

**Oral antibiotics for the management of Bone and Joint Infections – adult patients
Shared Care Protocol**

This protocol provides prescribing and monitoring guidance for oral antimicrobial therapy used in the treatment of Bone and Joint Infections. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the [BNF](#).

Shared Care Responsibilities

Shared care assumes communication and agreement between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. Specialists must contact GPs as soon as decision is made to commence treatment with the antibiotic regimen to ensure adequate time for full communication, support and agreement to be made. Specialists must retain prescribing until the patient's clinical condition is stable or predictable.

Specialist

- Complete pre-treatment assessment and communicate results to the GP
- Specify the patient's treatment plan and ensure that it is communicated to GP at the point of transfer of prescribing. Each patient will have targeted treatment which could include more than one agent depending on cultures and sensitivities. Examples of commonly used regimens include:
 - Rifampicin and Ciprofloxacin
 - Rifampicin and Clindamycin
 - Rifampicin and Doxycycline
 - Amoxicillin (monotherapy)
 - Doxycycline (monotherapy)
- Initiate treatment and prescribe until the patient is discharged, and then 28 days to be provided on discharge from hospital
- Where the patient is receiving Rifampicin and LFTs are required, state on the discharge letter the date when the next LFT blood test is due
- If your patient is receiving Rifampicin, the patient must be counselled to report any side effects specifically fever, malaise, vomiting, jaundice or unexplained deterioration during treatment and during any further interaction with the patient they must be asked if they have experienced any side effects
- To carry out a medical follow-up outpatient appointment 6 weeks following discharge, and communicate any changes to treatment to the GP
- Specify proposed duration of therapy and monitoring requirements, communicating the plan to the GP at the point of transfer of prescribing
- Ensure the patient understands the nature and complications of drug therapy and their role in reporting adverse effects promptly
- Provide a copy of patient information leaflets
- Be available to give advice to GP and patient during treatment

GP

- Prescribe medication as recommended below, once transfer of prescribing is complete
- Ensure all monitoring is completed in accordance with 'on-going monitoring' section
- Monitor patient for adverse effects, contraindications and precautions as listed below
- Take subsequent recommended actions as outlined below, including referral back to specialist if appropriate
- If your patient is receiving Rifampicin, during medication reviews they must be asked if they have experienced any side effects (see rifampicin section below)

Patient

- Agree to treatment and monitoring after making an informed decision
- Agree to being under the shared care of the GP and specialist
- Attend for blood tests and monitoring when required
- **Report any side effects to your GP, pharmacist or a member of the specialist team**
- If you are taking Rifampicin - during any interactions with healthcare professionals, including when your medication is dispensed, state that you are on this medication and if applicable report any side effects

Background for Use

Bone and joint infection is a relatively rare condition which usually requires a combination of surgical and medical management. Definitive treatment therefore most commonly commences in hospital. Until recently, the initial course of post-operative antibiotic therapy was routinely administered intravenously, and management of such patients in the community was supervised by the Outpatient Parenteral Antibiotic Therapy (OPAT) team. There has recently been a shift to earlier oral antibiotic therapy such that most patients are discharged on oral antibiotic therapy. This has the advantages of earlier discharge from hospital, reduced costs and limitation of the risk of complications relating to long-term intravenous access devices. The majority of bone and joint infection patients will now be going home on oral antimicrobial therapy, with the initial 4 week supply of oral medicines provided by the hospital, and the remainder of the course through primary care. Where the selected antibiotic is restricted to hospital prescription only, the entire course will be supplied by the hospital pharmacy.

Supporting Information

OVIVA (Oral versus intravenous antibiotics) trial compared oral and intravenous antibiotics for the initial 6 weeks of treatment for bone and joint infections (with oral follow-on permitted in both arms of the study). There was non-inferiority with treatment with oral antibiotics, with additional benefits to the Health Economy with reduced cost of treatment compared to IVs. The manuscript is still in press so the below link is to an abstract:

The OVIVA Trial. The Bone and Joint Journal (Online supplement Volume 99-B, Issue _22 / December 2017 pp 42

<https://online.boneandjoint.org.uk/doi/abs/10.1302/1358-992X.2017.22.042>

Antibiotics

Rifampicin

Dose: Usually 300mg BD, can be up to 450mg BD. Duration will be specified by the Bone Infection Team at OUHFT.

Pre treatment assessment

FBC, U&Es, LFTs

Ongoing monitoring

FBC and U&Es

According to clinical need only if directed by the specialist or in response to emerging clinical indicators– discuss any concerns with specialist

LFTs

In patients with pre-existing liver disease, hepatic impairment, or alcohol dependence:

- monitor liver function weekly for the first 2 weeks, then every 2 weeks until rifampicin stops.

In other patients:

- Hepatic function should be checked before treatment and then 1 month after starting rifampicin.
- If there is no evidence of liver disease (and pre-treatment liver function is normal), further checks are only necessary if the patient develops fever, malaise, vomiting, jaundice or unexplained deterioration during treatment. The patient should be specifically questioned during medication reviews concerning symptoms associated with adverse reactions.

Contraindications and precautions^{1,5}

Contra-indicated in:

- Previous Rifampicin hypersensitivity
- Hypersensitivity to any of the other Rifamycins
- Acute porphyria's
- Jaundice
- Concurrent use of Saquinavir/Ritonavir therapy
- Patients' taking Ticagrelor

Pregnancy and breast feeding^{1,5}

- Rifampicin should only be used in pregnancy if the benefit of treatment outweighs risk
- Rifampicin is excreted in breast milk but the amount is too small to be harmful

Actions to be taken

Side effect	Action
Signs of liver disorder: jaundice, malaise, pruritis, persistent nausea & vomiting	Check LFTs and discuss with specialist
Hypersensitivity reactions	Anaphylaxis, rash – stop Rifampicin and discuss with specialist
WBC less than $3.0 \times 10^9/L$ Neutrophils less than $2.0 \times 10^9/L$ Platelets less than $100 \times 10^9/L$	Repeat FBC - if low discuss with specialist
AST/ALT greater than 3 times the upper limit of normal reference range Bilirubin 3 times the upper limit of normal	Moderate rises in bilirubin and/or transaminase levels may occur and is not in itself a reason for stopping treatment. The decision should be made after repeating the tests, noting trends and considering them in conjunction with the patients' clinical condition and rate of change of parameters. Any concerns should be discussed with the specialist.

Notable drug interactions^{1,5}

Combined hormonal contraceptives	An alternative method of contraception (such as an IUD) is recommended. The alternative method of contraception should be continued for 4 weeks after stopping Rifampicin
Lamotrigine	Rifampicin markedly increases the clearance of Lamotrigine – adjust dose of Lamotrigine
Phenytoin	Rifampicin decreases the concentration of Phenytoin – manufacturer advises use with caution and adjust dose of Phenytoin
Warfarin	Rifampicin reduces the anticoagulant effect of Warfarin – monitor INR closely and adjust Warfarin dose accordingly. There is a significant risk of over-anticoagulation on stopping Rifampicin unless appropriate dose adjustments are managed in a carefully planned manner
Apixaban	Rifampicin reduces the anticoagulant effect of Apixaban. Avoid when given for the treatment of DVTs and PE's
Dabigatran	Rifampicin reduces plasma concentrations of Dabigatran; manufacturer advises avoid
Edoxaban	Rifampicin reduces plasma concentrations of Edoxaban

Rivaroxaban	Rifampicin is predicted to moderately decrease the exposure to Rivaroxaban. Manufacturer advises avoid unless patient can be monitored for signs of thrombosis
Ciclosporin	Rifampicin decreases the concentration of Ciclosporin – monitor Ciclosporin levels closely and the dose of Ciclosporin may need to be adjusted
Mycophenolate	Rifampicin decreases the concentration of Mycophenolate. Manufacturer advises monitor and adjust dose

Amoxicillin

Dose: 1g TDS. Dose may need to be adjusted in renal impairment. Duration will be specified by the Bone Infection Team at OUHFT.

Pre treatment assessment

FBC, U&Es

Ongoing monitoring

FBC and U&Es according to clinical need only if directed by the specialist or in response to emerging clinical indicators– discuss any concerns with specialist

Contra-indications or precautions^{1,2}

Contra-indications:

- History of penicillin allergy
- History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a Cephalosporin, Carbapenem or Monobactam)

Caution:

Convulsions may occur in patients with impaired renal function or in those receiving high doses of Amoxicillin or in patients with predisposing factors (e.g. history of seizures, treated epilepsy or meningeal disorders)

Pregnancy and breast feeding^{1,2}

Safe for use in pregnancy and breast feeding

Actions to be taken

Side effects	Action
Hypersensitivity reactions	Anaphylaxis, rash – stop Amoxicillin and discuss with specialist
Diarrhoea	If persistent, severe, or associated abdominal pain/distension then stop and contact specialist
Deterioration in renal function to CrCl less than 30ml/min	Look for alternative causes. Repeat U&Es; if abnormal results then discuss with specialist
Convulsions	Withhold amoxicillin and discuss with specialist

Additional side effects or problems should be discussed with the specialist.

Notable drug interactions^{1,2} – see BNF and SPC for complete list

Increased risk of toxicity when given with Methotrexate – monitor FBC, U&ES, and LFTs

Amoxicillin potentially alters the anticoagulant effect of Warfarin. Monitor INR and adjust Warfarin dose accordingly with the addition or withdrawal of Amoxicillin

Concomitant use of Probenecid with Amoxicillin may result in increased and prolonged blood levels of Amoxicillin

Ciprofloxacin

500mg BD (dose increased to 750mg in *Pseudomonal* infection). Dose may need to be adjusted in renal impairment. Duration will be specified by the Bone Infection Team at OUHFT.

Pre treatment assessment

FBC, LFTs, U&Es

Ongoing monitoring

FBC, LFTs, U&Es according to clinical need only if directed by the specialist or in response to emerging clinical indicators (see 'actions to be taken table below') – discuss any concerns with specialist

Contra-indications and precautions ^{1,3}

Contra-indications

- Previous hypersensitivity to ciprofloxacin or other quinolones
- Those with a history of tendon disease/ disorder related to quinolone use
- Patients taking Methotrexate
- Concomitant use of Tizanidine

Caution

- Patients with myasthenia gravis
- Patients at risk for torsades de pointes arrhythmia – Ciprofloxacin can prolong the QT interval
- Patients with glucose-6-phosphate dehydrogenase deficiency. Haemolytic reactions have been reported. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk
- Patients with central nervous system disorders which may be pre-disposed to seizure

Pregnancy and breast feeding ^{1,3}

- Avoid in pregnancy
- Excreted in breast milk – manufacturer advises avoid

Actions to be taken^{1,3}

Side effects	Action
Hypersensitivity reactions	Anaphylaxis, rash – withhold Ciprofloxacin and discuss with specialist
Seizures	Discontinue Ciprofloxacin and contact specialist
Psychiatric disorders e.g. hallucinations, depression, anxiety, confusion	Discuss with specialist
Tendonitis or tendon rupture	Discontinue Ciprofloxacin and contact specialist
Diarrhoeal states	Discuss with specialist
Signs of hepatic disease e.g. anorexia, jaundice, dark urine, pruritus or tender abdomen	Re-check LFTs. If results are abnormal then discuss with specialist

- taking NSAIDs at the same time as Ciprofloxacin may increase the risk of seizures
- Tendon damage can occur within 48 hours of starting treatment; cases have also been reported several months after stopping treatment. Patients over 60 years old are more prone to tendon damage, and the risk is increased by concomitant use of corticosteroid
- Patients taking another medication which may prolong the QT interval should **ideally** have a follow-up ECG at least a week after starting Ciprofloxacin. If QT is lengthening, discuss with specialist.

Notable drug interactions^{1,3} – see BNF and SPC for complete list

Use of Ciprofloxacin with either Methotrexate or Tizanidine is contra-indicated

Increased risk of seizures when given with NSAIDs

Increased anticoagulant effect of Warfarin – monitor INR closely or switch to an alternative anticoagulant

Do not take milk, indigestion remedies or medicines containing calcium, magnesium, aluminium, iron or zinc. Ciprofloxacin should be administered 1-2 hours before or at least 4 hours after you take these preparations

Clindamycin

300-450mg TDS. Duration will be specified by the Bone Infection Team at OUHFT.

Pre treatment assessment

FBC, LFTs, U&Es

Ongoing monitoring

FBC, LFTs, U&Es according to clinical need only if directed by the specialist or in response to emerging clinical indicators– discuss any concerns with specialist

Contra-indications and precautions^{1,4}

Contra-indications:

- Hypersensitivity to Clindamycin
- Diarrhoeal states
- Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption
- Avoid in acute porphyrias

Pregnancy and breast feeding^{1,4}

Safe for use in pregnancy and breast feeding

Actions to be taken

Side effects	Action
Diarrhoea	Withhold treatment and discuss with specialist
Hypersensitivity reactions	Anaphylaxis, rash, Stevens-Johnson syndrome – stop Clindamycin and inform specialist

Notable drug interactions^{1,4}– see BNF and SPC for complete list

No notable drug interactions

Doxycycline

Dose: 100mg BD. Duration will be specified by the Bone Infection Team at OUHFT.

Pre treatment assessment

FBC, LFTs, U&Es

Ongoing monitoring

FBC, LFTs, U&Es according to clinical need only if directed by the specialist or in response to emerging clinical indicators (see 'actions to be taken table below') – discuss any concerns with specialist

Contra-indications and precautions^{1,5}

Contra-indicated in patients with hypersensitivity to Doxycycline or other Tetracyclines

Caution in:

- Myasthenia gravis (muscle weakness may be increased)
- Systemic lupus erythematosus (may be exacerbated)
- Alcohol dependence
- Patients with hepatic impairment or those receiving potentially hepatotoxic drugs

Patients should be advised to avoid exposure to sunlight or sun lamps and wear sunscreen

Pregnancy and breast feeding^{1,5}

Contraindicated in pregnancy

Contraindicated in breast feeding

Actions to be taken^{1,5}

Side effects	Action
Hypersensitivity reactions	Anaphylaxis, rash, exacerbation of systemic lupus erythematosus – stop Doxycycline and inform specialist
Headache and visual disturbance	May indicate benign intracranial hypertension – withhold treatment and discuss with specialist
AST/ALT greater than 3 times the upper limit of normal	Look for alternative causes. Repeat LFTs: if abnormal results then discuss with specialist
Diarrhoea	Discuss with specialist if symptoms are severe, persistent or worsening

- Sunscreens and protective covering should be encouraged to reduce sunlight exposure

Notable drug interactions^{1,5}– see BNF and SPC for complete list

Do not take indigestion remedies or medicines containing iron or zinc, 2 hours before or after you take this medicine

Increased anticoagulant effect of Warfarin – monitor INR closely

Doxycycline may increase the plasma concentration of Ciclosporin and increase the risk of nephrotoxicity. Co-administration should only be undertaken with appropriate monitoring.

Back-up Information and Advice

Contact details	Oxford University Hospitals NHS Foundation Trust	
Monday to Friday during working hours	BIU registrar (bleep 7186)	OUH switchboard: 0300 304 7777
Weekend and out of hours	Microbiology registrar	OUH switchboard 0300 304 7777
Non-urgent queries	Via e-mail: boneinfectionadvice@nhs.net	

References

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