NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Chloramphenicol in Adults SAPG consensus Guidance

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Approval Group:	Antimicrobial Utilisation Committee

Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

Chloramphenicol Prescribing In Adult Patients - Consensus Guidance

Background

This guidance has been produced to support prescribing of chloramphenicol, in non-pregnant, adult patients, in NHS Scotland Boards. Systemic chloramphenicol treatment is rarely used in clinical practice, as less toxic antibacterials are preferred. However, as it is active against a range of bacteria, in certain circumstances where treatment options are limited by resistance, intolerance or allergy it may be required. Detailed advice on a number of factors that should be considered prior to prescribing are provided to support safe and effective treatment.

Use of systemic chloramphenicol **must be authorised** by a member of the Infectious Diseases or Microbiology teams prior to prescribing. Note there may be some local exceptions to requirement for ID/Micro approval e.g. for empirical use in meningitis in penicillin allergy as per local NHS Board guidance.

Key points to remember when prescribing chloramphenicol

- **Dose adjustment may be required in patients who are obese (BMI > 30), and in patients with renal impairment or hepatic impairment**
- **Check for potential drug interactions prior to prescribing**
- **Follow administration instructions carefully to minimise adverse effects**
- **Monitoring of full blood count (FBC), urea & electrolytes (U&Es) and liver function tests (LFTs) is required**
- **Therapeutic drug monitoring is required for treatment > 48 hours duration**
- **Be alert to potential adverse effects**
- **Counsel patients who have received treatment about the risk of aplastic anaemia and ensure note about risk added to primary care clinical record.**

Prepared by: Association of Scottish Antimicrobial Pharmacists
Approved by SAPG: April 2021
For Review: April 2024

Indications for use

Licensed indications: Severe life threatening infections, including meningitis, particularly those caused by *Haemophilus influenzae*

Off label indications: For other severe infections, if less toxic alternatives are not available/suitable: bone and joint infections, respiratory infections, CNS infection

Antimicrobial Activity: Bacteriostatic (bactericidal at high concentrations)
Usually sensitive:

- **Gram positive:** Staphylococci, Streptococci, Enterococci
- **Gram negative:** Haemophilus, Meningococci, Gonococci, Enterobacteriaceae
- **Anaerobes:** including Bacteroides
- **Atypical bacteria**

Resistance: *Pseudomonas spp, Mycobacteria*

Clinical Notes:

- Contra-indications
    - acute porphyria
    - Blood dyscrasias and patients taking medicines liable to suppress bone marrow
    - pregnancy and breast feeding
- Avoid repeated courses

Pharmacokinetics:

Absorption: Well absorbed (80% bioavailability, some sources quote 90-100%)
Distribution: Small molecule that diffuses well into many body tissues including CSF (even in absence of inflamed meninges), eye, pleural fluid, synovial fluid, ascitic fluid, liver and kidneys.

- CSF concentrations 50% -65% of serum concentrations
- Volume of distribution 0.5 – 1 L/kg
- Highly lipid soluble, not highly protein bound (≈50%)
- Crosses placenta

Metabolism: Metabolised in liver (90%) to inactive metabolite with very small amounts of active drug are recovered in the bile
Excretion: 90% excreted in urine (only 5-10% as active drug)

- Half-life = 1.5 to 4 hours
- If CrCl <40ml/min, urinary concentrations are insufficient to treat susceptible organisms

Dosage

Usual dose:

- 50mg/kg /day usually in 4 divided doses – usual maximum 4g/day
- 100mg/kg/day can be given for a short period e.g. first 24-48 hours of meningitis treatment – maximum 2g QDS (8g/day) then adjust as per levels. EUCAST suggests always using IV 2g QDS (high dose) for meningitis
- Increase risk of bone marrow toxicity if >4g/day
- Oral dose needs to be rounded to nearest 250mg (as this is only available capsule strength)
- Depending on levels (see below) can reduce total dose and give in 2 or 3 divided doses

Dosing for obese patients:

- Consider use of adjusted body weight (AdjBW) if the patient's total body weight is >20% over ideal body weight (IBW)
    - Ideal body weight table
    - AdjBW= IBW + 0.4 (actual body weight – IBW)
- As above maximum 8g/day for first 24-48 hours adjust dose based on levels

Dosing for patients with renal impairment:

- No dose reduction required in patients with renal impairment
- Dialysis patients – discuss with pharmacist
- Do not use for urinary tract infections if CrCl <40ml/min

Dosing for patients with hepatic impairment:

- Avoid or decrease dose - conjugated at slower rate to metabolite
- Higher risk of bone marrow suppression - use TDM (see below) to adjust dosing

Route of Administration:

This guidance covers oral and parenteral (IV and IM) routes of administration only.

Oral: Well absorbed (bioavailability at least 80%). Take with or without food.

Intravenous: Pro drug (sodium succinate ester) hydrolysed to active chloramphenicol

- Active drug levels in serum are only 70% of oral levels due to incomplete hydrolysis
- IV injection over 3-5 minutes (maximum concentration 100mg/ml) - intensely bitter taste if rapid administration or more concentrated solution
- IV infusion over 20-30 minutes
- Further information on reconstitution and administration on Medusa website

Intramuscular: Non-preferred route

- Whilst this is an option it has important practical implications - administration of a 1g dose would need to be split and given via 3 or 4 sites
- Older reports suggest slow and unpredictable absorption but appears from results of a number of studies to be clinically effective
- 30% unhydrolysed in urine (due to delayed absorption of ester not decreased hydrolysis)

Monitoring:

Haematology/biochemistry

- Baseline – FBC, LFTs, U&Es
- Week 1 – every 3-4 days – FBC (increase frequency if the patient is hospitalised and unwell)
- Week 2 onwards – weekly FBC and U&Es/LFTs every 2 weeks
- Be aware of potential for delayed blood dyscrasias after course complete

Therapeutic Drug Monitoring (TDM)

- Narrow therapeutic index so recommended in any patients where therapy is likely to continue for >48 hours and especially in patients with hepatic disease and patients who are elderly, obese, or may have drug-drug interactions

- Short half-life so can be done after 24 hours if required
- Samples sent to the Bristol Antimicrobial Reference Laboratory for measurement of serum levels
- Pre dose level ideally <10mg/L but definitely <15mg/L. If level too high, extend dosage interval e.g. from 6 hourly to 8 hourly
- Post dose (2h) level 10-25mg/L. If level too high, consider omitting doses and restart at reduced dose
- Repeat TDM at 5-7 days if in range (or sooner if outwith range)

Interactions: Inhibits CYP2C9/2C19/3A4

- Interactions with warfarin, tacrolimus, anti-epileptics, sulphonylureas, voriconazole
- Can also decrease response to Fe/B12 supplements
- Paracetamol warning in SPC but refer to data in Stockley's Drug Interactions

Adverse Drug Reactions:

- Haematologic
    - Bone marrow suppression – increased risk with dose >4g/day or level >25mg/L
    - Aplastic anaemia (rare but often fatal) – 1:24,000 to 40,000 patients
        - Often not dose related
        - 22% happen around the time of the chloramphenicol course but many happen weeks to months later
        - Counsel patient and request addition to primary care clinical record re risk
- Fever, rash
- Anaphylactoid reactions
- Optic atrophy/neuropathy – very rare
- Ototoxicity
- Digital parasthesias
- Minor disulfiram type reactions
- GI symptoms – less common than tetracyclines

References used:

1. The Sanford Guide to Antimicrobial Therapy 2019
2. Summary of Product Characteristics accessed via MHRA website
3. BNF accessed online
4. Kucers' The Use of Antibiotics accessed online
5. Micromedex drug information accessed online
6. A Spec et al Comprehensive Review of Infectious Diseases accessed online
7. John Hopkins Antimicrobial Guide accessed online
8. Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases accessed online
9. Medusa Injectable Medicines Guide accessed online
10. Martindale The Complete Drug Reference accessed online