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
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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
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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
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10. Martindale The Complete Drug Reference accessed online