accessed via https://www.crediblemeds.org/
Further Information	Further guidance can be obtained from your local microbiology department/ antimicrobial pharmacists.

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