Name of Document	Pathogen-Specific, Targeted Antibiotic Therapy for Bacteremia and Bone and Joint, Urinary Tract, and Central Nervous System Infections MSF internal protocol
Publication	December 2019 Version 1.0
Owner of the document	Antibiotic Resistance Task Force, Antibiotic Stewardship subgroup Chief author: Marcio Da Fonseca Editor: Emma Veitch
Contact email	antibiotic-resistance@msf.org
Contributors, in alphabetical order	**MSF Antibiotic Stewardship contact group:** Marjolein de Bruycker, Kate Clezy, Caroline Henry-Ostian, Carolina Jiménez, Rupa Kanapathipillai, Ernestina Repetto, Emma de Miguel **Other MSF working groups :** Critical Care WG, Gynecology & Obstetrics WG, Pediatrics WG, Pharmacy WG, Laboratory WG, Surgery WG **External reviewers:** Bone and joint infection: Nico Hartwig, Paul Krogstad, Leonard Marais, Clint Murray, Trisha Peel, Mauro Salles, Pablo Yagupsky, Werner Zimmerli Bacteremia: Madji Al-Hasan, Nick Danema, Christina Hoffer, Andi Lee, Paul O Lewis, Jesús Rodríguez-Baño, Pranita Tamma Urinary tract infection: Nathan P Beahm, Cristina Barroso, James Johnson, Florian M Wagenlehner Central nervous system infection: Michael A Apicella, Nadia Deborah Friedman, Fiona MgGill, Joan L. Robinson, Elizabeth Molyneux
Review date	December 2020
Electronic store	https://msfintl.sharepoint.com/sites/msfintlcommunities/abr/SitePages/Home.aspx

Pathogen-Specific, Targeted Antibiotic Therapy for Bacteremia and Bone and Joint, Urinary Tract, and Central Nervous System Infections

Contents

Abbreviations and Acronyms

ABR	Antibiotic Resistance
ABS	Antibiotic Stewardship
AmpC	Class C Beta-Lactamase (Ambler Classification)
ABS	Antibiotic Stewardship
AMR	Antimicrobial Resistance
AST	Antibiotic Susceptibility Testing
ATB	Antibiotic
BC	Blood Culture
BL/BLI	Beta-Lactam/Beta-Lactamase Inhibitor Combination
BSI	Bloodstream Infection
B&J	Bone and Joint
CBC	Complete Blood Count
CSF	Cerebrospinal Fluid
CNS	Central Nervous System
CoNS	Coagulase Negative *Staphylococcus*
CrCl	Creatinine Clearance
CRP	C-reactive Protein
CT	Computed Tomography
CVC	Central Venous Catheter
DM	Diabetes Mellitus
EOS	Early Onset Neonatal Sepsis
ESBL	Extended-Spectrum Beta-Lactamase
GAS	Group A *Streptococcus* (*S. pyogenes*)
GBS	Group B *Streptococcus* (*S. agalactiae*)
GI	Gastrointestinal
GNB	Gram-Negative Bacilli
GPC	Gram-Positive Cocci
GU	Genitourinary
HCAI	Healthcare Associated Infection
"I"	Intermediary (an antibiogram/AST result; for EUCAST, "Susceptible - Increased Exposure")
ID	Infectious Diseases
IE	Infective Endocarditis
IM	Intramuscular
IPC	Infection Prevention & Control
IU	International Units
IV	Intravenous
LOS	Late Onset Neonatal Sepsis
LP	Lumbar Puncture
MDR	Multi Drug-Resistant
MIC	Minimum Inhibitory Concentration
MRCoNS	Methicillin-Resistant Coagulase-Negative *Staphylococcus*
MRI	Magnetic Resonance Imaging
MSCoNS	Methicillin-Susceptible Coagulase-Negative *Staphylococcus*
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Susceptible *Staphylococcus aureus*
NTM	Non-Tuberculous Mycobacteria
OPAT	Outpatient Parenteral Antimicrobial Therapy
PCP	*Pneumocystis* Pneumonia
PCT	Procalcitonin
PO	*Per os* (oral antibiotics)
"R"	Resistant, an antibiogram/AST result that shows antibiotic is ineffective against the pathogen
RMP	Rifampicin
"S"	Susceptible, an antibiogram/AST result that shows antibiotic is effective against the pathogen
SIRS	Systemic Inflammatory Response Syndrome
SSI	Surgical Site Infection
SOPs	Standard Operating Procedures
ST	Septic Thrombophlebitis
TB	Tuberculosis
TDM	Therapeutic Drug Monitoring
USG	Ultrasonography
UTI	Urinary Tract Infection
VUR	Vesicoureteral Reflux
WBC	White Blood Cell Count
XDR	Extensively Drug-Resistant
VRE	Vancomycin-Resistant *Enterococcus*

Introduction

Section 1 covers key principles of antibiotic therapy, and Section 2 gives specific guidance to help you choose the correct antibiotic therapy for specific pathologies and patients. Sections 3, 4, and 5 provide detailed information on oral antibiotics, optimal antibiotic durations, and possible complications. The annexes provide more detail on sampling, side effects, dosing, drug monitoring, antibiotics classes and spectra, and lab result interpretation to inform optimal treatment.

Section 1: The Basics of Antibiotic Therapy

This chapter provides guidance on antibiotic choices for **targeted** (directed/definitive) antibiotic treatment that occurs after bacteriological culture and antibiotic susceptibility testing (AST) results are available. It focuses on four important biological samples and respective infectious syndromes:

1. **Blood culture** - **bacteremia** (bloodstream infections - BSI), including the primary focus of infection and metastatic infections;
2. **CSF culture** - central nervous system (CNS) infections, especially **acute bacterial meningitis**;
3. **Bone & joint sample cultures** – **osteomyelitis** and **septic arthritis**;
4. **Urine culture** - Urinary tract infections (UTI) extending beyond the bladder: **upper urinary tract infections** (**pyelonephritis**) and **prostatitis**, but excluding simple cystitis.

The main goals of antibiotic therapy for patients admitted into MSF care are to foster rational, appropriate antibiotic use, to improve patient outcomes, to prevent antimicrobial resistance (AMR) by avoiding the excessive use of broad-spectrum antibiotics, and to potentially decrease costs. These are also the main goals of antibiotic stewardship (ABS) actions. The key stages for successful antibiotic treatment in MSF settings and facilities include:

Stage 1: Empiric Antibiotic Treatment

For serious infections, patients are given broad-spectrum **empiric antibiotic treatment** covering the most likely pathogens, initiated before the exact cause of infection is known. This decision is guided by knowledge of the most common causes of infection, based on local resistance data where available, and aiming to use those antibiotics most likely active[1] against the most likely pathogens involved. The MSF Clinical Guidelines, Pediatric Guidelines and Neonatal Guidelines can help guide empiric antibiotic choices. Antibiotics should never be delayed in severe cases; however, whenever possible antibiotics should begin only after appropriate specimens/samples have been obtained for culture since, once antibiotics have been initiated, culture results may have a lower sensitivity.

Stage 2: Review of Culture/AST Results

Once positive culture results are available from samples taken on first suspicion of infection, and usually after 48-72 hours of empiric antibiotic treatment, treatment can be adjusted towards targeted antibiotic therapy[2]. This decision should be based on knowledge of the bacterial or fungal species, and its pattern of antimicrobial susceptibility. When pathogens are known to be susceptible to various antibiotics, choices can be made that prevent use of last-resort antibiotics, therefore

[1]In this document an "active" antibiotic is defined as one against which a pathogen is demonstrated to be susceptible ("S") by culture/AST and therefore can potentially be eradicated by it.
[2]The term "targeted therapy" used in this guideline is also referred to as directed or definitive therapy.

reserving them for patients infected with highly-resistant bacteria against which options are limited. Key points for targeted therapy:

- Pathogens susceptible ("S") to various antibiotics: regimen should be changed to the simpler therapy. Antibiotics with a broader spectrum and/or active against multi-drug resistant (MDR) or extensively-drug resistant (XDR) bacteria should be reserved for patients infected with resistant bacteria. De-escalation, or transition of treatment to simpler regimens, should occur as soon as “S” results are received.
- Pathogens resistant ("R") to all empiric antimicrobials: the antibiotics in use must be stopped, and an antibiotic against which the isolate is “S” must be immediately started.
- When an empiric antibiotic regimen was not started: an antibiotic against which the isolate is “S” should now be initiated, avoiding last-resort antibiotics as often as possible.

Stage 3: Assessing Antibiotic Response

When an active antibiotic is used and proper source control has been achieved (table 1.1), most infections will show some clinical signs of response after 72 hours of treatment (often also tallying with the time taken for positive culture results to return from the laboratory). If an antibiotic against which the isolate is “S” was already in use, the patient’s antibiotic response can be assessed at this time (Section 3):

- Clinical response judged adequate: consider shift to step-down, per os (PO; oral) antibiotics after a minimum intravenous (IV) period, unless full IV treatment is recommended – see Section 3.
- Clinical response judged insufficient or in doubt: investigate accordingly (sections 3 and 5), and discuss with specialists - antibiotic stewardship MD on the ground and/or infectious diseases (ID)/AMR advisor; involve pediatricians and surgeons or other specialists as needed and feasible).

Step-by-Step: Using Lab Culture Results to Guide Antibiotic Choices

Even if the above stages and procedures are followed to initiate, assess, and de-escalate antibiotic therapy, they are not useful unless clinicians (with the support from MSF Lab specialists/referents) are correctly interpreting laboratory results from AST and culture testing. Figure 1 outlines the specific steps that should be followed once laboratory results are returned. Reporting of results usually follows European (EUCAST) or American (CLSI)[3] standards, though in some cases MSF may use external laboratories with different standards. Because of this, some AST results may not be reported. Nevertheless, the susceptibility of some unreported antibiotics can be inferred by reviewing results for other antibiotics, or by using knowledge of the intrinsic resistance of the species. Additional information can be found in Annex 3, Basics of Antibiotics. When in doubt, discuss with your MSF ID/AMR and/or Lab Advisor.

[3]EUCAST = European Committee on Antimicrobial Susceptibility Testing; CLSI = Clinical and Laboratory Standards Institute.

Figure 1: Using Lab Culture Results to Guide Antibiotic Choices

STEP 1

Check results from a properly collected and representative culture

- Note the species (isolate) and the antibiotics reported as Susceptible ("S");
- For urine and blood culture isolates, assess clinical relevance - contaminant or true pathogen.

STEP 2

Choose the correct antibiotic: refer to Section 2

Note: If active empiric antibiotics were used, there may already be signs of clinical response when results arrive. If not, consider complications (see Section 5 and discuss with specialist).

IF	**Results show the isolate is sensitive ("S") to all antibiotics**
THEN	Choose **one** IV antibiotic from the first-choice antibiotics group

⇩

IF	**Results show the isolate is not sensitive to ANY reported first-choice antibiotic**
THEN	Choose **one** IV antibiotic from the second-choice antibiotics group

⇩

IF	**Isolate is not sensitive to ANY reported first or second-choice antibiotic**
THEN	Choose **one** IV antibiotic from the third-choice antibiotics group

- Confirm the chosen antibiotic is not among the antibiotics to avoid list (Table 1.3)
- Check the patient's history of drug allergies and reactions
- Consider intrinsic resistance (which may not be reported in AST results – see Annex 3)

STEP 3

Prescribe IV or PO antibiotic(s) in the recommended dose and duration

- For most infections (see exceptions, table 3.1, section 3), stepping down from IV to PO antibiotics is recommended when improving. Use the same culture results to choose an oral antibiotic to complete treatment.
- For neonatal doses: see Annex 4.
- In cases of renal dysfunction, adjust dose accordingly (Annex 5).

STEP 4

If isolate is **Resistant** ("R") to all 1st, 2nd, and 3rd choice antibiotics (MDR/XDR)

- Discuss with specialist; ABS physician and/or ID/AMR Advisor in headquarters; use of Intermediate ("I") antibiotics may be the only option.
- Discussion is compulsory whenever treating Carbapenem-resistant gram-negative bacilli.

Criteria for Severe Infection

In this guide, a severe infection is defined by the presence of one of the following characteristics:

- Sepsis or septic shock (see MSF Clinical, Pediatric or Neonatal guidelines) or
- Severe immunodeficiency (criteria below), or
- Complicated infections (criteria below).

Severe immunodeficiency
• Advanced HIV infection (WHO stages 3 or 4, or CD4<200/mm3; children <5 years: CD4<25% or <750/mm3); • Severe Acute Malnutrition • Neutropenia (Neutrophils <500/mm³) • Cancer, with chemotherapy in the last month • Corticosteroids: prednisone (or equivalent) ≥20mg/day (adults) or ≥0.5mg/kg/day for ≥2 weeks (children) • Poorly controlled diabetes mellitus • Sickle cell disease • Splenectomy (anatomic or functional, e.g. thalassemia). • Extremes of age: neonates or elderly

Complicated infections	
Bacteremia	• Infective endocarditis (IE) or septic thrombophlebitis (ST) • CNS involvement (be it the primary focus or a metastatic infection secondary to bacteremia seeding); • Necrotizing fasciitis
CNS Infections	• **All** CNS infections are considered severe
Bone & Joint Infections	• Associated with severe soft tissue infection • High risk of amputation (as per surgical judgment)
UTIs	• Abscess (renal, perinephric, or prostatic) • Emphysematous pyelonephritis • Urinary tract obstruction (upper or lower urinary tract) • Fungus ball (*Candida* sp) • Associated with increasing creatinine/renal dysfunction

Other Important Components of Therapy

Beyond choosing the right antibiotic regimen, dose, and duration and administering it correctly, the following are key considerations:

- Source control
- Timing of antibiotic initiation
- Supportive treatment
- Anaerobic antibiotic coverage
- Pharmacokinetic / pharmacodynamic considerations

Source Control

Source control is essential for cure, and includes key actions for control of infection. Source control reduces favorable conditions that promote microorganism growth, which impair both patients' immunologic response and the action of antibiotics. Source control, along with active antibiotics and supportive treatment, form the foundations of effective treatment. If source control is needed but is improperly done or not done at all, the risk of therapy failing is very high, even when the correct (active) antibiotic is used. Often source control requires surgical intervention, so discussing approaches with the surgeon is necessary for optimal management. Source control measures vary

by infection. When needed, they must occur as soon as possible, especially for severe infections. Examples of source control interventions are listed below.

Table 1.1: Key Source Control Interventions by Infection and Focus Area

Source control measure	Infection-specific action or area of focus Note: contact the surgeon to discuss such cases, and always involve the surgery advisor for complex cases.
Drain abscesses and pus collections; debride necrotic tissue	• **Bacteremia**: Abscesses in various sites (be it the primary source of bacteremia or metastatic infection secondary to bacteremia seeding). Cases of necrotizing fasciitis require urgent and repeated debridement, sometimes amputation. • **CNS infections**: Brain abscesses (except for those that are small or not accessible or if no capacity/not feasible), subdural empyema and epidural abscesses. Also consider the sources of these collections (e.g. mastoiditis, chronic sinus infections, cranial osteomyelitis). • **Bone & Joint Infections**: Necrotic bone and abscesses. Septic arthritis functions as a closed abscess - always drain it, via arthrotomy or, if not possible, serial aspirations. Curing osteomyelitis also depends on satisfactory soft tissue coverage (may require flaps) and the management of dead space. • **Urinary Tract Infections (UTI)**: Renal/perinephric/prostatic abscesses, necrotizing emphysematous pyelonephritis, and fungus balls.
Remove or exchange foreign bodies	Bacteria adhere to foreign surfaces and dead bone/tissue to form a biofilm, which severely impairs antibiotic action. Therefore, all foreign surfaces must be removed or exchanged whenever possible. • **Bacteremia**: Central venous catheters (CVC) should be removed or exchanged to a new site (especially if *S. aureus, Candida* sp. or gram-negative bacilli; GNB); attention also with peripheral IV catheters. • **CNS Infections**: Cerebrospinal fluid (CSF) drains, such as intra-ventricular shunts should be removed or exchanged. • **Bone & Joint Infections**: hardware (eg fracture fixations) should be removed/exchanged (exceptions only if approved by orthopedic surgeon advisor). Dead bone (sequestrum) should be completely removed. • **UTIs**: Urinary catheters should be removed or exchanged at the start of treatment. Calculi and other devices (e.g. stents, drains) may make the eradication of bacteria difficult and also cause relapse – may need removal.
Relieve obstructions	UTIs associated with urinary tract obstruction (e.g. pyonephrosis due to calculi, tumors, papillary necrosis in sickle cell disease); biliary sepsis/bacteremia with obstructed duct and cholangitis; ventriculitis and obstructive hydrocephalus.

Timing of Antibiotic Initiation

Severe infections, as defined above, are medical emergencies; particularly bacterial meningitis and sepsis. For these patients, it is critical to immediately start supportive treatment, initiate empiric antibiotic therapy after taking biological samples for AST, aiming to start within the first hour of identification of sepsis, and carry out early source control (e.g. for necrotizing fasciitis). Every hour counts and delays are associated with increased morbidity and mortality. Therefore, if there are

sampling delays, antibiotics should be initiated even before cultures are taken; in this case, sampling can be done just before the next antibiotic dose. Clinicians must also receive positive culture results as soon as they are generated in the lab, regardless of whether a patient's pathogen is found to be susceptible ("S"), intermediate ("I"), or resistant ("R") to antibiotics.

Supportive Treatment

Supportive treatment is the third fundamental component of therapy, crucial for treatment of severe infections, especially sepsis; risk of death is increased without proper supportive treatment, even if the right antibiotics are used. Lifesaving measures include fluid resuscitation, glycemic control, supplemental oxygen, electrolyte management, vasopressor/inotropic therapy if available, measures for intracranial pressure and seizures, and other interventions (see MSF Clinical, Pediatric and Neonatal guidelines).

Anaerobic Antibiotic Coverage

Anaerobic culture is technically demanding and will not be available in most laboratories. As a result, anaerobic bacteria will usually not be isolated in cultured specimens. Thus, **empiric anaerobic antibiotic coverage** must be added to the treatment that a patient is already being given for aerobic bacteria identified in culture for the following situations:

Table 1.2: Empiric Anaerobic Antibiotic Coverage

Infection	Details
Bacteremia and/or sepsis	Associated with intra-abdominal or pelvic/genital tract complicated foci of infection (e.g. appendicitis, diverticulitis, abscess, viscus perforation, pelvic inflammatory disease, endometritis, etc.), necrotic skin/soft tissue infections (e.g. pressure wounds, chronic ulcers, diabetic foot), or infections in the perineum/groin area.
CNS	Intra-cranial suppurations such as cerebral or epidural abscesses or subdural empyema, if they are secondary to sinusitis/otitis/mastoiditis or open skull fracture with gross contamination.
• Use Metronidazole IV (not necessary if using a beta-lactam/beta-lactamase inhibitor such as amoxicillin/clavulanate or piperacillin/tazobactam; or meropenem). • In the case of necrotizing fasciitis involving gram-positive bacteria (*Staphylococcus* sp., *Streptococcus* sp. or *Clostridium* sp.), add Clindamycin instead of Metronidazole. • Emphysematous pyelonephritis is rarely caused by anaerobes - coverage is not necessary. • Deep head and neck infections commonly involve anaerobes from the oral cavity, which in most cases are susceptible to clindamycin or amoxicillin/clavulanate.	

Pharmacokinetic / Pharmacodynamic Considerations

- Severe infections and all CNS infections should start with an IV antibiotic.
- CNS infections should receive the highest doses of IV antibiotics with good penetration through the blood-brain barrier.

- Other infections demand high doses of antibiotics because of the difficulty in achieving high concentrations at the site of infection. These include infective endocarditis, bone and prostate infections, and infections involving foreign bodies, due to biofilm formation.
- Whenever switching to an oral antibiotic, preference is given to antibiotics with good absorption and high bioavailability (e.g. fluoroquinolones, cotrimoxazole). This is particularly important for adults and/or for infection sites mentioned directly above.
- UTI's: most antibiotics will reach required concentrations in urine and kidneys, enabling lower doses of oral or IV antibiotics to be used. However, some antibiotics recommended for cystitis, such as oral nitrofurantoin or fosfomycin, should NOT be used for pyelonephritis or invasive UTI's because insufficient levels are reached in blood and kidney.
- For non-severe cases, full treatment with PO antibiotics can be provided.

Antibiotics to Avoid in Specific Patient Groups

Table 1.3: Antibiotics to Avoid in Specific Patient Groups

Pregnant Women	Neonates	Children
• Aminoglycosides • Chloramphenicol • Cotrimoxazole[1] • Doxycycline • Fluoroquinolones[3]	• Amoxicillin/Clavulanate • Ceftriaxone[2] • Chloramphenicol • Cotrimoxazole[1] • Doxycycline • Fluoroquinolones[3] • Tigecycline	• Doxycycline (<8y)[4] • Fluoroquinolones[3] • Tigecycline (<8y)[4]

[1]Pregnancy: avoid if 1st trimester or last month. Neonates: use only if no alternative and no hyperbilirubinemia.
[2]Preference for cefotaxime (or ceftazidime if GNB). May use ceftriaxone if none available.
[3]Use only if no other antibiotic options. Preference for ciprofloxacin.
[4]May use maximum 21 days for children if no other option.

Section 2: Targeted Antibiotic Therapy by Culture Result

|This section gives IV and PO antibiotic recommendations, for both adults and children, by isolate and pattern of antimicrobial susceptibility, as well as additional information for specific samples and associated infections. The pathogens covered here are listed in alphabetical order for easy reference; this order does not reflect their prevalence in MSF settings.

- For neonatal IV doses, see Annex 4, table A4.1
- For oral doses, see Annex 4, table A4.2
- For treatment duration, including minimum IV phase, when to step down to PO antibiotics, and total duration, see section 3.

For each organism, a series of tables details the choice of antibiotics for specific infections and patient groups. Priority antibiotics, along with first, second, and third-line options are given, and for some pathogens, oral (PO) step-down antibiotic choices by patient group, and choices by infection site, are also given, where appropriate.

Part 1: Gram-Positive Bacteria

[1] *Enterococcus* sp.

Table 2.1: *Enterococcus* sp – IV Antibiotic Choices, Oral Step-Down Antibiotic Choices, and Recommendations by Infection Site

IV Antibiotic Choices		
Priority	**Antibiotic**	**Notes**
1st choice	**Ampicillin**	• 2 g every 4 hours (if UTI & no sepsis nor bacteremia, every 6 hours) • Children: 50 mg/kg (max: 2g) every 6 hours (if CNS, every 4 hours)
2nd choice	**Vancomycin**	• 1 - 1.5 g every 12 hours (15 - 20 mg/kg/dose) • Children: 15 mg/kg (max: 500 mg) every 6 hours (if CNS, max: 750 mg)
• Vancomycin Resistant *Enterococcus* (VRE, commonly *E. faecium*): discuss with specialist • Alternative to Ampicillin: Penicillin G (same doses as *S. pneumoniae*, see below) • Alternative to Vancomycin: Teicoplanin (same doses as *S. aureus*, see below) • Last-resort for XDR: Linezolid and Tigecycline (approval from ABS MD compulsory)		

Oral (PO), Step-Down Antibiotic Choices	
Priority	**Antibiotic**
1st choice	**Amoxicillin**

Recommendations and Comments by Infection Site	
Sample	**Notes**
Blood	• If endocarditis due to *E. faecalis*, **add** Ceftriaxone (100 mg/Kg every 24 hours) to Ampicillin
CNS	• Usually associated with neurosurgery or open cranial trauma
Urine	• More common among men with urinary obstruction
Bone & Joint	• If polymicrobial infection (e.g. diabetic foot), use Amoxicillin/Clavulanate; if VRE plus other pathogenic bacteria isolated and not severe, may add VRE treatment only later, if no improvement (may resolve eradicating other pathogenic bacteria identified in culture)

[2] *Listeria monocytogenes*

Table 2.2: *Listeria monocytogenes* - IV Antibiotic Choices, Oral Step-Down Antibiotic Choices, and Recommendations by Infection Site

IV Antibiotic Choices		
Priority	**Antibiotic**	**Notes**
1st choice	**Ampicillin**	• 2 g every 4 hours • Children: 50 mg/kg (max: 2 g) every 6 hours (4 hours if CNS)
	Penicillin G	• 3 - 4 million IU/dose every 4 hours • Children: 50,000 IU/kg (max: 4 million IU) every 6 hours (4 hours if CNS)
2nd choice	**Cotrimoxazole**	• **Not** for neonates (unless no alternative and no jaundice) • 1200 mg/240 mg every 12 hours (every 6 hours if CNS) • Children: 4 mg (Trim.)/kg (max: 240 mg) every 12 hours (6 hours if CNS)
• Alternative: Meropenem if neither Penicillins nor Cotrimoxazole can be used		

Oral (PO), Step-Down Antibiotic Choices	
Priority	**Antibiotic**
1st Choice	**Amoxicillin**
2nd Choice	**Cotrimoxazole**

Recommendations and Comments by Infection Site	
Sample	**Notes**
Blood	• More severe in pregnancy: risk of complications for both mother and fetus
CSF	• Unusual unless neonate or immunodeficient (including age > 60 years). • Neonates with early response: 14 days. • Adults: minimum 21 days; ideally confirm CSF sterilization with a control LP and CSF culture after 3-5 days of treatment (repeat after 5-7 days if still positive) and provide at least 14 days after last negative culture. • If severe, add Gentamicin (or Cotrimoxazole if renal dysfunction) until clinical improvement.

[3] *Staphylococcus aureus*

Table 2.3 – *Staphylococcus aureus* - IV Antibiotic Choices, Oral Step-Down Antibiotic Choices, and Recommendations by Infection Site

IV Antibiotic Choices*		
Priority	**Antibiotic**	**Notes**
1st choice (obs: MSSA)	**Cloxacillin**	• 2 g every 4 hours (if UTI without bacteremia or sepsis: every 6 hours) • Children: 50 mg/kg (max: 2 g) every 6 hours (if CNS or severe infection or sepsis: every 4 hours)
	Cefazolin	• **Not** for CNS infection • 2 g every 8 hours (if non-severe UTI without bacteremia or sepsis: 1 g) • Children: 50 mg/kg (max: 2 g) every 8 hours (if non-severe UTI without bacteremia or sepsis: 25 mg/kg, max: 1 g)
2nd choice (obs: MRSA)	**Vancomycin**	• 1 - 1.5 g every 12 hrs (15 – 20 mg/kg) • Children: 15 mg/kg (max: 500 mg) every 6 hours (if CNS, max: 750 mg). • If severe infection including sepsis or CNS: start with loading dose of 20 mg/Kg, then follow doses above
	Clindamycin	• **Only** for bone/joint infections without bacteremia • 600-900 mg every 8 hours • Children: 10 mg/kg (max: 900 mg) every 8 hours
*Cotrimoxazole is another alternative if cannot use any of the above.		
Prosthetic Valve IE		• Add PO **Rifampicin** to above regimens during the IV phase if "S" or not tested • For osteomyelitis, add PO **Rifampicin** only after minimum 1-week IV antibiotics **and** proper source control; continue during the PO phase
Osteomyelitis with orthopedic hardware		
CSF shunt associated meningitis / ventriculitis		
• **Last-resort**: Linezolid (approval from ABS physician compulsory).		

Oral (PO), Step-Down Antibiotic Choices			
Infection site	**Patient group**	**Priority**	**Antibiotic**
Obs: *S. aureus* bacteremia and CNS infections demand full treatment IV.			
Urinary Tract Infection	Women and Children	1st Choice	**Cephalexin, Cloxacillin, Cotrimoxazole**
		2nd Choice	**Ciprofloxacin, Doxycycline, Amoxicillin/Clavulanate**
	Adult Men	1st Choice	**Cotrimoxazole**
		2nd Choice	**Ciprofloxacin**
		3rd Choice	**Amoxicillin/Clavulanate, Cephalexin, Cloxacillin**
Bone and Joint Infection	Adults	1st Choice	**Levofloxacin (or Ciprofloxacin) + Rifampicin***
		2nd Choice	**Clindamycin; Cotrimoxazole; Fusidic Acid + Rifampicin*; Doxycycline**

		3rd Choice	**Cephalexin, Amoxicillin/Clavulanate**
	Children	1st Choice	**Cephalexin; Amoxicillin/Clavulanate; Clindamycin**
		2nd Choice	**Fusidic Acid + RMP*; Cotrimoxazole; Levofloxacin (or Ciprofloxacin) + RMP*** (last option)

*Add **Rifampicin** (**RMP**) even if no hardware.

Recommendations and Comments by Infection Site	
Sample	**Notes**

Blood	• Full treatment IV (no PO step down).
	• High risk of complications and death - close follow up and proper source control.
	• Ideally confirm sterilization of blood repeating BCs after 3-7 days of treatment.
	• Extend IV treatment duration if complicated course (consider endovascular infections as endocarditis or septic thrombophlebitis, see Section 4, Tables 4.1 & 4.2):
	  ○ Fever ≥ 4 days: collect new blood culture, extend if still positive - persistent bacteremia
	  ○ Metastatic infection (new distant focus of infection due to bacterial seeding during bacteremia)
	  ○ Proper source control not possible
	• **Never consider** *S. aureus* a blood culture contaminant – always need IV antibiotics.
	• **CVC**: **remove** (or exchange and insert in another site if still needed);
	• If Necrotizing Fasciitis or Staphylococcal Toxic Shock Syndrome: **add** Clindamycin (until improvement).
	• Relapse of bacteremia: discuss with specialist; may need prolonged combined antibiotics; search for metastatic infections (including IE) and reassess source control.
	• **Teicoplanin**: may use for continuation of treatment after improvement and stable (dose under B&J).

CSF	• Uncommon cause of meningitis except complicating neurosurgery (SSI), open trauma or if CSF shunt/drain. If none, may be secondary to bacteremia: collect blood culture, if positive consider infective endocarditis. • CSF drain (or other foreign body): remove/exchange; if not possible, add PO Rifampicin if “S” or not tested.
Urine	• Uncommon cause of UTI unless surgical site infection (SSI) or urinary catheter (or other foreign body) or neonates; uncommonly may cause prostatitis. • Isolation of *S. aureus* in urine may be secondary to bacteremia: collect blood culture. If bacteremia confirmed, manage as per bacteremia (see above). • If prostatitis strongly suspected, preference for Ciprofloxacin.

Bone and joint	• **Teicoplanin** may be used instead of Vancomycin (also for IM continuation of treatment after improvement). Dose: adults – 400 - 800 mg/dose (6-12 mg/Kg) every 12 hours for 3 doses, then every 24 hours; children: 6 - 12 mg/kg/dose (max: 800 mg) every 12 hours (3 doses), then every 24 hours.
	• Add PO **Rifampicin** (if "S" or not tested) for implant/hardware associated infections if curative goal:
	  ○ Do not use for chronic suppression if only for palliation
	  ○ Hardware (like fracture fixation) needs to be removed/exchanged (exceptions only if approved by orthopedic surgeon advisor). Dead bone (sequestrum) needs to be completely removed
	  ○ Screen clinically for Tuberculosis before start (do **not** use if in doubt – see MSF TB guidelines).
	  ○ Never use Rifampicin as monotherapy.
	  ○ Start only after minimum 1-week IV antibiotics and proper source control.

[4] Coagulase-Negative *Staphylococcus* (CoNS)

Table 2.4: Coagulase-Negative *Staphylococcus* (CoNS): IV Antibiotic Choices, Oral Step-Down Antibiotic Choices, and Recommendations by Infection Site

<table>
<tr><th colspan="3">IV Antibiotic Choices</th></tr>
<tr><th>Priority</th><th>Antibiotic</th><th>Notes</th></tr>
<tr><td rowspan="2">1st choice</td><td>Cloxacillin</td><td>• 2 g every 4 hours (if UTI without bacteremia nor sepsis: every 6 hrs)
• Children: 50 mg/kg/dose (max: 2 g) every 6 hours (if CNS or severe infection incl. septic shock: every 4 hours)</td></tr>
<tr><td>Cefazolin</td><td>• Not for CNS infection
• 2 g every 8 hours (1 g for non-severe UTI without bacteremia nor sepsis)
• Children: 50 mg/kg (max: 2 g) every 8 hours (25 mg/kg every 8 hours for non-severe UTI without bacteremia nor sepsis)</td></tr>
<tr><td rowspan="2">2nd choice</td><td>Vancomycin</td><td>• 1 - 1.5 g every 12 hours (15 - 20 mg/kg)
• Children: 15 mg/kg (max: 500 mg) every 6 hours (if CNS, max: 750 mg/dose)
• If CNS infection, loading dose: 20 mg/Kg, then follow doses above</td></tr>
<tr><td>Clindamycin</td><td>• Only for bone/joint infections without bacteremia
• 600-900 mg every 8 hours
• Children: 10 mg/kg (max: 900 mg) every 8 hours</td></tr>
<tr><td colspan="3">Cotrimoxazole is another alternative if cannot use any of the above (not for neonates, unless no alternative, and no hyperbilirubinemia/jaundice).</td></tr>
<tr><td>Prosthetic Valve IE</td><td colspan="2" rowspan="3">• Add PO Rifampicin to above regimens during the IV phase if "S" or not tested
• For osteomyelitis, add PO Rifampicin only after minimum 1-week IV antibiotics and proper source control; continue during the PO phase</td></tr>
<tr><td>Osteomyelitis with orthopedic hardware</td></tr>
<tr><td>CSF shunt associated meningitis / ventriculitis</td></tr>
<tr><td colspan="3">• Linezolid is a therapy of last resort (compulsory approval from an ABS physician).
• S. epidermidis is the most common and important species.
• Some labs may report as Staphylococcus non-aureus.
• Teicoplanin may be used for continuation of treatment after clinical improvement (doses below under Bone & Joint); may use IM after improvement.
• Most strains are Methicillin Resistant (MRCoNS), resistant to Cloxacillin and Cefazolin. If no AST results have been reported, assume to be a MRCoNS and use 2nd choices above.</td></tr>
</table>

<table>
<tr><th colspan="4">Oral (PO), Step-Down Antibiotic Choices
(NOT for Meningitis or Complicated Bacteremia Patients)</th></tr>
<tr><th>Infection site</th><th>Patient group</th><th>Priority</th><th>Antibiotic</th></tr>
<tr><td rowspan="2">Bacteremia (not CNS & no complications)</td><td rowspan="2">All</td><td>1st Choice</td><td>Cephalexin, Amoxicillin/Clavulanate</td></tr>
<tr><td>2nd Choice</td><td>Clindamycin, Cotrimoxazole, Doxycycline (adults)</td></tr>
<tr><td rowspan="2">Urinary Tract Infection</td><td rowspan="2">Women and Children</td><td>1st Choice</td><td>Amoxicillin/Clavulanate, Cephalexin, Cloxacillin, Cotrimoxazole</td></tr>
<tr><td>2nd Choice</td><td>Ciprofloxacin, Doxycycline</td></tr>
</table>

	Adult Men	1st Choice	**Cotrimoxazole**
		2nd Choice	**Ciprofloxacin**
		3rd Choice	**Amoxicillin/Clavulanate, Cephalexin, Cloxacillin**
Bone & Joint Infection	Adults	1st Choice	**Levofloxacin (or Ciprofloxacin) + Rifampicin***
		2nd Choice	**Clindamycin; Cotrimoxazole; Fusidic Acid + Rifampicin*; Doxycycline**
		3rd Choice	**Cephalexin, Amoxicillin/Clavulanate**
	Children	1st Choice	**Cephalexin; Amoxicillin/Clavulanate; Clindamycin**
		2nd Choice	**Fusidic Acid + RMP*; Levofloxacin (or Ciprofloxacin) + RMP*; Cotrimoxazole**
*Add **Rifampicin** (**RMP**) even if no hardware.			

Recommendations and Comments by Infection Site	
Sample	**Comments**
Blood	• For positive blood cultures, must always differentiate true pathogen (needs antibiotic treatment) versus skin contaminant (does not need treatment). The two main criteria to support a true pathogen are: a) Growth in ≥ 2 BC bottles collected from different sites (if only one was initially collected, collect a new BC if in doubt regarding pathogen versus contaminant); b) Presence of foreign body – intravascular (e.g. CVC) or at the presumed source of bacteremia (e.g. orthopedic hardware, prosthetic heart valve, CSF shunt, etc). ○ If either "a" or "b" is present: consider true pathogen - treat. ○ If neither "a" nor "b" is present and it is NOT a sepsis case – do NOT treat (contaminant). Continue empiric antibiotic regimen; consider a new BC (especially if not improving). ○ If neither "a" nor "b" is present but the patient has sepsis: check if the CoNS isolate is "S" to any of the empiric antibiotics: ✓ If "R" to all but improving, consider contaminant; ✓ If "S" to any, continue full empiric antibiotic regimen but collect new BCs and reassess. • **CVC: remove** (or change and use another site if still needed). • Some patients promptly respond to CVC removal with resolution of fever – in this case, 3 days of antibiotic therapy is enough. • ***S. lugdunensis*** should NEVER be considered a contaminant: always provide minimum 2 weeks of IV therapy (similar to *S. aureus*). 1st choice: **Penicillin G Crystalline** if "S" (same doses as for *S. pneumoniae,* see below), otherwise follow antibiotic recommendations above.
CSF	• CoNS are an uncommon cause of meningitis except in patients who have a surgical site infection, a CSF shunt or other foreign body, or in hospitalized neonates (especially premature and/or low birth weight babies). If none of these conditions are present, the isolate may be a contaminant: in this case, add directed therapy against CoNS, but continue the empiric antibiotics and perform a new lumbar puncture for CSF culture. • Remove/exchange CSF drains, shunts, and other foreign bodies. If impossible, add oral Rifampicin if "S" (**not** in TB suspects – see MSF TB guidelines).
Urine	• CoNS are an uncommon cause of UTI unless the patient is a hospitalized neonate (especially premature and/or low birth weight) or has a urinary catheter or other foreign body (e.g. stents). If none of those are present, continue the empiric regimen and collect a new urine culture (possible contaminant).

	• *S. saprophyticus* is a common cause of simple cystitis in young women but not a common cause of pyelonephritis - continue empiric regimen and repeat urine culture.
Bone and Joint	• Teicoplanin may be used as alternative to Vancomycin (see above under *S. aureus*). • Add Rifampicin (if "S" or not tested) for hardware associated infections if curative goal; start only after proper source control is conducted (including hardware removal/exchange). • The use of antibiotic impregnated cement does not influence the choice of systemic antibiotics.

[5] *Streptococcus pneumoniae*

Table 2.5: *Streptococcus pneumoniae*: IV Antibiotic Choices, Oral Step-Down Antibiotic Choices, and Recommendations by Infection Site

IV Antibiotic Choices		
Priority	**Antibiotic**	**Notes**
1st choice	**Penicillin G** (preferable)	• 3-4 million IU every 4 hours • Children: 50,000 IU/kg (max: 4 million IU) every 6 hours (CNS: 4 hours)
	Ampicillin	• 2 g every 4 hours • Children: 50 mg/kg/dose (max: 2 g) every 6 hours (4 hours if CNS)
2nd choice	**Ceftriaxone***	• 2 g every 24 hours (CNS: every 12 hours) • Children: 50 mg/kg (max: 2 g) every 24 hours (CNS or B&J: 12 hours)
	Clindamycin Bone and joint infections	• **Not** for CNS infections • 600-900 mg every 8 hours • Children: 10 mg/kg (max: 900mg) every 8 hours
3rd choice	**Vancomycin**	• 1 - 1.5 g every 12 hours (15 - 20 mg/kg/dose); • Children: 15 mg/kg (max: 500 mg) every 6 hours (if CNS, max: 750 mg) • Meningitis: if "R" to Penicillin and "R" and Ceftriaxone, **add** Ceftriaxone (CNS doses)
*For neonates, preference for Cefotaxime over Ceftriaxone.		

Oral (PO), Step-Down Antibiotic Choices			
Infection	**Patient group**	**Priority**	**Antibiotic**
Bone and Joint Infections	Adults	1st Choice	**Levofloxacin**
		2nd Choice	**Clindamycin; Doxycycline; Cotrimoxazole** (3rd option: **Amoxicillin**)
	Children	1st Choice	**Amoxicillin**
		2nd Choice	**Clindamycin; Cotrimoxazole** (3rd option: **Levofloxacin**)
Other Infections NOT CNS	All	1st Choice	**Amoxicillin**
		2nd Choice	**Clindamycin; Cotrimoxazole; Doxycycline; Azithromycin** (not for bacteremia)
• Last option: Levofloxacin and Linezolid (only with ABS MD approval). • Ceftriaxone single daily IM dose may be used to complete treatment after stabilization.			

Recommendations and Comments by Infection Site	
Sample	**Notes**
Blood	• If suspected or confirmed meningitis: **inform the lab** - breakpoints for AST are different.

CSF	• If Penicillin and Ceftriaxone non-susceptible: use combination Vancomycin + Ceftriaxone.
	  ○ If renal failure, use instead Ceftriaxone + Rifampicin PO.
	  ○ If severe beta-lactam allergy, use instead Vancomycin + Ciprofloxacin 400mg 8/8 hours (children: 10 mg/kg [max: 400 mg] every 8 hours) or Vancomycin + Rifampicin PO.

[6] *Streptococcus* other than pneumococcus

Includes *S. pyogenes* ("beta-hemolytic group A", GAS), *S. agalactiae* ("beta-hemolytic group B", GBS), group Viridans streptococci, groups C & G streptococci, and *S. bovis*.

Table 2.6: *Streptococcus* other than pneumococcus: IV Antibiotic Choices, Oral Step-Down Antibiotic Choices, and Recommendations by Infection Site

IV Antibiotic Choices		
Priority	**Antibiotic**	**Notes**
1st choice	**Penicillin G** (preferable)	• 3 - 4 million IU every 4 hours • Children: 50,000 IU/kg (max: 4 million IU) every 6 hours (CNS: 4 hours)
	Ampicillin	• 2 g every 4 hours; • Children: 50 mg/kg (max: 2 g) every 6 hours (CNS: 4 hours)
2nd choice	**Clindamycin**	• **Not** for CNS • 600 - 900 mg every 8 hours • Children: 10 mg/kg (max: 900 mg) every 8 hours
	Ceftriaxone*	• 2 g every 24 hours (CNS: 12 hours) • Children: 50 - 75 mg/kg (max: 2 g) every 24 hours (CNS or B&J: 12 hours)
3rd choice	**Vancomycin**	• 1 - 1.5 g/dose every 12 hours (15 - 20 mg/kg) • Children: 15 mg/kg (max: 500mg) every 6 hours (if CNS, max: 750 mg)
*For neonates, preference for Cefotaxime over Ceftriaxone.		

Oral (PO), Step-Down Antibiotic Choices			
Infection	**Patient group**	**Priority**	**Antibiotic**
Bone & Joint Infections	Adults	1st Choice	**Levofloxacin**
		2nd Choice	**Clindamycin; Doxycycline; Cotrimoxazole** (3rd option: **Amoxicillin)**
	Children	1st Choice	**Amoxicillin**
		2nd Choice	**Cephalexin, Clindamycin** (3rd option: **Levofloxacin)**
Other Infections	All	1st Choice	**Amoxicillin**
		2nd Choice	**Cephalexin, Clindamycin**
• Ceftriaxone single daily IM dose may be used to complete treatment after stabilization.			

Recommendations and Comments by Infection Site	
Sample	**Notes**
Blood	• If *S. pyogenes* (GAS) + toxic shock syndrome or necrotizing fasciitis: add **Clindamycin** (until stable) to the recommended antibiotic. • If endocarditis + Penicillin non-"S", **add** Gentamicin for synergism: 1mg/kg every 8 hours.
CSF	• *S. agalactiae* (GBS): important cause in neonates (with or without neonatal sepsis). If severe, consider addition of Gentamicin for synergism (dose above, maximum 7 days). Risk of suppurative complications (cerebritis, ventriculitis, abscess) – discuss with specialist.

Urine	• *S. agalactiae* (GBS): not common unless in pregnant, neonate, or immunodeficient. • Pregnant w/ GBS: risk of neonatal sepsis; intra-partum neonatal disease prophylaxis recommended irrespective of UTI treatment outcomes (see MSF obstetric guidelines). • If neonate, collect blood culture and assess neonatal sepsis.
B&J	• Option for polymicrobial infections: Amoxicillin/Clavulanate.

Part II: Gram-Negative Bacteria

[7] Enterobacterales Group 1; potential ESBL-producers: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* (*Proteus* indole-negative)

Table 2.7: Enterobacterales Group 1; potential ESBL-producers: IV Antibiotic Choices, Oral Step-Down Antibiotic Choices, and Recommendations by Infection Site

IV Antibiotic Choices			
Infection	**Priority**	**Antibiotic**	**Notes**
CNS Infections	1st Choice	**Ceftriaxone**	• **Not** for ESBL • 2 g every 12 hours • Children: 50 mg/kg (max: 2 g) every 12 hours
	2nd Choice	**Meropenem**	• 2 g every 8 hours • Children: 40 mg/kg (max: 2 g) every 8 hours
	3rd Choice	**Ciprofloxacin**	• 400 mg every 8 hours • Children: 10 mg/kg (max: 400 mg) every 8 hours
		Cotrimoxazole	• **Not** for neonates unless no jaundice & no alternative • 800 mg/160 mg every 6 hours • Children: 4 mg (Trim.)/kg (max: 240 mg) every 6 hours
Other Infections (Non-CNS)	1st Choices	**Ampicillin**	• **Not** for *K. pneumoniae* or ESBL • 2 g every 4 hours (if non-severe UTI without bacteremia or sepsis: 6 hours) • Children: 50 mg/kg (max: 2 g) every 6 hours
		Cotrimoxazole	• **Not** for neonates unless no jaundice & no alternative • 800 mg/160 mg every 12 hours • Children: 4 mg (Trim.)/kg (max: 160 mg) every 12 hours
		Cefazolin	• **Only** non-severe UTI + no bacteremia or sepsis + Not ESBL • 1 g every 8 hours • Children: 50 mg/kg (max: 1 g) every 8 hours
		Amoxicillin/ clavulanate	• **Not** for ESBL nor children • 1.2 g every 8 hours
		Gentamicin	• **Only** for neonates; for others, only for UTI • 5 mg/kg every 24 hours (for adults and children)
	2nd Choices	**Ceftriaxone**	• **Not** for ESBL • 2 g every 24 hours • Children: 50-75 mg/kg (max: 2 g) every 24 hours (if bone/joint infection, every 12 hours)
		Piperacillin/ Tazobactam	• **Not** for ESBL (unless non severe UTI without bacteremia) • 4.5 g every 8 hours • Children: 80-100 mg (Pipe.)/kg (max: 4.5 g) every 8 hours
		Ciprofloxacin	• **Not** for neonates unless Colistin only alternative • 400 mg every 12 hours • Children: 10 mg/kg (max: 400 mg) every 12 hours
		Amikacin	• **Only** for neonates; for others, only for UTI • 15 mg/kg every 24 hours (for adults and children)

	3rd Choice	**Meropenem**	• 1 g every 8 hours • Children: 20 mg/kg (max: 1 g) every 8 hours
Notes	If resistant ("R") to all above - see XDR Carbapenem-Resistant Gram-Negative Bacilli, Table 2.16		
*For neonates, preference for Cefotaxime (or Ceftazidime) over Ceftriaxone.			

Oral (PO), Step-Down Antibiotic Choices		
Patient group	**Priority**	**Antibiotic**
Children (all infections) & adult women with UTI	1st Choice	**Amoxicillin** (not for *K. pneumoniae* or ESBL), **Cotrimoxazole**
	2nd Choice (Not for ESBL)	**Amoxicilin/Clavulanate, Cephalexin** (only for UTI)
	3rd choice	**Cefixime** (preferable for children), **Ciprofloxacin**
Adults: men (all infections) & women (not UTI)	1st Choice	**Cotrimoxazol, Ciprofloxacin** (1st choice bone/joint - also **Levofloxacin)**
	2nd Choice	**Amoxicillin, Amox./Clav., Cephalexin** (only for UTI), **Cefixime**
• After improvement may complete treatment with single daily IM doses of Ceftriaxone, Gentamicin or Amikacin, if among the choices for IV treatment.		

Recommendations and Comments by Infection Site	
Sample	**Notes**
Blood	• Short IV phase (72 hours) only if stepping down to oral (PO) Ciprofloxacin or Cotrimoxazole, otherwise minimum 5 days IV.
Urine	• For milder ESBL UTIs without risk factors, complications nor bacteremia/sepsis, may use IV Amoxicillin/Clavulanate or Piperacillin/Tazobactam. • For neonates: collect blood cultures if urine positive (if not already done). • May complete treatment with IM Aminoglycosides (Gentamicin or Amikacin).
CSF	• Difficult to cure; if failure, consider intra-thecal antibiotics if feasible (discuss with specialist). • **Add** Ciprofloxacin or Gentamicin if severe or not responding (discuss with specialist).
Bone & Joint	• May use Amoxicillin/Clavulanate or Piperacillin/Tazobactam for polymicrobial infections not ESBL.

[8] Enterobacterales Group 2; potential AmpC producers: *Enterobacter* sp, *Serratia marcescens, Citrobacter* sp, *Providencia* sp, *Morganella morganii, Proteus vulgaris* (indole-positive)

Table 2.8: Enterobacterales Group 2; potential AmpC producers: IV Antibiotic Choices, Oral Step-Down Antibiotic Choices, and Recommendations by Infection Site

IV Antibiotic Choices			
Infection	**Priority**	**Antibiotic**	**Notes**
CNS Infections	1st Choice	**Meropenem**	• 2 g every 8 hours • Children: 40 mg/kg (max: 2 g) every 8 hours
	2nd Choice	**Ciprofloxacin**	• 400 mg every 8 hours • Children: 10 mg/kg (max: 400 mg) every 8 hours
	3rd Choice	**Cotrimoxazole**	• **Not for neonates** unless no jaundice & no alternative • 800 mg/160 mg every 6 hours • Children: 4 mg (Trim.)/kg (max: 240 mg) every 6 hrs
Other infections (not CNS)	1st Choice	**Cotrimoxazole**	• **Not for neonates** unless no jaundice & no alternative • 800 mg/160 mg every 12 hours • Children: 4 mg (Trim.)/kg (max: 160 mg) every 12 hours
		Gentamicin	• **Only for neonates**; for others, only for UTI • 5 mg/kg every 24 hours (for adults and children)
	2nd Choices	**Ciprofloxacin**	• **Not for neonates** unless Colistin only alternative • 400 mg every 12 hours • Children: 10 mg/kg (max: 400 mg) every 12 hours
		Piperacillin/ Tazobactam	• **Not** for severe infection, bone & joint infections or where proper source control is not possible • 4.5 g every 8 hours • Children: 80-100 mg (Pipe.)/kg (max: 4.5 g) every 8 hours
		Amikacin	• **Only for neonates**; for others, only for UTI • 15 mg/kg every 24 hours (for adults and children)
	3rd Choice	**Meropenem**	• 1 g every 8 hours • Children: 20 mg/kg (max: 1 g) every 8 hours
• If resistant ("R") to all above – see XDR Carbapenem-Resistant Gram-Negative Bacilli, Table 2.16. • There are concerns that resistance to Piperacillin/Tazobactam may arise during treatment (ampC Beta-Lactamase), so close follow-up is essential. Do not use if the patient has severe infection or Cefoxitin Resistance ("R") or bacteremia. • May complete treatment with single daily IM doses of Gentamicin or Amikacin, if among recommended IV choices. • For *Citrobacter koseri*, may use Ceftriaxone if Cefoxitin "S" **and** Ceftriaxone "S" and **not** "R" to any other 3rd generation Cephalosporin.			

Oral (PO), Step-Down Antibiotic Choices	
Priority	**Antibiotic**
1st Choice	**Cotrimoxazole**
2nd Choice	**Ciprofloxacin** (1st choice for adult bone/joint inf., also Levofloxacin)

Recommendations and Comments by Infection Site	
Sample	**Notes**
Blood	• May use Piperacillin/Tazobactam if not severe **and** urinary or biliary

	source **and** Cefoxitin “S”.
Urine	• For neonates, collect blood culture (if not yet done).
CNS	• Difficult to cure; if failure, consider intra-thecal antibiotics if feasible (discuss with specialist). • **Add** Ciprofloxacin or Gentamicin if severe or not responding (discuss with specialist).
B&J	• Avoid Piperacillin/Tazobactam (unless polymicrobial infection not severe)

[9] Gram-Negative Bacilli Non-Fermenters Group 1: *Acinetobacter* sp, *Pseudomonas aeruginosa*

Table 2.9: Gram-Negative Bacilli Non-Fermenters Group 1: IV Antibiotic Choices, Oral Step-Down Antibiotic Choices, and Recommendations by Infection Site

IV Antibiotic Choices			
Infection	**Priority**	**Antibiotic**	**Notes**
CNS Infections	1st Choice	**Ceftazidime**	• 2 g every 8 hours • Children: 50 mg/kg (max 2 g) every 8 hours
	2nd Choice	**Meropenem**	• 2 g every 8 hours • Children: 40 mg/kg (max: 2 g) every 8 hours
	3nd Choice	**Ciprofloxacin**	• 400 mg every 8 hours • Children: 10 mg/kg (max: 400 mg) every 8 hours
		Cotrimoxazole	• **Not for neonates** unless no jaundice & no alternative • **Not** for *P. aeruginosa* • 800 mg/160 mg every 6 hours • Children: 4 mg (Trim.)/kg (max: 240 mg) every 6 hours
Other infections (not CNS)	1st IV Choices	**Ciprofloxacin**	• **Not for neonates** unless Colistin only alternative • 400 mg every 8 hours • Children: 10 mg/kg (max: 400 mg) every 8 hours
		Ceftazidime	• 2 g every 8 hours • Children: 50 mg/kg (max 2 g) every 8 hours
		Gentamicin	• **Only for neonates**; for others, only for UTI • 5 mg/kg every 24 hours (for adults and children)
	2nd IV Choices	**Cotrimoxazole**	• **Not for neonates** unless no jaundice & no alternative • **Not** for *P. aeruginosa* • 800 mg/160 mg every 8 hours • Children: 4 mg (Trim.)/kg (max: 160 mg) every 8 hours
		Piperacillin/ Tazobactam	• 4.5 g every 6 hours • Children: 80-100 mg (Pipe.)/kg (max: 4.5 g) every 6 hours
		Amikacin	• **Only for neonates**; for others, only for UTI • 15 mg/kg every 24 hours (for adults and children)
	3rd IV Choice	**Meropenem**	• 2 g every 8 hours • Children: 40 mg/kg (max: 2 g) every 8 hours • If not bone/joint infection nor severe infection, use 1 g or 20 mg/kg every 8 hours
• If resistant ("R") to all above - see XDR Carbapenem-Resistant Gram-Negative Bacilli, Table 2.16. • Resistance may arise during treatment, so close follow-up is essential. If insufficient response after 48-72 hours or recurrence of fever at any point, collect new cultures. If signs of sepsis appear while awaiting these new results, empirically change the patient's treatment to the next priority group of antibiotics (if any "S" antibiotics are available according to their initial AST). Always discuss these cases with a specialist. • Hard-to-treat infection (e.g. osteomyelitis associated with hardware, CNS) not responding to monotherapy may benefit from combination therapy: discuss with specialist.			

Oral (PO), Step-Down Antibiotic Choices	
Priority	**Antibiotic**
1st Choice	• **Ciprofloxacin** (1st choice adult bone/joint, or Levofloxacin), **Cotrimoxazole** (not for *P. aeruginosa*)
2nd Choice	• **Doxycycline** (not for *P. aeruginosa*)

Recommendations and Comments by Infection Site	
Sample	**Notes**
Blood	• If CVC, remove (if still needed, change to new catheter in a new site)
CNS	• Difficult to cure; if failure, consider intra-thecal antibiotics if feasible (discuss with specialist). • **Add** Ciprofloxacin or Gentamicin if severe or not responding (discuss with specialist).
Urine	• For neonates, collect blood culture (if not yet done).
Bone & Joint	• Difficult to cure; consider associating Ciprofloxacin, Gentamicin or Amikacin if severe or not responding (discuss with specialist).

[10] Gram-Negative Bacilli Non-Fermenters Group 2: *Burkholderia cepacia*, *Stenotrophomonas maltophilia*

Table 2.10: Gram-Negative Bacilli Non-Fermenters Group 2: IV Antibiotic Choices, Oral Step-Down Antibiotic Choices, and Recommendations by Infection Site

IV Antibiotic Choices		
Priority	**Antibiotic**	**Notes**
1st Choice	**Cotrimoxazole**	• **Not for neonates** unless no jaundice & no alternative • 1200 mg/240 mg every 8 hours • Children: 4 mg (Trimethoprim)/kg (max: 240 mg) every 8 hours
2nd Choice	**Ciprofloxacin**	• **NOT for neonates** unless Colistin only alternative • 400 mg every 8 hours • Children: 10 mg/kg (max: 400 mg) every 8 hours
	Ceftazidime	• 2 g every 8 hours • Children: 40 mg/kg (max 2 g) every 8 hours
3rd Choice	**Meropenem**	• **Not** for *S. maltophilia* • 2 g every 8 hours • Children: 40 mg/kg (max: 2 g) every 8 hours
• If resistant ("R") to all above - see XDR Carbapenem-Resistant Gram-Negative Bacilli, Table 2.16. • If allergy to Cotrimoxazole, consider desensitization (discuss with specialist). • Chloramphenicol may be active (although not ideal).		

Oral (PO), Step-Down Antibiotic Choices	
Priority	**Antibiotic**
1st Choice	**Levofloxacin** or **Ciprofloxacin** (1st choice – adult bone/joint infection); **Cotrimoxazole**
2nd Choice	**Doxycycline**

Recommendations and Comments by Infection Site	
Infection site	**Duration**
Blood	10-14 days (minimum IV: 72 hours)
Urine	See Tables 4.7 & 4.8
CNS	21 days (from negative CSF culture)
Bone & Joint	See Table 4.5

[11] *Haemophilus influenzae*

Table 2.11: *Haemophilus influenzae*: IV & PO Antibiotic Choices

IV & PO Antibiotic Choices		
Priority	**Antibiotic**	**Notes**
1st IV Choice	**Ampicillin**	• 2 g every 4 hours • Children: 50 mg/kg (max: 2 g) every 6 hours (CNS: every 4 hrs)
2nd IV Choice	**Ceftriaxone**	• 2 g every 24 hours (if CNS, 12 hours) • Children: 50 mg/kg (max: 2 g) every 24 hours (if CNS or B&J: 12 hrs)
	Amoxicillin/ Clavulanate	• **Not for children** • 1.2 g every 8 hours
3rd IV Choice	**Ciprofloxacin**	• 400 mg every 8 hours • Children: 10 mg/kg (max: 400 mg) every 8 hours
Step-down, Oral (PO) NOT CNS	1st Choice: **Amoxicillin**	
	2nd Choice: **Amoxicillin/Clavulanate, Cefixime**	
	3rd Choice: **Ciprofloxacin** (1st options for bone & joint infections in adults)	
• Uncommon in adults. • Ceftriaxone single daily IM dose may be used to complete treatment after stabilization. • For neonates, preference for Cefotaxime over Ceftriaxone. • Also active but not ideal: Chloramphenicol.		

[12] *Kingella kingae*

Table 2.12: *Kingella kingae*: IV & PO Antibiotic Choices

IV & PO Antibiotic Choices		
Priority	**Antibiotic**	**Notes**
1st IV Choice	**Penicillin G**	• 3-4 million IU every 4 hours • Children: 50,000 IU/kg (max: 4 million IU) every 6 hours
	Ampicillin	• 2 g every 4 hours • Children: 50 mg/kg (max: 2 g) every 6 hours
	Cefazolin	• 2 g every 8 hours • Children: 50 mg/kg (max: 2 g) every 12 hours
2nd IV choice	**Ceftriaxone**	• 2 g every 24 hours • Children: 50 mg/kg (max: 2 g) every 12 hours
Step-down PO	• **Amoxicillin, Cephalexin, Cefixime**	
• Also active: Cotrimoxazole. • Causes bone and joint infections in children (rare in adults and neonates). • Culture yield increases if inoculation in blood culture bottles (joint fluid, deep bone abscess fluid).		

[13] *Salmonella enterica* Non-Typhoidal, *Shigella* sp.

Attention: for *Salmonella enterica* var Tyhpi/Paratyphi (enteric / typhoid fever): see MSF Clinical Guidelines 2019.

Table 2.13: *Salmonella enterica* non-Typhoidal & *Shigella* sp: IV Antibiotic Choices, Oral Step-Down Antibiotic Choices, and Recommendations by Infection Site

IV Antibiotic Choices			
Infection	**Priority**	**Antibiotic**	**Notes**
CNS Infections	1st Choice	**Ceftriaxone**	• **Not for ESBL** • 2 g every 12 hours • Children: 50 mg/kg (max 2 g) every 12 hours
	2nd Choice	**Meropenem**	• 2 g every 8 hours • Children: 40 mg/kg (max: 2 g) every 8 hours
	3rd Choice	**Ciprofloxacin**	• 400 mg every 8 hours • Children: 10 mg/kg (max: 400 mg) every 8 hours
		Cotrimoxazole	• **Not for neonates** unless no jaundice & no alternative • 800 mg/160 mg every 6 hours • Children: 4 mg (Trim.)/kg (max: 240 mg) every 6 hours
Other Infections (not CNS)	1st IV Choices	**Ampicillin**	• **Not for ESBL** • 2 g every 4 hours • Children: 50 mg/kg (max: 2 g) every 6 hours
		Cotrimoxazole	• **Not for neonates** unless no jaundice & no alternative • 800 mg/160 mg every 12 hours • Children: 4 mg (Trim.)/kg (max: 160 mg) every 12 hours
	2nd IV Choices	**Ciprofloxacin**	• **Not for neonates** unless no alternative in this table • 400 mg every 12 hours • Children: 10 mg/kg (max: 400 mg) every 12 hours
		Ceftriaxone	• **Not for ESBL** • 2 g every 24 hours • Children: 50 – 75 mg/kg (max: 2 g) every 24 hours (if bone & joint infection, every 12 hours)
	3rd IV Choice	**Meropenem**	• 1 g every 8 hours • Children: 20 mg/kg (max: 1 g) every 8 hours
• For neonates, preference for Cefotaxime (or Ceftazidime) over Ceftriaxone. • Also active but not ideal: Chloramphenicol.			

Oral (PO), Step-Down Antibiotic Choices			
Infection	**Patients**	**Priority**	**Antibiotic**
Bone & Joint	Adults	1st Choice	**Ciprofloxacin (or Levofloxacin)**
		2nd Choice	**Cotrimoxazole**
		3rd Choice	**Amoxicillin (**preferred**), Amoxicillin/Clavulanate**
	Children	1st Choice	**Amoxicillin (**preferred**), Amoxicillin/Clavulanate, Cotrimoxazole**
		2nd choice	**Ciprofloxacin (or Levofloxacin)**
Other Infections	All patients	1st Choice	**Azithromycin (***not for bacteremia***), Amoxicillin, Cotrimoxazole**

		2nd Choice	**Ciprofloxacin**
Ceftriaxone single daily IM dose may be used to complete treatment after stabilization.			

Recommendations and Comments by Infection Site	
Sample	**Notes**
Blood	• 2 weeks minimum duration (minimum 1 week IV) • Extend to 4 weeks (minimum 2 weeks IV) if HIV/AIDS or immunodeficient or slow response or metastatic infection • Risk of metastatic infection or septic thrombophlebitis
CNS	• If slow response or HIV/AIDS, extend duration (minimum 4 weeks); and consider, after IV phase, PO Ciprofloxacin for 2-4 weeks
Bone & Joint	• Risk increased in sickle cell disease; may be difficult to differentiate from vaso-occlusive crisis (which are much more common)

[14] *Neisseria meningitidis*

Table 2.14: *Neisseria meningitidis*: IV Antibiotic Choices and Recommendations by Infection Site

IV Antibiotic Choices		
Priority	**Antibiotic**	**Notes**
1st Choice	**Penicillin G** (preferred)	• 4 million IU every 4 hours • Children: 100,000 IU/kg (max: 5 million IU) every 6 hours
	Ampicillin	• 2 g every 4 hours • Children: 50 mg/kg/dose (max: 2 g) every 4 hours
2nd Choice	**Ceftriaxone**	• 2 g every 12 hours • Children: 50 mg/kg (max: 2g) every 12 hours
3rd Choice	**Ciprofloxacin**	• 400 mg every 8 hours • Children: 10mg/kg (max: 400mg) every 8 hours
• If AST not reported, preference for Ceftriaxone • Full treatment IV for CNS or bacteremia (no PO phase) • Ceftriaxone single daily IM dose may be used to complete treatment after stabilization • For neonates, preference for Cefotaxime over Ceftriaxone • Also active **but not ideal**: Chloramphenicol		

Recommendations and Comments by Infection Site	
Sample	**Notes**
Blood and/ or CSF	• Meningococcemia and sepsis are very severe: aggressive supportive treatment is essential • If using any antibiotic other than Ceftriaxone (or Ciprofloxacin), give a single dose of Ceftriaxone (IM) or Ciprofloxacin (PO) upon discharge • In an epidemic situation, follow MSF Meningococcal Outbreak manual

[15] *Neisseria gonorrhoeae*

Table 2.15: *Neisseria gonorrhoeae*: IV, IM & PO Antibiotic Choices

IV, IM & PO Antibiotic Choices		
Priority	**Antibiotic**	**Notes**
1st IV Choice	**Penicillin G** (preferred)	• 3 million IU every 6 hours • Children: 50,000 IU/kg (max: 3 million IU) every 6 hours
	Ampicillin	• 2 g every 4 hours • Children: 50 mg/kg (max: 2 g) every 6 hours
2nd IV choice	**Ceftriaxone**	• 2 g every 24 hours • Children: 50 mg/kg (max: 2 g) every 24 hours
3rd IV choice	**Ciprofloxacin**	• 400 mg every 12 hours • Children: 10 mg/kg (max: 400 mg) every 12 hours
Complete with	**Ceftriaxone** IM (same dose as above)	
PO Alternatives	**Ciprofloxacin, Doxycycline** (1st options for adults) **Cefixime, Amoxicillin** (1st options for children)	

- If AST not reported, preference for Ceftriaxone
- If severe Beta-Lactam allergy, use Ciprofloxacin or desensitize (discuss w/ specialist)
- If XDR, may need Meropenem - discuss with specialist
- Always add Azithromycin PO single dose (adults: 1g; children: 10 mg/Kg, max 1 g) for treatment of possible *Chlamydia trachomatis* coinfection and to prevent escalation of resistance

[16] XDR Carbapenem-Resistant Gram-Negative Bacilli

Always discuss these cases with specialist.

Table 2.16: Carbapenem-Resistant Gram-Negative Bacilli: Combination Antibiotic Therapy

Combination Antibiotic Therapy	
IV Antibiotic	**Notes**
Colistin Colistimethate Sodium (CMS)	• **Not for** *Serratia marcescens*, *Salmonella* spp, *Morganella morganii*, *Proteus* spp, *Providencia* sp or *B. cepacia* (intrinsic resistance); use one or two antibiotics from options below • 9 million IU CMS loading dose, then 4.5 million IU CMS every 12 hours • Children: 150,000 IU CMS/kg loading dose, then 75.000 IU CMS/kg every 12 hours
Plus: Choose one of the following according to AST (choose whichever is "S" or, if none, "I"); take into account intrinsic resistance (see "important information", below, and Annex 3).	
Amikacin	• **Not for *B. cepacia* or *S. maltophilia*** (intrinsic resistance) • 15 mg/kg every 24 hours (for adults and children)
Gentamicin	• **Not for *B. cepacia* or *S. maltophilia*** (intrinsic resistance) • 5 mg/kg every 24 hours (for adults and children)
Meropenem	• **Not for *S. maltophilia*** (intrinsic resistance) • 2 g every 8 hours • Children: 40 mg/kg (max: 2 g) every 8 hours
Ciprofloxacin	• 400 mg every 8 hours • Children: 10 mg/kg (max: 400 mg) every 8 hours
Cotrimoxazole	• **Not for neonates** unless no jaundice & no alternative • **Not for *P. aeruginosa*** (intrinsic "R") • 800 mg/160 mg every 8 hours (if CNS inf., every 6 hours) • Children: 4 mg (Trim.)/kg (max: 240 mg) every 8 hours (if CNS inf., every 6 hours)
Tigecycline	• **Not for UTI** • **Not for *P. aeruginosa*, *Proteus sp*, *Providencia sp* or *M. morganii*** (intrinsic "R") • 100 mg loading dose then 50 mg every 12 hours • Children (≥8 years): 1.2 mg/kg every 12 hours (max: 50 mg/dose)
If none "S" or "I"	• Consider any other antibiotic(s) that tests "S" or "I" - discuss with specialist.
2nd Phase of Treatment: Oral (PO) Antibiotics - If any alternatives are available, discuss with a specialist.	

Important information:

- Use Colistin even if not reported in AST results, unless there is intrinsic "R". There are no breakpoints for disc diffusion, so no AST results may be reported. If MIC testing is available and Colistin (or Polymyxin B) is reported "R", then avoid Colistin and discuss with specialist
- Use high-dose Meropenem if "R" to all antibiotics for combination and intrinsic resistance to Tigecycline; three-hour infusion if possible (check with pharmacist). If MIC, use only if ≤ 8mg/L

- Monitor creatinine closely when using Colistin + Aminoglycoside
- Tigecycline AST disc diffusion breakpoints are available only for *E. coli*: no AST results will be reported for non-*E. coli* species unless MIC testing is available: may use if no intrinsic "R"
- Some strains may be susceptible to less commonly used drugs like Chloramphenicol and Doxycycline (e.g. *Acinetobacter* sp) - may use as second drug if no alternative above
- Colistin monotherapy may be used if UTI without bacteremia, nor sepsis

It is essential to manage Carbapenem-resistant gram-negative bacilli with specialist support (AMR/ID Advisor, or ABS physician when available) and to keep the following in mind:

- Pay special attention to source control
- Pay special attention to IPC recommendations for transmission-based precautions
- In hard to treat infections not improving, local administration of antibiotics may be considered (e.g. inhalation for pneumonia, intrathecal for meningitis, etc.), depending on the setting and resources – discuss with specialist

Part III: Fungi

[17] *Candida* sp.

Table 2.17: *Candida* sp.:IV Antibiotic Choices, Oral Step-Down Antibiotic Choices, and Antibiotic Choices by Infection Site

IV Antibiotic Choices			
Infection	**Priority**	**Antibiotic**	**Notes**
Blood, UTI, Bone & Joint	1st Choice	**Fluconazole**	• **Not if severe** + recent Fluconazole use (last 3 months) + no AST results reported • 800 mg loading dose, then 400 mg every 24 hours • Children: 12 mg/kg (max: 800 mg) every 24 hours • (if UTI without fungemia: 400 mg or 6 mg/kg)
	2nd Choice	**Amphotericin B lipid formulation**	• **Not for UTI** • 3-5 mg/kg every 24 hours (for adults and children)
	3rd Choice	**Conventional Amphotericin B (Deoxycholate)**	• 1 mg/kg every 24 hours for adults and children; max: 50 mg • If UTI w/out fungemia: 0.5 mg/kg
CNS	1st Choice	**Amphotericin B lipid formulation (liposomal)**	• 3-5 mg/kg every 24 hours (for adults and children)
	2nd Choice	**Conventional Amphotericin B (Deoxycholate)**	• 1 mg/Kg every 24 hours for adults and children; max: 50 mg
	3rd Choice	**Fluconazole (IV)**	• 800 mg every 24 hours • Children: 12 mg/kg (max: 800 mg) every 24 hours

• If AST results not reported/done but species identification is possible, take into account
  ○ Resistant to Fluconazole: *C. krusei* (all), *C. auris* (most), *C. glabrata* (many);
  ○ Resistant to Amphotericin B: *C. lusitaneae* (all), *C. auris* (some).
  ○ If species identification is not possible: risk of Fluconazole resistance is higher among *Candida* non-albicans (identified by a negative germ tube test result, if done). In this case, Amphotericin B is preferred over Fluconazole for severe infections, sepsis, neutropenia, metastatic infection, proper source control not possible or Fluconazole use in the last 3 months.
• If culture results report only "Yeast," consider *Candida* sp and treat accordingly.			

Step-down, Oral (PO) Antibiotics	
Priority	**Antibiotic**
1st Choice	**Fluconazole**

Antibiotic Choices by Infection Site	
Sample	**Notes**

Blood	• Ideally repeat blood culture 5-7 days after start of antifungal. If still positive, repeat every 5-7 days until negative, investigate complications (see below) and prolong treatment.
	• Prolong to 4-6 weeks total if **complicated course**:
	  ○ Persistent fever and fungemia ≥7 days
	  ○ Metastatic infection (e.g. endocarditis, visceral abscess, endophthalmitis)
	  ○ Proper source control not possible
	  ○ Persistent neutropenia (neutrophils <500/mm³).
	• If CVC: remove (if still needed, exchange using new catheter in new site).
	• *Candida* sp should **never** be considered a contaminant.
	• May use Amphotericin B for 3-7 days and then shift to Fluconazole PO if improvement.

CSF	• Repeat LP weekly to assess response (CSF sterilization + cell count, protein and glucose normalization). Once clinical response + CSF trending towards normal, change to PO Fluconazole (same dose as IV) and continue until CSF normalization + clinical improvement + no lesions in brain imaging (if available). • If creatinine not possible: maximum 1-week Amphotericin B (change to Fluconazole). • Foreign bodies must be removed (or at least exchanged if still needed). • If no AST and no response to Fluconazole, change to Amphotericin B.

Urine	• If neither severe nor suppurations, full treatment PO Fluconazole.
	• For *Candida* sp, any growth in urine is "significant" (no quantitative results needed).
	• Pyuria cannot distinguish UTI (needs antifungal treatment) from asymptomatic candiduria (most cases do not need specific therapy – see below).
	• Candiduria is frequently asymptomatic and common in patients with urinary catheter. If asymptomatic/mild symptoms and an alternative possible focus of infection identified:
	  ○ Remove/exchange the urinary catheter and collect a new urine culture after: many cases will resolve. If candiduria persists, then treat with antifungal.
	  ○ Always treat (even if asymptomatic) if: neonate (especially premature), neutropenia <500/mL, urologic surgery, or invasive procedures/manipulations with risk of mucosa bleeding.
	• For all severe infections + candiduria, always collect a blood culture both to assess candidemia (if positive, follow recommendations under “blood” above) and to investigate if there is another bacterial infection causing the severe infection (as most candidurias are not severe). If positive, see recommendations under “blood”, above.
	• Neonates: always collect a blood culture. Treat for 10-14 days.
	• Complications such as an abscess or fungus ball demand prolonged treatment and source control.
	• Urinary catheter: always remove/exchange.
	• If treatment failure, proceed with imaging and blood culture (see Urinary Tract Complications, section 5).

Section 3: The Second Phase of Treatment

Step-Down, Oral (PO) Antibiotics

Attention: PO antibiotic doses can be found in Annex 4.

Stepping down antibiotic therapy (going from IV to oral treatment) is recommended for most clinical situations. It helps avoid complications associated with IV catheters, and enables outpatient continuation of treatment. When transitioning from IV to oral antibiotics, it is important to consider the following, each discussed in detail below:

- Infections which require IV antibiotics for the full treatment course
- Criteria for safe transition from IV to oral antibiotics
- Minimum IV duration and total treatment duration

When IV Antibiotics are Required for the Full Treatment Course

The following conditions will not have an oral phase of treatment; the full course of treatment involves IV antibiotics:

Table 3.1: Conditions that Require IV Antibiotic Therapy (No Oral/PO Phase)

Condition	Comments
Neonatal sepsis	All cases
CNS infections	All acute bacterial meningitis cases
Infective Endocarditis	All (exceptions only after discussion with specialist)
S. aureus bacteremia	All cases
Resistant isolates	Isolates that are not susceptible ("S") to **any** available oral antibiotic

Note that:

- Ceftriaxone, Aminoglycosides (Gentamicin and Amikacin), and Teicoplanin may be used to complete treatment using single daily IM doses that can be administered within outpatient care, if proper monitoring is feasible.
- If feasible, IV antibiotics may be administered under the supervision of a medical professional as outpatient/home/day hospital, ideally using a peripherally inserted central catheter (PICC) if the treatment course is long (e.g. osteomyelitis).

Guidance on Decision-Making for Shifting from IV to Oral Antibiotics

Criteria for shifting from IV to oral antibiotics include that:

- Proper source control has been achieved, if indicated.
- The minimum IV duration has been met (see Section 4); if the empiric regimen already included an active antibiotic, count those days as well
- Clear signs of antibiotic response have been seen – emphasis on **clinical signs**:
    - Clinical signs - most importantly: no fever (axillary temperature <38°C) + reversion of shock/hypoperfusion, if present at admission + normal mental status + clinically stable and looking better.

    - Laboratory signs (blood): can be helpful to assess whenever in doubt; comparing to baseline, trend towards normalization of inflammatory markers such as: white blood cell count (decreasing if initial leukocytosis, or increasing if initial leukopenia), c-reactive protein (CRP) and/or procalcitonin (both decreasing if initially high); if creatinine and/or lactate were initially elevated, at this point they should be trending towards normal as well, unless chronic renal disease.
    - Imaging signs: if available; progressive decrease in the size of pus collections, very helpful for suppurative infections (abscesses, empyema) when available.
- The patient has good oral ingestion tolerance.
    - If a patient lives far from the health facility, keep them hospitalized for at least 24 hours with oral antibiotics to check tolerance.

- **Signs of clinical response are expected within 72 hours** of treatment with an active antibiotic for most bacterial infections. If not, suspect the development of complications and investigate accordingly (see Section 5).
    - For patients whose empiric antibiotic regimens already included an active antibiotic, when positive results arrive (usually after 48-72hr after collection), many will already have improved and can have their antibiotic treatment be shifted to PO antibiotic based on culture result.
    - For bone and joint or CNS infections, see additional considerations below.

- **If there is insufficient response after 72 hours of an active antibiotic**, consider:
    - Assessing for complications (see Section 5) for each infection
    - Development of resistance and/or a new infection (e.g. health care associated infection): collect new cultures and investigate based on clinical presentation
    - Confirming that antibiotics have been properly administered in the right doses and frequency
    - Reassessing the initial diagnosis
    - Checking the laboratory results again (contact the lab if needed)
    - Reassessing the supportive treatment provided
    - Discussing with specialist – consider escalating empiric antibiotics

Minimum IV Antibiotic Treatment Duration And Total Treatment Duration

To determine a patient's treatment duration, count from day 1 of their receiving an **active** antibiotic (for which the isolate is susceptible - "S"). If an empiric antibiotic regimen already included an active antibiotic, count those days as well, even if they were different from the antibiotic chosen after culture results. If any abscesses were present, start counting from the date of adequate drainage, if conducted. The same principles apply to surgical procedures for debridement, or resolution of urinary obstruction.

If the patient responds to antibiotics early (afebrile by 72 hours of treatment), aim for the shortest duration recommended. Exceptional cases may need longer treatment than recommended below, so always discuss with a specialist.

Section 4: Treatment Durations

Bacteremia: Treatment Duration

To determine the total treatment duration needed for bacteremia, check the minimum duration recommended by isolate and source of bacteremia (or by metastatic infection foci) and **follow whichever treatment duration is longest.**

Table 4.1: Bacteremia & Fungemia: Antibiotic Treatment Duration by Isolate

Bacteria (or fungus)	Minimum IV duration	Total duration
Staphylococcus aureus[1]	2-4 weeks (Full treatment IV)	
Coagulase-negative staphylococci[2]	3 days	5-10 days
Streptococcus pneumoniae	5 days	10-14 days
Streptococcus other than pneumococcus	5 days	10-14 days
Enterococcus sp	3 days	7-10 days
Listeria monocytogenes	3 days	14 days
Enterobacterales	3 days	7-14 days
GNB non-fermenters	3 days	10-14 days
Salmonella enterica non-typhoidal[3]	1 week	2-4 weeks
Shigella sp	3 days	10-14 days
Hemophilus influenzae	3 days	10-14 days
Neisseria meningitidis	5-7 days (Full treatment IV)	
Candida sp.[4]	1 week	2-6 weeks

1) Prolong to 4 weeks IV phase if complicated course (see Isolates section above).
2) If judged to be a skin contaminant only, do not treat.
3) 4 weeks (minimum 2 weeks IV) if HIV/AIDS, immunodeficient, or slow response or metastatic infection.
4) Minimum 2 weeks from last negative culture; prolong if complicated (see Isolates section above).

Table 4.2: Bacteremia - Treatment Duration by Bacteremia Source and/or Metastatic Infection

Source or metastatic infection	Total treatment duration (IV+PO) - minimum
Skin and soft tissue	5-10 days (necrotizing fasciitis: 2 weeks from definitive debridement)
Bone and joint	See: bone & joint infections, Table 4.5
Respiratory	5-10 days (Empyema: 14 days)
GI/GU/Biliary/Abdominal/Pelvic	Intra-abdominal/pelvic abscess and peritonitis: 5-10 days
Urine	See: UTI, Table 4.7 & 4.8
Central nervous system	See: CNS infections, Table 4.3 & 4.4
Cardiovascular	Endocarditis: 2-6 weeks Septic Thrombophlebitis: 2-3 weeks
Neonatal sepsis	10-14 days
Unknown/Undetermined	7-14 days

If source control indicated (e.g. abscess, empyema), start counting from the day it was properly done.

CNS Infections: Treatment Duration

For acute bacterial meningitis, treatment durations are determined by the microbial cause.

Table 4.3: Bacterial or *Candida* Meningitis – Total Treatment Duration by Isolate

Isolate	Total duration (full treatment IV)
N. meningitidis	5-7 days[1]
S. pneumoniae	10-14 days
H. influenzae	7-10 days
S. agalactiae (GBS)	14-21 days
GNB: Enterobacterales and non-fermenters[2]	21 days
Salmonella sp[2]	3-4 weeks[3]
L. monocytogenes[2]	21 days
Staphylococcus aureus	14-21 days
Coagulase-negative *Staphylococcus*	10-14 days
Candida sp[4]	Many weeks (includes prolonged PO phase)
1) Refers to treatment duration outside of an outbreak context. 2) Ideally confirm CSF sterilization: repeat LP after 3-5 days of treatment (if still positive, repeat every 5-7 days until negative); duration: 2 weeks after the first negative CSF culture or 21 days (whichever longer) 3) If slow response or HIV/AIDS, extend (minimum 4 weeks); consider, after IV, PO Ciprofloxacin 2-4 weeks 4) Continue until clinical signs + CSF abnormalities (+ imaging, if available) resolve and CSF culture negative – usually many weeks. Shift from Amphotericin to Oral Fluconazole when improving (minimum IV: 2 weeks)	

Table 4.4: Intracranial Suppurative Infections – Total Treatment Duration

Condition	Comments
Cerebritis Ventriculitis Brain Abscess Epidural Abscess Subdural Empyema	• 4-8 weeks of antibiotic therapy. • For **selected cases** (discuss with specialist), PO shift possible if clear signs of clinical improvement + brain imaging lesions improvement + minimum 3 weeks IV treatment + proper source control (especially drainage of abscess/empyema) + availability of oral antibiotic options with good absorption (Fluoroquinolones, Cotrimoxazole,Metronidazole) + patient/caretaker expected to adhere.
Imaging is particularly important to assess response and decide on duration (CT or, less commonly available, MRI). If not available, keep on IV antibiotics (refer to another hospital if possible).	

Bone and Joint Infections: Treatment Duration

For all patient groups apart from neonates, after reaching minimum IV duration, shift to PO if:

- Disappearance of fever - afebrile for at least 48 hours
- Alleviation of local inflammatory signs and pain
- Surgical wound dry
- For septic arthritis: no further accumulation of joint fluid if doing serial aspirations
- Proper source control achieved (all necrotic bone debrided, collections drained and hardware removed/exchanged)

- For children with hematogenous osteomyelitis or septic arthritis, may help to check laboratory markers of inflammation:
    - C-Reactive protein (CRP) - compared to baseline, 50% decrease **or** <2 mg/dL
    - Other (ESR, Procalcitonin, Leukocytosis if initially present): trend towards normalization

For neonates, aim for a full treatment course IV (no PO phase). However, if venous access is impossible, may complete treatment with high-dose PO antibiotics (discuss with specialists, including pediatricians).

For the end of treatment, beware of the existence of residual pain – this does not demand prolongation of antibiotics. It may help to look for:

- Normalization of erythrocyte sedimentation rate (ESR)
- Imaging (if available): no new lesions

If there is both osteomyelitis and septic arthritis, aim for the longest recommended duration.

Table 4.5: Bacterial Bone & Joint Infections – Antibiotic Treatment Durations

Infectious syndrome	Minimum IV phase	Total duration (minimum)
Acute/subacute hematogenous osteomyelitis in children (no hardware)	5 days	3-4 weeks
Osteomyelitis in children with hardware; All adult osteomyelitis cases[1]	1 week[2]	6 weeks
Relapse (only if curative goal - debridement and hardware removal/exchange possible)[3]	2 weeks	Septic Arthritis - 6 weeks Osteomyelitis - 12 weeks
Septic Arthritis Note: prosthetic joint infections not included	Adults: 1 week Children: 5 days	Adults[4]: 3 weeks Children[4]: 10-14 days
1) Fracture-associated osteomyelitis: if hardware cannot be removed/exchanged (e.g. malunion or unstable fracture), continue PO antibiotics until union and hardware removal (discuss with specialist). 2) Two weeks if adult who will use a beta-lactam antibiotic (penicillins, cephalosporins) in the PO phase. 3) If cure is not possible (e.g. full debridement & hardware removal not possible), consider chronic suppressive PO antibiotics - discuss with specialist. 4) *N. gonorrhoeae* septic arthritis: 7-10 days (14 days if severe and frankly purulent).		

Table 4.6: *Candida* Bone & Joint Infections – Antifungal Treatment Durations

Syndrome	Minimum IV phase	Total duration (minimum)
Osteomyelitis	2 weeks	6 months
Septic Arthritis	1 week	6 weeks

Prolonged PO Antibiotic Suppression for Osteomyelitis:

Prolonged PO antibiotics beyond the usual recommended duration for the treatment of osteomyelitis: **always discuss with specialist.**

Indications:

- **Curative** goal **-** Fracture-associated osteomyelitis:
    - Prolonged PO antibiotics, after the IV phase, this may be necessary in the case of non-union or long need for fixation: continue PO antibiotics until bone fusion is achieved; stop PO antibiotics only when removal of fixation hardware is finally possible.
- **Palliative** goal – There are situations when cure is unlikely; chronic antibiotic use may alleviate symptoms and prevent progression of infection:
    - Hardware not removable/exchangeable and/or necrotic bone not amenable to full debridement.
    - Second relapse after adequate antibiotic treatment and proper source control.
    - Duration: maximum 6 months. After this period, stop and reassess (some patients may achieve resolution/remission; otherwise, restart).
    - For prolonged PO chronic suppressive treatment without curative goal, do NOT use Rifampicin, Linezolid or Levofloxacin.

Urinary Tract Infection: Treatment Duration

Duration of treatment for uncomplicated UTI is determined by the antibiotic used for treatment. If using different antibiotics IV and PO, follow the duration recommended for the oral antibiotic.

There is no minimum IV duration; shift to PO whenever stable. For non-severe cases, treatment can be started PO (this may be associated with one or two doses of Ceftriaxone or Aminoglycosides, if using PO beta-lactams).

Table 4.7: UTI Total Treatment Durations – Children or Adult Women

Antimicrobial	Total duration
• Fluoroquinolones: Ciprofloxacin, Levofloxacin • Aminoglycosides (full treatment IV/IM): Gentamycin, Amikacin • Amphotericin B	5-7 days
• Beta-Lactams - full treatment IV/IM: ○ Cephalosporins: Cefazolin, Ceftriaxone ○ Penicillin: Ampicillin, Amoxicillin/Clavulanate, Piperacillin/Tazobactam ○ Carbapenems: Meropenem	7-10 days
• Cotrimoxazole • Oral Beta-Lactams: ○ Cephalosporins: Cephalexin, Cefixime ○ Penicillin: Amoxicillin, Amoxicillin/Clavulanate	10-14 days
Fluconazole	14 days

Table 4.8: UTI Treatment Durations – Other Patient Groups and Complicated UTI's

Patient Group/UTI Complication	Duration
UTI - Neonates	7 - 10 days (always check associated bacteremia; if present, see Bacteremia, above)
UTI - Adult Men	14 days
Renal/Perinephric Abscess	2 weeks from definitive drainage (or from diagnosis, if not done)
Emphysematous Pyelonephritis	2 weeks from definitive debridement or from first day afebrile (whichever longer)
Acute Prostatitis	2-4 weeks (longer if not using fluoroquinolones or cotrimoxazole, or if sepsis)
Chronic Prostatitis	6 weeks
Fungal mass (fungus ball)	Continue until resolution; may need surgical removal
S. aureus UTI with bacteremia	Prolonged IV treatment phase is needed: follow Bacteremia recommendations, Table 4.1
Candida sp UTI with fungemia	

Section 5: Complications

This section presents some complications for each of the four main infectious syndromes covered in this document, which may explain lack of clinical improvement (even using the right active antibiotics against which the isolate is "S"). Some information on diagnosis and management can be found below. Of note, for many of these complications, definitive diagnosis depends on imaging, from simpler abdominal/pelvic ultrasonography for abscesses in those locations to less commonly available techniques, such as computed tomography with contrast for intra-cranial suppuration. In those cases where imaging is not available, and referral to another hospital with such capacity is neither feasible nor safe, presumptive diagnosis should be made on clinical grounds. Similarly, for treatment more complex surgical procedures may be necessary for source control, but which may not be available, e.g. neurosurgery for intra-cranial suppurations. In such cases, if referral is neither safe nor feasible, provide antibiotic treatment as recommended, aiming for the longer duration; prolonged treatment may be necessary. **Always discuss with specialists** (depending on the case, may need to include not just ID/AMR, but also pediatric and surgical advisors).

Bacteremia Complications

Death may occur as a consequence of sepsis, or complications linked to a bacteremia source or metastatic focus of infection.

When a patient shows no improvement or worsens after 48-72 hours of **active** IV antibiotics:

- Assess for complications
- Collect new blood culture(s) and other samples according to other foci of infection (Annex 1)
- Reassess source control
    - Initial source of sepsis (repeated drainage or debridement may be necessary);
    - New metastatic infections;
    - Remove/exchange (if possible) IV catheters (especially if CVC);
- Consider escalation/addition of antibiotics if frank worsening – discuss with specialist
    - **Do not** stop the antibiotic targeting the initial blood culture isolate.

The bacteremia complications discussed here are:

[1] Metastatic Foci of Infection
[2] Infective Endocarditis (IE)
[3] Septic Thrombophlebitis
[4] Bacteremia Relapse

[1] Metastatic Foci of Infection

This refers to any site in the body seeded with bacteria (and, in cases of infective endocarditis, with septic emboli) where a new infectious focus of infection may develop. The highest risk occurs with *Staphylococcus aureus* bacteremia and candidemia. Candidemia may also cause endophthalmitis.

Investigations (including imaging and culture of other samples, if available) must be guided by clinical signs. Some possibilities:

Table 5.1: Bacteremia Complications – Metastatic Foci of Infection

Organ	Foci
Lungs	Pneumonia, Empyema, Abscess
Bone & Joints	Osteomyelitis, Septic Arthritis (any bone/joint can be affected)
CNS	Meningitis, Abscess
Viscera	Abscesses in various organs; peritoneal/pelvic
Soft tissue/subcutaneous	Abscesses
Endovascular	Infective Endocarditis, Septic Thrombophlebitis (infected thrombosis)

[2] Infective Endocarditis

The risk of IE is particularly high in the case of:

- *Staphylococcus aureus* bacteremia
- Previous heart valve lesions (including cardiac prosthetic material or previous endocarditis)
- Intravenous drug users

Clinical suspicion of infective endocarditis should occur if:

- Patient has persistent fever and/or persistent positive blood cultures ≥72 hours after initiating active antibiotics
- Other suggestive clinical signs:
    - New or changing cardiac murmur
    - New-onset heart failure
    - Peripheral emboli: petechial lesions of eye conjunctiva, fundi, and extremities of fingers
    - Pulmonary emboli if right side/tricuspid endocarditis (common among people who inject IV drugs): cough, chest pain, hemoptysis; radiography: multiple embolic lung images (may cavitate)
    - CNS emboli: headache and various neurologic symptoms

Table 5.2: Bacteremia Complications – Infective Endocarditis: Diagnosis & Treatment

Diagnosis	Treatment

• Repeat blood cultures (to demonstrate persistent/continuous bacteremia)
• Echocardiogram (if easy access, consider for all *S. aureus* bacteremia)
	• If echocardiogram is not available, treat if there is clinical suspicion together with persistent bacteremia in spite of at least 7 days of active antibiotic
	• Prolonged antibiotics – minimum 4 weeks full IV treatment (discuss with specialist)
	• Combination antibiotic regimens are recommended for:
	  ○ *Enterococcus faecalis*: add Ceftriaxone high dose to Beta-Lactam or Vancomycin
	  ○ *Pseudomonas aeruginosa:* add Aminoglycoside (Gentamicin preferred, otherwise Amikacin) to Beta-Lactam if "S" (if not, add Ciprofloxacin)
	  ○ *Staphylococcus* spp: add Rifampicin and Gentamicin if prosthetic valve
	  ○ Streptococci Viridians group: add Gentamicin to Penicillin

	• Cardiac surgery may be needed – ideally transfer to a hospital with such capacity asap If available and feasible, otherwise prolonged PO antibiotic suppression may be the only alternative

[3] Septic Thrombophlebitis

Septic thrombophlebitis is defined as a venous thrombosis that becomes infected; most commonly associated with a CVC. Longer antibiotic treatment and removal/exchange of intravascular catheters is needed.

Table 5.3: Bacteremia Complications – Septic Thrombophlebitis: Diagnosis & Treatment

Diagnosis	Treatment
• Suspect if persistent (≥72 hours) fever and bacteremia, in spite of active antibiotic • More likely if CVC in place • More likely if *S. aureus* or *Salmonella enterica* bacteremia or *Candida* sp fungemia • Clinical signs involving a peripheral vein: inflammatory signs along the vein pathway • Clinical signs involving a deep/visceral vein: localizing signs absent or only nonspecific pain; eventually, edema on the body parts drained by the vein (e.g. inferior cava – lower limbs edema) • If imaging available: filling defects/thrombus noted on the affected vein	• Prolonged antibiotic treatment – at least 2 full weeks of IV antibiotics • Source control: always aim to remove/exchange IV catheters (especially CVCs) • If endovascular prosthesis, provide combination antibiotic treatment as for Endocarditis • Surgical treatment (vein excision, thrombectomy) may be needed in case of failure or progression of thrombus with antibiotics alone – contact surgeon

[4] Bacteremia Relapse

- If a patient's fever relapses in the weeks following the end of their treatment, consider all complications above and investigate/treat accordingly. The risk is particularly high for *S. aureus* bacteremia.
- Investigate the metastatic foci of infection and endovascular infection (especially IE).
- Collect new blood cultures before initiating empiric antibiotics.
- If there is no other explanation for fever: restart antibiotics used for the last bacteremia episode.
- Re-treat with a longer duration, and potentially a combination antibiotic regimen. Aim for 3-4 weeks of antibiotic treatment, including 2 weeks of a full IV course. For relapses of *S. aureus, P. aeruginosa*, or *Enterococcus* sp, consider combination antibiotic regimens (such as those used for endocarditis, see above).
- **Always discuss with a specialist**.

Bacterial Meningitis Complications

Bacterial meningitis is very serious. Without proper treatment, 100% of such patients may die. Even with adequate treatment, there is still a considerable risk of death and permanent neurologic sequelae among survivors, potentially including hearing loss, vision loss, extremity amputations due to necrosis (especially due to severe meningococcemia/sepsis), and various forms of neurologic impairment (cognitive, motor, speech, learning difficulties, etc.). Complications are more likely

during the first 3-5 days of treatment. Of the three most common causes of bacterial meningitis, pneumococcus is associated with the worst prognosis, more complications, and slower response, including a longer time for defervescence. Gram-negative bacilli (Enterobacterales and non-fermenters), *L. monocytogenes and Candida* sp can be particularly difficult to cure and demand confirmed CSF sterilization with repeated CSF cultures while on treatment. Prognosis is also worse among neonates, the elderly, and those who are immunocompromised.

Delaying active antibiotic initiation is associated with worse prognoses – **do not delay**!

If using corticosteroids, provide it before or at the same time IV antibiotics are started.

Whenever there is no improvement after 48-72 hours of active antibiotics, suspect a complication:

- **Repeat a lumbar puncture** if the patient has no contraindications to doing so (see the MSF Clinical, Pediatric, and Neonatal Guidelines. Send the CSF for culture, Gram stain, protein, glucose and cell count.
    - **Signs of response:** CSF sterilization (negative culture); trends towards normalization of nonspecific parameters (protein, glucose, cell counts).
    - **Attention to AST:** resistance may have escalated (higher risk for Enterobacterales and GNB non-fermenters; risk also for pneumococcus).
- **Conduct imaging** to check for suppurative CNS infections. If imaging is not available, the patient should be transferred to another hospital when possible. Suppurative CNS infections may be a complication of acute bacterial meningitis (particularly among neonates) or a sole diagnosis, mimicking meningitis. These infections include cerebritis/brain abscesses, ventriculitis, subdural empyema, and epidural abscess. They demand that the following be done, when available:
    - Cranial ultrasonography (only for neonates)
    - Cranial CT **with contrast**. Contrast is essential (pay attention to hydration – nephrotoxic)
    - MRI testing is the most sensitive but the least commonly available procedure in resource-limited settings
    - Besides suppurative intra-cranial complications, these procedures may reveal a potential focus of CNS infection in need of source control (e.g. chronic sinusitis, mastoiditis), or other complications (hydrocephalus, cerebrovascular events as hemorrhage or ischemia/infarct, venous sinus septic thrombosis, etc.).

Some common features to all the complications listed above:

- Persistent fever (may be absent if cerebrovascular complications or hydrocephalus)
- Persistent/worsening of neurological signs, particularly impaired mental status and/or focal neurologic signs
- Diagnosis can be established by proper neuroimaging
- Treatment: most need neurosurgical evaluation. Drainage may be needed (source control) plus prolonged antibiotic treatment
- **Attention**: whenever cultures are persistently negative for bacteria and there is no response to recommended empirical antibiotics, suspect tuberculosis meningitis and investigate accordingly (see MSF TB Guidelines).

Neurologic sequelae: some patients achieve CSF sterilization and normalization of other parameters, therefore achieving eradication of infection, but may survive with severe neurologic damage and permanent sequelae. Prolonging antibiotics beyond the recommended duration is **not** indicated if there is clear CSF evidence of response (discuss with specialists, including pediatricians and intensivists).

Urinary Tract Infection Complications

Death may occur as a consequence of these complications, especially severe sepsis, severe renal infection, or decompensated comorbidities. In children, there is a risk of renal scarring, chronic kidney disease, or hypertension, especially if repeated and/or associated with anatomic/functional urinary tract abnormalities (e.g. vesicoureteral reflux).

The following are risk factors for a complicated course/severe UTI:

- Adult male
- Pregnancy
- Neonate
- Chronic renal insufficiency
- Anatomic/functional urinary tract abnormality*
- Sickle cell disease
- Poorly controlled diabetes mellitus (DM)
- Post-operative urologic surgery
- Severe immunodeficiency
- Foreign body**

*e.g. obstructing tumor, vesicoureteral reflux, neurogenic bladder esp. spinal cord injury
**e.g. stents, nephrostomy, urinary catheter

Whenever there is no improvement after 48-72 hours of active antibiotics, suspect a complication:

- Collect new urine cultures
- Reassess source control measures - check if abscess, necrosis or urinary obstruction with **imaging**:
    - Ultrasonography (USG) of bladder & kidneys (if not available, consider referral to another hospital).
    - CT also very good option - very sensitive but less available.
    - Plain radiography is less sensitive but may show calculi or signs of urinary obstruction.

Some important possibilities to evaluate when assessing UTI complications are detailed below. They are **all associated with persistent fever and/or sepsis**:

- Emphysematous pyelonephritis
- Local or distant extension of infection
- Prostatic abscess
- Recurrent UTI
- Renal or perinephric abscesses
- Urinary tract obstruction

Emphysematous Pyelonephritis

Table 5.4: UTI Complications – Emphysematous Pyelonephritis

Clinical manifestations	Treatment
• Severe necrotizing form of pyelonephritis - gas seen in imaging • Associated with sepsis and/or acute renal failure • Same etiologies as uncomplicated pyelonephritis • Risk factors: poorly controlled DM (main risk factor), obstruction, severe immunodeficiency	• Urgent debridement/drainage may be needed (incl. nephrectomy) - contact surgeon • Extend IV antibiotics until proper debridement + stable and 48 hours without fever • Minimum 2 weeks of antibiotics (if slow response, prolong) • Note: addition of antibiotics against anaerobic bacteria is **not** necessary

Local or distant extension of infection

Table 5.5: UTI Complications – Extension of Infection

Clinical manifestations	Treatment
• Local extension to abdominal/ pelvic structures: psoas or pelvic abscesses, pelvic or vertebral osteomyelitis, septic thrombophlebitis, etc • Distant extension due to bacteremia may happen (including endocarditis), although uncommon • Clinical manifestations guide investigation of distant metastatic infections • Blood cultures	• If abscess detected, contact surgeon • Prolong treatment according to affected site (see Bacteremia and Bone & Joint Infection sections)

Prostatic abscess

Table 5.6: UTI Complications – Prostatic Abscess

Clinical manifestations	Treatment
• In men, persistent pelvic or perineal pain • Very painful rectal examination (not essential but, if doing it, **do it gently** - risk of provoking bacteremia and sepsis)	• Total treatment duration: 4 weeks • Contact surgeon - drainage may be needed (but may respond to antibiotics only) • Extend IV antibiotics until 48 hours without fever + involution of abscess seen on imaging • PO antibiotics: preference for Ciprofloxacin. If Resistant ("R"), choose Cotrimoxazole

Recurrent UTI

Table 5.7: UTI Complications – Recurrent UTI

Clinical manifestations	Treatment

• Suspect insufficient source control and continuous source of bacteria (especially if same isolate):
  ○ Obstruction
  ○ Abscess
  ○ Chronic prostatitis
  ○ Anatomic/functional abnormality of urinary tract including calculi (even if not obstructing)
  ○ Vesicoureteral reflux (more common in children)
• If child, educate mother/caretakers to come ASAP for evaluation if there is a recurrence of UTI symptoms
	• Use results from urine culture from last episode(s) to guide empiric antibiotic for relapsed episode
	• New urine culture should be taken before initiating empiric antibiotics
	• Imaging: USG abdominal/pelvic or CT (if available, consider doing already during the first episode in children - see MSF Neonatal/Pediatric Guidelines)
	• If imaging abnormal, contact surgeon (referral may be needed)
	• In men, consider chronic prostatitis
	• If only cystitis (no signs of extension): may defer start of antibiotic until results of culture available

Renal or Perinephric Abscess

Table 5.8: UTI Complications – Renal or Perinephric Abscess

Clinical manifestations	Treatment
• Costovertebral pain, back pain • Increased risk if urinary obstruction or poorly controlled DM	• Drainage may be needed, depending on size and location: contact surgeon • Extend IV antibiotics until 48 hours without fever and no more need for drainage • Minimum 2 weeks of antibiotics (if slow response, prolong)

Urinary Tract Obstruction

Table 5.9: UTI Complications – Urinary Tract Obstruction: Diagnosis & Treatment

Diagnosis	Treatment
• Increasing creatinine (decreasing estimated creatinine clearance) and/or decreasing urinary output • Increased risk: history of calculi, anatomic abnormality, sickle cell disease	• Urgent relief of obstruction: contact surgeon • Extend IV antibiotics until obstruction relieved + stable and 48 hours without fever • Minimum 2 weeks of antibiotics (similar to abscess, above)

Bone and Joint Infection Complications

Death due to sepsis is more likely in hematogenous osteomyelitis. There may be persistent local pain. Severe cases may demand amputation. Vertebral osteomyelitis with neurologic compression may cause permanent sequelae.

Whenever there is no improvement (based on clinical signs or lab parameters), consider:

- Antibiotic resistance
- Insufficient debridement, new collections, necrotic tissue
- Hardware/implant with the development of biofilm
- For septic arthritis related to trauma, consider a foreign body (ideally, use radiography to assess)
- Repeat debridement (osteomyelitis) or joint aspirate (septic arthritis - consider arthrotomy) and send new sample for culture
- Imaging (if available): may demonstrate new areas of collection of necrosis or unstable fixation in need of surgical evaluation

Annexes

Annex 1: Additional Aspects of Clinical Management

Bacteremia

Bacteremia (or blood stream infection, BSI) is defined as the presence of bacteria in the bloodstream or a positive blood culture (BC) result. Many cases can be linked to a primary source of infection in the body; circulating bacteria can also seed new secondary foci of metastatic infection.

Microbiological sampling: for further guidance see the MSF protocols and SOPs for microbiology sampling and transport:

- **Blood Culture**: proper technique is essential to avoid contamination with resident skin bacteria.
- **Sampling other foci of infection**: applies to both the source of sepsis and investigation of possible metastatic foci.

There may be restrictive criteria for samples other than blood - check with lab before sampling.

Table A1.1: Recommended Sampling per Focus of Infection

Focus	Additional samples for culture
Skin/Soft Tissue	Pus (closed lesion aspiration/puncture or surgery – **not** swabs of open lesions)
Bone and Joint	Joint fluid (arthrocentesis); deep bone/soft tissue samples (surgical debridement/ biopsy or needle aspiration - **do not send** swabs of open lesions)
Respiratory	Pleural fluid (thoracentesis; pericardial fluid if pericarditis); sputum only if quantitative culture (and tracheal aspiration and/or via bronchoscopy)
GI/GU/Biliary/ Abdominal/Pelvic	Peritoneal fluid (paracentesis); pus (deep abscess - surgery, endoscopy or needle aspiration); stool (invasive diarrhea)
Urinary Tract	Urine culture (**do not send tip of vesical catheter** for culture)
CNS	CSF or pus from deep abscess (surgery)
Endovascular	If CVC is removed, may send tip for semi-quantitative culture

Potential Skin Contaminants

- Avoid collecting through IV catheters if possible, as contamination is more likely. However, for cases such as extensive burns, it may not be possible to identify peripheral veins for sampling - collecting via IV catheters such as CVC is acceptable
- *Staphylococcus aureus* and *Candida* spp should **never** be considered contaminants
- *Staphylococcus* coagulase-negative (CoNS) are the most important potential contaminants (*S. epidermidis* is the most important species). Always assess if it is a true pathogen versus a skin contaminant
- *Micrococcus* sp, *Bacillus* sp, and *Corynebacterium* species other than *Corynebacterium diphtheriae* are all **rarely clinically significant**; if repeated isolation together with severe immunodeficiency, discuss with specialist

Catheters: Intra-Vascular Related Infections & Catheter Removal

Central venous catheters (CVC) are much more commonly prone to infectious complications than peripheral catheters are. Infected catheters are a source of bacteremia. Their removal may be necessary for cure (source control).

Criteria for catheter removal:

- Check if a new IV access is possible before removing
- CVC not needed any more: change as soon as possible to peripheral IV access (check daily).
- The CVC must **always be removed/exchanged** if:
    - Longer permanence CVCs (tunneled, implanted): signs of tunnel/pocket infection (inflammatory signs extending ≥ 2 cm from insertion site over tunneled or pocket area)
    - Sepsis
    - Persistent bacteremia after 72 hours of an active antibiotic
    - Endocarditis or septic thrombophlebitis not responding to antibiotics (72 hours)
    - *Staphylococcus aureus* or *Pseudomonas aeruginosa* bacteremia or candidemia

Signs that the **CVC may be the source** of bacteremia:

- CVC **plus** no other obvious focus of infection/source of bacteremia
- Pus or inflammatory signs at the site of catheter skin insertion
- Signs of sepsis (altered mental status, hypotension) abruptly after catheter infusion
- Catheter malfunction (obstruction)
- Endocarditis and/or embolic disease (metastatic infection or emboli) or septic thrombophlebitis
- *S. aureus* or CoNS or *Candida* sp isolate (but other bacteria can be involved as well, e.g. GNB)
    - Resolution of fever within 24 hours of catheter removal is **very** suggestive (may resolve CoNS infection)

Saving the catheter:

- This can be done only if the patient's infection in not severe, or in circumstances like a long-term catheter for chemotherapy or hemodialysis
- Collect at least 1 (ideally 2) blood culture bottles, one from a peripheral vein and one from the catheter hub:
    - *If the same isolate is found in both the catheter and peripheral vein samples*, then catheter is probably infected and the source of bacteremia. Remove or exchange IV catheter if possible.
    - *If a negative blood culture is collected via catheter* then there is a low likelihood that the catheter is infected.
    - *If there is CoNS growth on more than one blood culture*, it is probably a true pathogen.

Important: *S. aureus* and *Candida* sp growth in a blood culture in the presence of a CVC should **never** be treated only with catheter removal: systemic antimicrobials are **always** needed.

Acute Bacterial Meningitis

Acute bacterial meningitis is almost uniformly fatal without adequate antibiotic treatment. Even with the right antibiotics, it still carries a considerable risk of death or sequelae among survivors.

- **Microbiological Sampling** – CSF culture (for further guidance please see the MSF protocols & SOPs for microbiology sampling and transport).

When bacterial meningitis is suspected, proceed **immediately** with a lumbar puncture for CSF sampling **unless** there are contraindications (listed below) for it; see also the MSF Clinical, Pediatric, and Neonatal Guidelines). Start empiric antibiotics **immediately** after the lumbar puncture.

Contra-indications for Lumbar Puncture:

- Signs of intracranial hypertension: hypertension with bradycardia, coma, papilledema, anisocoria
- Focal neurologic signs
- Skin infection at the puncture site
- Bleeding disorder
- Shock (first stabilize)

If any of the above contraindications for LP are present:

- Collect blood cultures immediately and start empiric antibiotics shortly thereafter
- For focal neurologic signs or signs of intracranial hypertension: conduct brain imaging if possible (CT w/ contrast, MRI)
- LP may be done after stabilization (and according to imaging results).

If a CSF shunt/drain is present: Do NOT collect from drain (perform a normal lumbar puncture). To monitor other biochemical or cellular parameters, CSF may be collected from the drain.

- **Blood culture** – Blood culture is particularly important when there are contra-indications for lumbar puncture. For *Staphylococcus aureus* meningitis, **always collect blood cultures:** CNS infection may be a consequence of bacteremia. The same principle applies to *Candida* sp CNS infections, especially among neonates.

Urinary Tract Infections

This document focuses specifically on more complicated and potentially life-threatening UTIs, including cases of **pyelonephritis** (ascending infections affecting the kidney), which may progress to bacteremia and sepsis (urosepsis), or severe local complications such as abscesses or necrosis (emphysematous pyelonephritis). Isolated cystitis, for which routine cultures should **not** be collected, is **not** included in this protocol; **antibiotic recommendations are different**. Do **not** follow this protocol for cystitis but see instead the MSF Pediatric and Clinical Guidelines for empiric therapy recommendations.

The recommendations here also apply for **prostatitis.**

Signs that an UTI Extends Beyond the Bladder

- Fever

- Back/flank pain or costovertebral angle tenderness
- Systemic manifestations (sepsis related as chills or less specific as important fatigue and malaise, ill-appearing, important nausea/vomiting - particularly relevant in children)
- In men, pelvic/perineal pain (suggesting prostatitis)

Important Notes

- It is difficult to clinically distinguish cystitis from pyelonephritis in neonates and children <2 years. Consider all UTIs as potentially severe
- UTI in pregnancy creates increased risk of both maternal and fetal complications. Even asymptomatic bacteriuria must be treated (see below and in the MSF Obstetric Guidelines)
- Neonates and children have increased risk of renal scarring and long-term sequelae (hypertension, chronic kidney disease); UTI may be linked to anatomic abnormalities (see MSF Neonatal and Pediatric Guidelines)
- Urinary tract manipulation with bleeding (e.g. surgery) carries the risk of bacteremia. Asymptomatic bacteriuria must be treated

UTI Diagnosis, Including Asymptomatic Bacteriuria

UTI Diagnosis Using Dipstick and Urine Microscopy

The presence of **pyuria** (leukocyte esterase positive or >5 leukocytes/high-power field) and/or **bacteriuria** (nitrite positive - enterobacteriuria) can support the **suspicion** of an UTI, especially if both are positive. However, the clinical picture is always the most important parameter. Pyuria can be found both in UTI or in simple asymptomatic bacteriuria **- cannot use it to distinguish.** Dipstick and/or urine microscopy help mainly with dubious cases, especially in children. Other causes of pyuria include pelvic/genital inflammation, vaginitis, urethritis, other genital infections, prolonged urinary catheter, DM, old age, urinary tuberculosis, urinary schistosomiasis, etc.

Table A1.2: Urine Dipstick (or Microscopy) Interpretation

Result	Interpretation	Detail
Pyuria negative	UTI is unlikely	Investigate other diagnoses. However, negative pyuria may also happen with complete obstruction or frequent urination. If strongly suggestive, proceed with a urine culture.
Pyuria and bacteriuria positive	Suggestive of UTI	However, if the patient is asymptomatic or has symptoms that are not suggestive of UTI, do **not** treat them for UTI, except in the case of pregnant women (see MSF Obstetric guidelines), or urologic surgery.

Important Notes

- If persistent pyuria + urine cultures are repeatedly negative for bacteria + no improvement with empiric antibiotics: **consider genitourinary tuberculosis** (see MSF Tuberculosis Guidelines).

- Microscopic hematuria is not a sign of severe infection. In endemic areas, consider schistosomiasis. If macroscopic and important pain, consider calculi (do USG if feasible).

UTI Diagnosis Using Urine Culture (UC):

- This is the gold standard for the diagnosis of UTI **if there are clinical manifestations** suggestive of UTI
- Traditional threshold: ≥100,000 CFU/mL + suggestive clinical manifestations
- If suggestive clinical picture + pyuria + typical urinary pathogen (*Enterobacterales,* especially *E. coli*):
    - Consider growth ≥ 10,000 CFU/mL as significant
    - If urinary catheter, consider ≥ 1,000 CFU/mL as significant if typical UTI manifestations and other foci of infection excluded
    - Contact the laboratory for exact CFU counts if clinical suspicion, as lab may not report a result if <100,000 CFU/mL
- Thresholds above apply for urine collected spontaneously or via urinary catheter
    - If collected **via supra-pubic puncture, any growth is significant** (inform laboratory)
- If repeated growth of bacteria not commonly involved in UTI, discuss with specialist

Blood culture (BC)

For most UTI cases, concomitant bacteremia does not change treatment, and blood cultures are not necessary. Though in some situations, bacteremia changes management and therefore blood cultures should be collected. These circumstances are listed below:

- *Staphylococcus aureus* or *Candida* sp in urine culture
- Neonates - investigate **neonatal sepsis** with blood cultures (see MSF Neonatal Guidelines)
- Used when there is doubt whether the UTI is the cause of the clinical picture, especially severe sepsis cases with minimal or no localizing urinary symptoms (e.g. urinary catheterization or spinal cord lesion)
- All severe cases including sepsis

Asymptomatic Bacteriuria:

- Growth ≥100,000 CFU/mL but **no clinical manifestations compatible with UTI - asymptomatic**
- Represents colonization of urinary tract with bacteria not causing disease
- **Do not** treat unless:
    - Pregnant woman (always treat - see MSF Obstetric Guidelines)
    - Preparation for urologic surgery or procedure involving mucosal bleeding (does **not** include insertion of urinary catheter)

UTI in Patients with Urinary Catheter:

- Changes in the appearance of urine (color, turbid, obstruction) are **not** signs of UTI - do **not** use the presence of these signs alone to treat the patient for UTI

- However, if a spinal cord injury has occurred, consider the patient's urine appearance and whether their spasticity or autonomic dysreflexia has deteriorated as signs of UTI. Investigate and treat accordingly
- Signs other than fever may be absent: if the patient is UC-positive and has no other likely focus of infection, treat accordingly. If there are other possible foci **and** severe infection, cover all possibilities in the antibiotic regimen

Microbiological Sampling – Urine for culture: (for further guidance please see the MSF protocols & SOPs for microbiology sampling and transport

- After sample collection, send immediately to laboratory (quantitative culture = delays cause false positive results). If a delay >1 hour is foreseen, keep refrigerated (4°C) until reaching lab

Sampling without an urinary catheter:

Proper technique is essential to avoid contamination

- If possible, the best sample is the first urine of the morning
- Clean external genitalia and urethral meatus (may use appropriate antiseptic solution)
- Spread the labia or retract the foreskin
- Discard the initial stream of urine; collect the mid-stream in a sterile container

Sampling with an urinary catheter:

Whenever possible, remove the urinary catheter as soon as it is no longer needed. For long-term use, intermittent catheterization is preferable, if feasible.

- If catheter no longer needed, remove and then collect mid-stream urine as above
- If still needed, exchange the catheter before collection (if >7 days in place)
- Collect from the appropriate port in the catheter system after proper disinfection (do **not** collect from collecting bag or open the system for collection)

Sampling in Children:

For children too young/not yet toilet trained:

- Sampling with a temporary urinary catheter is the best option in terms of contamination and feasibility (aseptic technique; remove immediately after)
- Collection with supra-pubic puncture is the least prone to contamination but the most invasive
- Attaching a bag to the perineum is not recommended because has there can be a very high rate of contamination (can use only for dipstick tests). A negative urine culture result collected with a bag attached to the perineum is useful to exclude UTI; however, given very high contamination, a positive result may or may not indicate a true UTI. May consider clean-catch collection, if parents able to help with sampling.

Contamination

Although urine inside the bladder is normally sterile, passage through the urethra contaminates it with bacteria from the resident microbiota (hence the need for quantitative culture). Proper collection is important to avoid contamination (see above).

Whenever there are signs of potential contamination, collect a new sample for culture:

- Polymicrobial result - 3 or more bacterial species;
- Growth of bacteria not usually associated with UTI (e.g. diphtheroid, lactobacilli, etc.).

Catheter-Related UTI and Catheter Management

Bacteria adhere to the catheter and form **biofilm** - more difficult for antibiotics to eradicate the infection.

- Remove/exchange the catheter at the start of antibiotic treatment (if not done yet for sampling)
- Reassess needs daily. Remove the catheter as soon as possible as each single day of use increases the risk of an UTI
- Urinary symptoms may be difficult to detect; fever may be the only manifestation. Investigate other possible sources of fever (consider blood cultures) and proceed with UTI treatment if there is no other probable focus of infection. If the infection is severe, cover all possible infectious foci
  Pyuria is very common among catheterized patients and **cannot** be used to confirm a true UTI over asymptomatic bacteriuria; however, if negative, UTI is unlikely (unless complete obstruction)
- Changes in the aspect of urine are not a sign of UTI (except in cases of spinal cord injury)
- In long term catheters (>1 month, intermittent or not), polymicrobial UTI is more likely
- Treatment recommendations as above. However, short treatment as for cystitis may be provided in young women without signs of upper UTI and no risk factors for complications, only simple cystitis developing after catheter removal. Preference for Nitrofurantoin PO 100mg/dose every 8 hours for 5 days
- Do **not** send urinary catheter tip for culture

Bone and Joint Infections

Osteomyelitis is a bone infection; any bone can be affected, and it is commonly caused by bacteria. *Staphylococcus aureus* is the most common etiology in all forms. According to the mechanism of infection, it is classified as:

- **Acute hematogenous**: bone is seeded during bacteremia; most common form in children (consider hematogenous if no other obvious mechanism of infection)
- **Direct inoculation**: bacteria directly inoculated into bone including fracture-related osteomyelitis (e.g. open fractures, especially Gustilo III) and, less frequently, post-surgical or bites. Fracture-related is the most common form in adults
- **Spread from contiguous focus of infection**: from chronic skin ulcer, pressure ulcer or diabetic foot; may be polymicrobial (including anaerobes, especially if necrotic tissue and/or vascular insufficiency) and may be difficult to cure if the primary condition is not resolved

Although osteomyelitis may be classified as acute (<2 weeks of history), subacute (2-6 weeks) and chronic (generally > 6 weeks), the main sign of chronicity is the presence of dead bone (sequestrum), which is more difficult to treat because of biofilm that forms there. Any relapsed osteomyelitis is also classified as chronic. For implant-associated infection (e.g. fracture fixation devices), infection is classified as acute when it occurs <4 weeks after hardware insertion. Unlike longer standing infections, acute hardware infections may be cured without implant removal/exchange, since biofilm may not be mature yet.

Septic Arthritis is the infection of joint space. It has a similar etiology and mechanisms of infection as osteomyelitis (with particularities, such as *Neisseria gonorrhoeae* among sexually active persons). There may be concomitant joint and bone infection.

Improperly treated acute osteomyelitis may progress to chronic illness, when the chances of cure will be lower. Chronic cases will also need more extensive debridement, which may cause bone defects in need of reconstructive surgery and more complex and prolonged treatment.

Table A1.3: Local Delivery of Antibiotics for Treatment of Bone and Joint Infections

Condition	Comment
Osteomyelitis	Choices of systemic antibiotics are not influenced by choices of antibiotic for impregnated cement
Septic arthritis	Instillation of antimicrobials inside the joint space is **not** recommended.

- Microbiological Diagnosis/Sampling & Empiric Antibiotic Therapy: (for further guidance please see the MSF SOPs for microbiology sampling and transport)
- Osteomyelitis: Deep intraoperative bone and tissue samples are essential for diagnosis and to guide antibiotic choices
- Specimens: bone, deep soft issue and fluids sampled during open surgery (ideal). Minimum: 3 samples
- Other Notes:

- Suspected acute hematogenous osteomyelitis or any severe infection: include blood cultures as well
- Pus from open wounds or sinus are **not recommended** because it is not possible to distinguish colonization/contamination from skin microbiota versus true infection
- Inoculation of fluids in blood culture bottles increases sensitivity (particularly for *K. kingae*)

- Timing of antibiotic initiation vs. sampling and surgery: antibiotics in use (prophylactic or therapeutic, especially if ≥72 hours) decrease the yield of cultures
- Osteomyelitis Treatment & Prophylaxis: see Tables A1.4 and A1.5

Septic Arthritis

- Cartilage destruction and sequelae develop fast if there are delays in antibiotics and source control
- There should be **no delay** in performing bedside joint aspiration for sampling and drainage (a portion of the fluid should be immediately inoculated in a blood culture bottle at the bedside)
- Immediate start of empiric antibiotics after sampling
- Technical difficulties in accessing the joint (e.g. hip): proceed immediately to operation theater for arthrotomy (or arthroscopy); if there are foreseen delays in surgery (or if not possible), do not delay antibiotics: start even before/without sample collection. Blood cultures should be collected as well
- Subacute/chronic arthritis with failure of empiric antibiotics and persistently negative cultures for bacteria: consider tuberculosis (see MSF TB Guidelines)

Table A1.4 Osteomyelitis Treatment – Timing of Antibiotic Start versus Sampling

Action	Detail
IF: Acute osteomyelitis is suspected/confirmed, but not yet on empirical antibiotic treatment	
Postpone antibiotics until after sampling if procedure foreseen within 72 hours **and** no signs of severity, otherwise start immediately.	For patients with strong suspicion of acute hematogenous osteomyelitis due to *S. aureus* (e.g. obvious skin port of entry for bacteremia; child osteomyelitis), do **not** delay antibiotic treatment ≥12 hours.
IF: Already on empiric antibiotic treatment (referrals) but needs new sampling	
Temporarily stop antibiotics – only if no sepsis and stable - for sampling, if possible for at least 72 hours	If not severe, wait the results to start directed antibiotics
IF: Chronic osteomyelitis	
Await results to start directed antibiotic therapy. If already in use, stop for at least 1 week.	Especially the case if hardware is present and/or patient is post-traumatic
IF: All severe cases/unstable patients	
Immediately start empirical antibiotics after blood collection for culture; if already in use, do not stop (but collect new blood cultures).	Sepsis, neurologic signs, necrotizing fasciitis

Table A1.5: Osteomyelitis-Related Orthopedic Surgery: Timing of Antibiotics for Surgical Prophylaxis versus Sampling

Action	Detail
IF: Surgery for sampling / microbiological diagnosis of **confirmed or suspected** osteomyelitis	
Delay administration of prophylactic antibiotics until after sampling	"Pre-op" antibiotic prophylactic dose postponed, administer "intra-op" just after sampling. Includes both initial debridement surgery or reassessment after osteomyelitis treatment failure.
IF: Microbiological sampling foreseen, but suspicion of active osteomyelitis is **low or absent**	
Do NOT delay prophylactic antibiotic administration (provide pre-op dose as recommended)	e.g. second-stage reconstructive surgery after apparent successful osteomyelitis treatment
IF: Revision surgery with sampling due to **doubts** that osteomyelitis has been cured	
Delay antibiotic prophylaxis until after sampling	Administer "intra-op" after sampling

Important: for initial surgical treatment of fractures at the moment of trauma (acute phase of trauma, damage control surgery), do NOT sample for culture if there is no suspicion of active infection.

Annex 2: Laboratory Testing and Monitoring

Monitoring for Antibiotic Side Effects

Recommended if locally available, particularly for severe infections:

- **Baseline** (minimum): Complete blood count (CBC); Biochemistry: Creatinine, ALT, electrolytes (sodium, potassium), glucose; Lactate if suspicion of sepsis
- **Follow-up**: Every 48-72 hours after IV antibiotic start until stable and/or PO shift, then weekly. Glucose: only while not accepting food by mouth

Additional tests for specific antibiotics:

- Aminoglycosides (Gentamicin & Amikacin), Glycopeptides (Vancomycin & Teicoplanin), Polymyxins (Colistin) and Amphotericin B: Renal function (creatinine and calculation of estimated clearance): baseline, 48 hours, day 5; then weekly. Potassium whenever increased creatinine
- Amphotericin: include potassium; if persistent hypokalemia, also magnesium (if not available, proceed with empiric oral magnesium administration together with potassium)
- Rifampicin: Liver enzymes weekly
- Linezolid: CBC twice weekly for first week then weekly

Therapeutic Drug Monitoring

Usually not available in MSF settings. If available, discuss with clinical pharmacist or ID specialist.

Vancomycin

Considerable variability in blood levels - measure blood levels prior to the 4th or 5th dose.

- Target: through levels of 15-20 µg/mL (for children, 10-20 µg/mL); no need to check peak levels
- Low blood levels: increased dose to 20 mg/kg every 6-8 hours (max: 2 g/dose) - more frequent creatinine monitoring needed
- High blood levels: decrease dose and check creatinine

Teicoplanin: Aim for through levels of 20-60 µg/mL.

Gentamicin & Amikacin

Concentration dependent - TDM useful for GNB treatment/single daily dosing - measure after 3rd day of use.

- Target (Gentamicin & Amikacin, respectively) peak: 15-20 µg/mL & 20-30 µg/mL; through: <1 µg/mL & 1-4 µg/mL. After reaching target, measure weekly (or if high creatinine)
- Low blood levels: increase to 7.5-10 mg/kg/day (Gentamicin) or 20-30 mg/kg/day (Amikacin)
- High blood levels or higher doses: more frequent creatinine monitoring needed.

Annex 3: Basics of Antibiotic Classes and Spectra

This section only includes antibiotics available in the MSF standard drug list at the time of writing. There is a preference for bactericidal antibiotics in cases of:

- CNS infections
- Endocarditis
- Sepsis
- Neutropenia
- Bacteremia

In cases with a history of allergy or drug reaction:

- If severe anaphylactic reactions such as angioedema, urticaria, hypotension, bronchospasm; reactions with mucosal lesions or skin breakdown such as Stevens-Johnsons syndrome, or toxic epidermal necrolysis; severe systemic symptoms: consider allergy cross-reactive with all other antibiotics in the same class, and **avoid** (if reaction against one subclass in the beta-lactams group, consider cross-reactive with all beta-lactams)
- If milder reactions involving beta-lactams, may consider use of a beta-lactam antibiotic from another subclass (e.g. mild reaction to penicillins - may use cephalosporins)

Antibiotic Classes

Beta-Lactams

These are bactericidal antibiotics, which inhibit cell wall synthesis and have time-dependent killing mechanisms (potentially better action if multiple daily doses or continuous infusion). Beta-lactams are first-line treatments for many infections, including many severe ones such as sepsis, bacteremia, central nervous system, etc.), given their potent action and safety of use. They also have good penetration in the CNS and most body sites (unless noted), and are well tolerated. There is risk of drug allergy and *C. difficile* diarrhea is particularly associated with Cephalosporins, but they are safe during pregnancy. Includes the following subclasses: Penicillins, Cephalosporins and Carbapenems.

Penicillins

Natural Penicillins

Active against *Streptococcus* spp (*S. pneumoniae* may be resistant). Commonly used for syphilis (first choice, especially in pregnancy). Active against most strains of *N. meningitidis* and *Clostridium* spp (except *Clostridioides difficile*) and *Corynebacterium diphtheriae.*

PO: Penicillin V (Phenoxymethylpenicillin)
IV: Penicillin G Crystalline (Benzylpenicillin)
IM: Penicillin Benzathine (Benzathine Benzylpenicillin); Penicillin Procaine

Aminopenicillins

Improved action against *Enterococcus* sp and some GNB from the community (*E. coli, P. mirablis* – but considerable level of resistance in most settings). Active also against *Listeria monocytogenes.*

PO: Amoxicillin
IV: Ampicillin

Beta-Lactam/Beta-Lactamase Inhibitor

Improved spectrum against GNB but not ESBL or AmpC beta-lactamases (consider both whenever resistant to 3rd generation cephalosporins); adds activity against *Staphylococcus aureus* and CoNS (but **not** methicillin-resistant, MRSA or MRCoNS); also active against most anaerobic bacteria. Piperacillin is an anti-pseudomonas penicillin, with improved action against *P. aeruginosa* and other GNB. Penetration of beta-lactamase inhibitors in CNS is not good – **avoid**.

PO & IV: Amoxicillin/Clavulanate
IV: Piperacillin/Tazobactam

Semisynthetic Anti-Staphylococcal Penicillin

Improved action against *Staphylococcus* spp but not MRSA/MRCoNS. Also active against *Streptococcus* spp but loses action against GNB and anaerobic bacteria; not active against *Enterococcus* spp. Risk of phlebitis and blood cytopenia.

PO & IV: Cloxacillin

Cephalosporins

Enterococcus spp and *L. monocytogenes* have intrinsic resistance against cephalosporins.

1st Generation

Active against *Staphylococcus* spp (but not MRSA/MRCoNS) and *Streptococcus* spp, but not *Enterococcus* spp. Action against a few GNB from the community (*E. coli, P. mirabilis)* but many are resistant; not active against *Pasteurella multocida* (dog/cat bites). Action against clostridia (except *C. difficile*). Commonly used for surgical prophylaxis. Penetration in CNS not good – avoid.

PO: Cephalexin
IV: Cefazolin

3rd Generation

Improved action against GNB including most from the community; however, resistance is increasing (ESBL, ampC). Very active against *Streptococcus* spp, less so for *Staphylococcus* spp than the 1st generation cephalosporins. Ceftazidime is an anti-pseudomonal cephalosporin, particularly active against pseudomonas (but there may be resistance, especially if healthcare-associated). *C. difficile* diarrhea: may be among the antibiotic classes with the highest risk.

PO: Cefixime
IV: Ceftriaxone; Cefotaxime; Ceftazidime

Carbapenems

Maintains coverage for most bacteria covered by the previous beta-lactams, but particularly active against most GNB, including ESBL and ampC; however, resistance is increasing. Since it is a “close to last resort” antibiotic for GNB, use must be restricted. Very active against anaerobic bacteria. Imipenem has a higher risk of seizures, preference is for Meropenem. Also useful for XDR-TB.

IV: Meropenem; Imipenem/Cilastatin

Aminoglycosides

Used only for GNB treatment (for gram-positive cocci – GPC - only for synergism). Bactericidal, concentration-dependent (single daily dose may be more potent). Nephrotoxic and ototoxic – use alternative if available. Less potent than beta-lactams or fluoroquinolones for GNB bacteremia: avoid. Poor penetration in CNS – avoid. Do not use during pregnancy. Amikacin usually has lower prevalence of resistance. Amikacin is also used for MDR-TB treatment.

IV & IM: Gentamicin; Amikacin

Anti-folate

Inhibits folate metabolism. Active against some GNB from community (including causes of diarrhea) and some respiratory pathogens, however resistance is increasing. Drug of choice for *Burkholderia* spp and *S. maltophilia* (but there may be resistance). Very useful for HIV patients for *Pneumocystis jiroveci* (PCP - prophylaxis and treatment) and *Isospora belli,* may be used for toxoplasmosis and also decreases risk of malaria. Risk of drug allergy. Avoid during first or third trimester of pregnancy if possible (unless benefit is bigger, e.g. PCP in HIV).

PO & IV: Cotrimoxazole (Sulfamethoxazole/Trimethoprim)

Fluoroquinolones

Good action against GNB (for Ciprofloxacin and Levofloxacin, includes *P. aeruginosa*). Bactericidal. Active against *S. aureus* but resistance may emerge during therapy if monotherapy. Levofloxacin more active against GPC and also very active against respiratory pathogens such as *S. pneumoniae, H. influenzae* , *Moraxella catarrhalis, Legionella* sp and *Mycoplasma pneumonia.* Levofloxacin and Moxifloxacin are also key drugs for MDR-TB treatment (avoid if other options are available for respiratory infections – risk of TB). Ciprofloxacin may be used for meningococcal disease prophylaxis. Very good absorption PO and distribution, including good bone and prostate concentration. Well-tolerated but avoid in children if other options are available (risk of cartilage toxicity in animals but, in humans, seems safe) and during pregnancy. Risk of cardiac arrhythmias, tendon rupture, and CNS side effects, especially in the elderly. *C. difficile* diarrhea: may be among the antibiotic classes with the highest risk. Useful for sexually transmitted infections (STIs) if resistance is not high (e.g. gonococcal urethritis).

PO & IV: Ciprofloxacin; Levofloxacin

Glycopeptides

Bactericidal. Active against GPC, key drugs against MRSA/MRCoNS, *Enterococcus* resistant to Ampicillin, and *S. pneumoniae* resistant to Penicillin and Ceftriaxone. Restricted use. For MSSA, preference for Cloxacillin or Cefazolin (more active). Penetration in CNS with inflamed meninges. Nephrotoxicity is the main risk; do not infuse faster than 60 minutes (“red man syndrome”).

IV: Vancomycin; Teicoplanin (may also use IM)

Glycylcyclines

Similar to Tetracyclines but much more active against GNB including MDR (but intrinsic resistance in some species, notably *P. aeruginosa*). Restricted use – last-resort antibiotic. May be useful as well for MDR GPC such as *Enterococcus* spp. Low concentration in urine; avoid use for UTI if possible.

IV: Tigecycline

Lincosamides

Inhibits protein synthesis. Bacteriostatic. Active against GPC, including some strains of MRSA from the community (but not *Enterococcus* spp). Active against anaerobes, but there may be resistance if from lower gastrointestinal tract (*Bacteroides* spp). *C. difficile* diarrhea: may be among the antibiotic classes with the highest risk. There may be cross-resistance (inducible) with Macrolides: lab should always do D test before confirming "S". Always add a lincosamide in cases where necrotizing fasciitis involves GPC or clostridia (inhibits toxin production).

PO & IV: Clindamycin

Macrolides

Inhibit protein synthesis. Bacteriostatic. Active against GPC but not MRSA; for GNB, Azithromycin useful for *Salmonella* sp, *Shigella* sp, *Campylobacter* sp, or *Bordetella pertussis.* Useful for some respiratory pathogens if not severe (*S. pneumoniae, H. influenzae, M. catarrhalis*, *Legionella* sp, *Mycoplasma pneumoniae, Chlamydia pneumoniae, C. psitacci* and *Corynebacterium diphtheriae*). Alternative for syphilis if penicillin allergy (but if syphilis in pregnancy, avoid – not effective to prevent neonatal disease: desensitize penicillin). Also useful for *Chlamydia trachomatis* (both STI and trachoma). Clarithromycin and Azithromycin useful for treatment of some non-tuberculous mycobacteria (NTM). Poor CNS penetration – do not use. Erythromycin has worse tolerance (GI side effects) and absorption. Drug interactions common with liver metabolized drugs – check. Risk of cardiac arrhythmias.

PO & IV: Erythromycin, Clarithromycin
PO: Azithromycin

Nitroimidazoles

Very active against most anaerobes (low level of resistance), not used for treatment against aerobes. Useful also for some protozoans (e.g. *Trichomonas vaginalis, Entamoeba hystolytica, Giardia lamblia*). Avoid in pregnancy. Good penetration in CNS, good absorption PO.

PO & IV: Metronidazole

Oxazolidinones

Key drug for MDR-TB – avoid use if other options. Active against most aerobic GPC, including MDR - alternative for MRSA/MRCoNS and *Enterococcus* sp resistant to Ampicillin and Vancomycin (VRE). Tolerance is difficult with long use: issues include hematological toxicity (cytopenias) and neuritis (including optic – may be irreversible).

PO: Linezolid

Polymyxins

Last-resort antibiotic for most GNB – **use is highly restricted** and subject to approval by ABS MD. Whenever treating MDR/XDR bacteria, use polymyxins together with a second antibiotic. Nephrotoxic; neurotoxicity is less common but possible.

IV: Colistin

Tetracyclines

Inhibits protein synthesis. Bacteriostatic. Useful for some infections from community (STIs, respiratory, rickettsiosis, brucellosis); however, there is escalating resistance. Avoid in children –may cause discoloration of teeth (but this does not seem a problem with Doxycycline < 21 days of use). Do not use in pregnancy, unless no alternative.

PO: Tetracycline; Doxycycline

Miscellaneous

PO: Fosfomycin and Nitrofurantoin – useful for cystitis but not pyelonephritis.
PO: Fusidic Acid – useful for some GPC if no other options (e.g. *S. aureus* osteomyelitis).
PO: Rifampicin – key drug for tuberculosis. Used only for synergism for GPC when foreign body present (e.g. osteomyelitis or endocarditis due to *S. aureus* and prosthetic material) or prophylaxis for contacts of meningococcal or *H. influenzae* bacterial meningitis. Fast emergence of resistance if used as monotherapy – contra-indicated.
PO & IV: Chloramphenicol – old antibiotic, still an alternative if no other is available, but issues with bone marrow toxicity - risk of aplasia, which may be irreversible. Contra-indicated in neonates.

Antifungal Classes

Azoles

Fungistatic but very active; resistance among *Candida* spp is increasing, especially non-*albicans* species. Itraconazole has worse absorption and more drug interactions (liver metabolism) but is more active against dimorphic fungi such as *Histoplasma capsulatum* and *Penicillium marnefei,* also *Sporotrix schenkii, Aspergillus* spp and *Mucorales.* Fluconazole is very well absorbed and tolerated, overall more potent against yeasts especially for *Candida* spp and *Cryptococcus neoformans.*

PO: Itraconazole
PO & IV: Fluconazole

Polyenes

Fungicidal and very active against most fungi; main issues are nephrotoxicity, hypokalemia (and hypomagnesemia) and infusion reactions; anemia is less common. Liposomal formulations are safer but are much more expensive, and also are a key drug for leishmaniasis treatment). However, liposomal amphotericin achieves low concentrations in the urine (do not use for UTI).

IV: Conventional Amphotericin B (deoxycholate), Liposomal Amphotericin B

Intrinsic Resistance and AST Interpretation – Cross-Resistance

Some bacteria are naturally resistant to some antibiotics, therefore they are normally not tested and not included in AST panels; they should not be used for treatment. Some examples:

- Metronidazole is only active against anaerobic bacteria, and some protozoans
- Clindamycin is not active against aerobic gram-negative bacteria
- Aminoglycosides are not used as monotherapy for gram-positive bacteria (but may be used in combination therapy for synergism). *Stenotrophomonas maltophilia* is intrinsically resistant

- Tigecycline is not active against *P. aeruginosa, Morganella morganii, Proteus* spp and *Providencia* spp
- Colistin (or Polymyxin B) is not active against *B. cepacia, Serratia marcescens, Salmonella* spp, *Shigella* spp, *Morganella morganii, Proteus* spp and *Providencia* spp; it is not active against any gram-positive bacteria
- Ampicillin and Amoxicillin are not active against *Klebsiella pneumoniae, Proteus vulgaris, Enterobacter* sp*, Citrobacter* sp, *Serratia marcescens, Morganella morgana, Providencia* sp
- Vancomycin and Teicoplanin are not active against aerobic gram-negative bacteria

AST: Results reporting usually follow European (EUCAST) or American (CLSI) standards. However, MSF may use external laboratories with different standards, hence this guidance. Sometimes the results from testing with some antibiotics are not reported, but it is still possible to infer if the bacterium is “S” or “R”, based on the results reported for other antibiotics and/or knowledge about the intrinsic resistance of the species.

Table A3.1: Spectrum of Antibiotic Activity

	Not recommended - no action, widespread resistance or no data
+/-	May be active but considerable resistance; may be useful for targeted therapy
+	Active against most bacteria in most settings (but there may be local variation)
C	Use only in combination with another active antibiotic
P	Use only for prophylaxis, not treatment

Table A3.1: Spectrum of Antibiotic Activity

		GRAM POSITIVE									GRAM NEGATIVE																		ANAEROBES		
		BACILLI	COCCI								COCCI		BACILLI																		
																GROUP 1			GROUP 2						Non-fermenters						
Class	Antibiotic	*L.monocytogenes*	*E.faecalis*	*E faecium*	*MRSA*	*MSSA*	*CoNS*	*GAS, GBS, GCS, GGS*	*Streptococci Viridans*	*S. pneumoniae*	*N.gonorrhoeae*	*N.meningitidis*	*S.enterica non Tyhpi*	*S.enterica Typhi/Paraty*	*Shigella spp*	*E. coli*	*Klebsiella spp*	*P.mirabilis*	*P.vulgaris*	*Serratia spp*	*Enterobacter spp*	*Citrobacter spp*	*Providencia spp*	*M.morganii*	*P.aeruginosa*	*Acinetobacter spp*	*B.cepacia*	*S.maltophilia*	*H.influenzae*	*C.perfringens*	oral cavity	abddpminal/pelvic
Penicillins	Penicillin G	+	+	+/-				+	+/-	+	+/-	+																		+	+	
	Ampicillin or Amoxicillin	+	+	+/-				+	+/-	+	+/-	+	+/-	+/-	+/-	+/-		+/-											+/-	+	+	
	Amoxicillin/Clavulanate	+	+	+/-		+	+/-	+	+/-	+	+/-	+	+	+/-	+	+	+/-	+	+/-											+	+	+	+
	Cloxacillin					+	+/-	+	+/-	+/-																						
	Piperacilline/Tazobactam	+/-	+	+/-		+	+/-	+	+/-	+	+/-	+	+	+	+	+	+	+	+/-	+/-	+/-	+/-	+/-	+/-	+	+/-	+/-		+	+	+	+
Cephalosporins	Cefazolin					+	+/-	+	+	+	+/-	+/-				+/-	+/-	+/-											+/-	+/-	+/-	
	Cephalexin					+	+/-	+	+	+/-		+/-				+/-	+/-	+/-											+/-	+/-	+/-	
	Cefixime							+	+	+/-	+/-	+	+	+	+	+	+	+	+/-				+/-						+	+/-	+/-	
	Cefotaxime or Ceftriaxone		C			+	+/-	+	+	+	+	+	+	+	+	+	+	+	+/-	+/-	+/-	+/-	+/-	+/-				+/-	+	+/-	+/-	
	Ceftazidime							+	+/-	+/-	+/-	+	+	+	+	+	+	+	+/-	+/-	+/-	+/-	+/-	+/-	+	+/-	+/-	+/-	+		+/-	
Carbapenems	Meropenem	+	+/-			+	+/-	+	+	+	+/-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+
Aminoglycosides	Gentamicin	C	C	C	C	C	C	C	C						+/-	+	+/-	+	+	+/-	+/-	+/-	+/-	+/-	+/-	+/-			+/-			
	Amikacin	C			C	C	C		C						+/-	+	+	+	+	+	+	+	+	+	+	+/-			+/-			
Anti-folates	Cotrimoxazole	+			+/-	+/-	+/-	+/-		+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-		+/-	+	+	+/-			
Fluoroquinolones	Ciprofloxacin	+/-	+/-		+/-	+	+/-	+/-		+/-	+/-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+/-	+/-	+/-	+			
	Levofloxacin	+/-	+		+/-	+	+/-	+	+	+	+/-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+/-	+/-	+/-	+	+/-	+/-	
Glycopeptides	Vancomycin or Teicoplanin	+	+	+	+	+	+	+	+	+																				+	+/-	
Glycylcyclines	Tigecycline	+	+	+	+	+	+	+	+	+	+/-		+	+	+	+	+			+	+	+				+/-	+/-	+/-	+	+	+	+
Lincosamides	Clindamycin				+/-	+	+/-	+	+/-	+/-																				+	+	+/-
Macrolides	Erythromycin	+/-				+/-	+/-	+/-		+/-	+/-	+/-																	+/-	+/-		
	Azythromycin	+/-				+/-		+/-		+/-	+	+	+/-	+	+														+	+/-		
Miscellaneous	Fusidic Acid				+	+	+/-	+/-	+/-	+/-	+/-	+/-																		+/-	+/-	
Nitroimidazoles	Metronidazole																													+	+/-	+
Oxazolidinones	Linezolid	+	+	+	+	+	+	+	+	+																				+/-	+/-	
Phenicols	Chloramphenicol	+/-	+/-	+/-	+/-	+/-	+/-	+	+/-	+/-	+/-	+	+/-	+/-	+/-	+/-	+/-	+/-	+/-								+/-	+/-	+	+	+/-	+/-
Rifampicin	Rifampicin	C	C	C	C	C	C	C	C	C		P																	P	+/-		
Tetracyclins	Doxycycline	+/-	+/-	+/-	+/-	+	+/-	+	+/-	+/-	+/-	+	+/-	+/-	+/-	+/-	+/-					+/-				+/-	+/-	+/-	+/-	+	+/-	
Polymixins	Colistin															+	+				+	+			+	+		+				

Table A3.2: Intrinsic Resistance, Cross-Resistance, and AST Interpretation

Bacteria	Detail
Enterobacterales GROUP 1*	Attention: If "R" to any 3rd generation Cephalosporin (Ceftriaxone or Cefotaxime or Ceftazidime), consider ESBL and avoid all Penicillins and all Cephalosporins currently available in the MSF standard drug list for severe infections (Ampicillin, Amoxicillin, Cefazolin, Cephalexin, Ceftriaxone, Cefotaxime, Ceftazidime); may consider Piperacillin/Tazobactam or Amoxicillin/Clavulanate for mild UTI cases without bacteremia nor risk factors for complications. 1) If Ampicillin "S", consider Amoxicillin "S" and vice-versa 2) if Cefazolin "S", consider Cephalexin "S" and vice-versa 3) if Ceftriaxone "S", consider Cefotaxime "S" and vice-versa 4) if Imipenem and/or Ertapenem "S" (and none "R") and Meropenem not tested/reported, consider Meropenem "S"; if, however any of the two "R" and Meropenem not tested, consider Meropenem "R" 5) If Ciprofloxacin "R", consider Levofloxacin "R" if not tested
Enterobacterales GROUP 2**	1) If Cefoxitin "R", do not use Piperacillin/Tazobactam nor Amoxicillin/Clavulanate (probable ampC producer) 2) If Imipenem and/or Ertapenem "S" (and none "R") and Meropenem not tested/reported, consider Meropenem "S"; if, however any of the two "R" and Meropenem not tested, consider Meropenem "R". 3) If Ciprofloxacin "R", consider Levofloxacin "R" if not tested.
Enterococcus sp	1) If Penicillin "S", consider Ampicillin and Amoxicillin "S"; 2) if Norfloxacin "S", consider Ciprofloxacin and Levofloxacin "S".
Hemophilus influenzae	1) If Penicillin "S", consider "S" to: Ampicillin, Amoxicillin, Ceftriaxone, Cefixime & Amoxicillin/Clavulanate; 2) If reported as beta-lactamase producer, consider "R" to Ampicillin and Amoxicillin. 3) if Nalidixic Acid "S", consider "S" to Ciprofloxacin & Levofloxacin.
Staphylococcus aureus	1) If MSSA, consider "S" to: Cloxacillin, Cephalexin, Cefazolin & Amoxicillin/Clavulanate; but if reported as MRSA, or "R" to Cefoxitin, or "R" to any of Oxa/Cloxa/Flucloxacillin, consider MRSA: "R" to all Penicillin and all Cephalosporins and Carbapenems available in MSF drug list 2) If Norfloxacin or Ciprofloxacin "S", consider Levofloxacin "S"; 3) Clindamycin: use only if D test negative (inducible resistance test - confirm with lab); 4) if Tetracycline "S", consider Doxycycline "S"; 5) Aminoglycosides (Gentamycin, Amikacin): even if "S", **never use as monotherapy**.
Staphylococcus non *aureus* – Coagulase-negative	1) If Oxacillin "S", consider "S" to: Penicillin, Ampicillin, Amoxicillin, Amoxicillin/Clavulanate & Ceftriaxone; 2) If Norfloxacin "S", consider Levofloxacin "S" 3) Clindamycin: use only if D test negative (inducible resistance test - confirm with lab); 4) If Tetracycline "S", consider Doxycycline "S".
Streptococcus pneumoniae	1) If Penicillin "S", consider "S" to: Ampicillin, Amoxicillin, Cefazolin, Cephalexin , Ceftriaxone & Amox./Clav 2) Clindamycin: use only if D test negative (inducible resistance test - confirm with lab) 3) If Tetracycline "S", consider Doxycycline "S" 4) If Norfloxacin "S", consider Levofloxacin "S"

Acinetobacter sp & *P. aeruginosa* *(GNB Non-Fermenters)*	1) Depending on lab, *Acinetobacter* sp results may not be reported for some antibiotics. Choose among reported. 2) Carbapenems do not share 100% the same antibiogram, however: if Imipenem "S" and Meropenem not tested/reported, consider Meropenem "S"; if however Imipenem "R" and Meropenem not tested, consider Meropenem "R". 3) If Ciprofloxacin "R", consider Levofloxacin "R" if not tested.
B. cepacia & *S. maltophilia* *(GNB Non-Fermenters)*	Depending on the laboratory, results may not be reported - in this case, start Cotrimoxazole and discuss with specialist (if *S.maltophilia* reported as "R," use Ceftazidime or Ciprofloxacin).
Candida sp	Some laboratories may not perform/report AST results; in this case, follow the same order of antifungal priorities. If species identification possible, consider Intrinsic Resistance when choosing (see Section 2.17).
Kingella kingae	If Penicillin "S", consider Ampicillin and Amoxicillin "S"; if beta-lactamase production, consider "R" to all 3 (preference for Ceftriaxone). Antibiotics may not be reported in AST – in this case follow the same order of priority recommedations.
Neisseria meningitidis	Some (or all) of the antibiotics may not be reported, depending on the lab; in this case, preference for Ceftriaxone (or, for neonates, Cefotaxime). If reported Ceftriaxone "S", consider Cefotaxime "S" and vice-versa (resistance to any of the two is very rare).
Neisseria gonorrhoeae	There are no breakpoints for disc diffusion, AST results may not be reported (unless MIC available) - in this case, use Ceftriaxone for full treatment.
Salmonella enterica & *Shigella* sp	If Pefloxacin "R", consider Ciprofloxacin "R"

GROUP 1 Enterobacterales: Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis (Proteus* indole-negative)

**GROUP 2 Enterobacterales *: Enterobacter* sp, *Serratia marcescens, Citrobacter* sp, *Providencia* sp, *Morganella morganii, Proteus vulgaris* (indole-positive)

MSSA: Methicillin Susceptible *S. aureus* – "S" to Cloxacillin, Cefazolin, Cephalexin, Amoxicillin/Clavulanate

MRSA: Methicillin Resistant *S. aureus* – "R" to all Beta-Lactams (Penicillin, Cephalosporins and Carbapenems) in MSF drug list.

GNB: Gram-Negative Bacilli

Annex 4: Antibiotic Doses – IV (Neonatal) and PO (Adults and Children)

Table A4.1: Neonatal Doses of IV Antimicrobials – First Phase of Therapy

Drug	Route	Dose per kg and frequency of administration			
		Body weight < 2kg		Body weight ≥ 2kg	
		0 – 7 days	8 – days to < 1 month	0 – 7 days	8 – days to < 1 month
Amikacin	IV	15 mg/kg every 48 hours	15 mg/kg every 24 hours	15 mg/kg every 24 hours	
Amphotericin B conventional	IV	1 mg/kg every 24 hours			
Amphotericin B Liposomal	IV	3 mg/kg every 24 hours			
Ampicillin	IV	50 mg/kg every 12 hours Meningitis: 100 mg/kg every 12 hours	50 mg/kg every 8 hours Meningitis: 100 mg/kg every 8 hours		
Cefazolin	IV	25 mg/kg every 12 hours	25 mg/kg every 8 hours	50 mg/kg every 12 hours	50 mg/kg every 8 hours
Cefotaxime	IV	50 mg/kg every 12 hours	50 mg/kg every 8 hours		
Ceftazidime	IV	50 mg/kg every 12 hours		50 mg/kg every 8 hours	
Ceftriaxone*	IV/IM	50 mg/kg every 24 hours Meningitis: 100 mg/kg every 24 hours			
Ciprofloxacin	IV	10 mg/kg every 12 hours (*Pseudomonas* or *Acinetobacter* every 8 hours, only if no alternative)			
Cloxacillin	IV	50 mg/kg every 12 hours	50 mg/kg every 8 hours	50 mg/kg every 8 hours	50 mg/kg every 6 hours
Colistin		150,000 IU/kg loading dose; 75,000 IU/kg every 12 hours			
Fluconazole	IV	12 mg/kg every 24 hours			
Gentamicin	IV	3 mg/kg every 24 hours	5 mg/kg every 24 hours		
Meropenem	IV	20 mg/kg every 12 hours	20 mg/kg every 8 hours (CNS dose of 40 mg/kg every 8 hours)		
Metronidazole	IV	Loading dose: 15 mg/kg			
		After 24 hours 7.5 mg/kg every 12 hours			15 mg/kg every 12 hours
Penicillin G	IV	50,000-100,000 IU/kg every 8 hours	50,000-100,000 IU/kg every 6 hours	50,000-100,000 IU/kg every 8 hours	50,000-100,000 IU/kg every 6 hours
Piperacillin tazobactam (calc. mg/kg for piperacillin)	IV	50-100 mg/kg every 12 hours	50-100 mg/kg every 8 hours		
Teicoplanin	IV	16 mg/kg loading dose Then 8 mg/kg every 24 hours			
Vancomycin	IV	15 mg/kg every 24 hours	15 mg/kg every 12 hours		15 mg/kg every 8 hours

Neonatal Dosing of Antibiotics: See Neonatal Care Clinical and Therapeutic Guidelines 2018 for more detailed information.
Always check: drug interactions with all others in use; drug allergy; renal and liver function (ideally including blood biochemistry if possible).
*Use for meningitis only if cefotaxime is not available.

Table A4.2: Doses of PO Antimicrobials

Antimicrobial	Adult dose	Pediatric dose (not for neonates)
Amoxicillin	500 mg-2 g/dose every 8 hours higher dose for bone or CNS infections	15-50 mg/kg/dose every 8 hours (max: 1-2g/dose) higher dose for bone or CNS infections
Amoxicillin/Clavulanate[1] 4:1 – 500/125 mg 7:1 – 875/125 mg 8:1 – 500/62.5 mg	875-1000 mg (Amox.)/dose every 12 hours (7:1 or 8:1) or 500 mg (Amox.)/dose every 8 hours (4:1)	50 mg (Amox.)/kg/dose every 12 hours (7:1 or 8:1) max: Clavulanate 375 mg/day or 12.5 mg/kg/day
Azithromycin	500 mg-1g/dose every 24 hours	10 mg/kg/dose every 24 hours (max: 1 g/dose)
Cefixime	400 mg/dose every 24 hours	4 mg/kg/dose every 12 hours (max: 200 mg/dose)
Cephalexin	500 mg-1g/dose every 6 hours lower dose for UTI (stable)	12.5-25 mg/kg/dose every 6 hours (max: 1 g/dose) higher dose for bone infections or severe infection
Chloramphenicol	500 mg-1g/dose every 6 hours higher dose for bone infections or severe infection	25 mg/kg/dose every 6 hours (max: 500 mg/dose) higher dose for bone infections or severe infection
Ciprofloxacin	500-750 mg/dose every 12 hours (higher dose for *P. aeruginosa* and *Acinetobacter* sp)	15 mg/kg/dose every 12 hours (max: 500 mg/dose (20 mg/Kg/dose (max: 750 mg) if *P. aeruginosa* or *Acinetobacter* sp)
Clindamycin	600 mg/dose every 8 hours or 450 mg/dose every 6 hours	10 mg/kg/dose every 8 hours (max: 600 mg/dose)
Cloxacillin	1 g/dose every 6 hours	30 mg/kg/dose every 6 hours (max: 1 g/dose)
Cotrimoxazole[2] (Sulfamethoxazole/Trimethoprim)	800-160 mg (double strength tablet) every 12 hours 800-160 mg every 8 hours for bone & joint or CNS	5 mg/kg/dose (TMP) every 12 hours (max: 320 mg TMP/dose) every 8 hours for bone & joint or CNS
Doxycycline[3]	100 mg/dose every 12 hours	2.2 mg/kg/dose every 12 hours (max 100 mg/dose)
Fluconazole	800 mg loading dose, then 400 mg/dose every 24 hours	12 mg/kg loading dose, then 6 mg/kg/dose every 24 hours (max: 400mg)
Fusidic Acid	500 mg/dose every 8 hours	20 mg/kg/dose every 8 hours
Levofloxacin[4]	750 mg/dose every 24 hours	6m - <5 ys: 10 mg/kg/dose (max: 375 mg) every 12 hours 5-12 ys: 10 mg/kg/dose (max: 750 mg) every 24 hours
Linezolid	600 mg/dose every 12 hours	< 12 ys: 10 mg/kg/dose, every 8 hours (max: 600 mg/dose) ≥ 12 ys: 600 mg/dose every 12 hours
Metronidazole	500 mg/dose every 8 hours	10 mg/kg/dose every 8 hours
Penicillin V	500 mg-1 g/dose every 6 hours	25 mg/kg/dose every 6 hours
Rifampicin[4]	600 mg/dose every 24hs (or 300 mg/dose every 12 hours)	10 mg/kg/dose every 24 hours (max: 600 mg) (may divide in 2 doses/day)

1) If only ratio 4:1 is available (not ideal) - adults: 500 mg (Amox)/dose every 8 hours; children: 15 mg (Amox.)/Kg/dose every 8 hours.
2) Oral suspension has 40 mg of TMP per 5 ml (8 mg/ml).
3) If <8 years, use only if no other alternative for a maximum of 21 days.
4) Always screen clinically for tuberculosis before prescribing Rifampicin (or Levofloxacin) to avoid development of DR-TB: check if cough>2 weeks, weight loss or night sweats; if there is any doubt postpone start of Rifampicin until TB is properly investigated (see MSF TB guidelines). Rifampicin interacts with many other drugs metabolized by the liver - always check interactions before starting (especially if HIV infection/use of antiretrovirals).

Annex 5: Antibiotic Dose Correction According to Renal Function

1) Calculate the estimated creatinine clearance using the Cockcroft-Gault formula:

$$CrCl = \frac{(140 - age) \times weight\ (in\ kg)}{72(serum\ creatinine^*)} \quad \times 0.85\ (if\ female)$$

*in mg/dL.

2) Check using the table below if dose correction is needed, according to the level of renal function (estimated creatinine clearance).
Dose adjustment may involve increasing the interval between each dose (in this case, the recommended new interval between each dose is presented) and/or decreasing the total amount of drug administered in each dose (in this case, the recommended decreased dose is presented).

Table A5.1: Dose Correction According to Renal Function/Estimated Creatinine Clearance

Antimicrobial	Dose Adjustment According to Level of Renal Function			
	≥50	30-49	10-29	<10[1]
Amikacin[2]	• >80: no adjustment • 60-79: 12 mg/kg/day • 50-59: 10 mg/kg/day	• 40-49: 7.5 mg/kg/day • 30-39: 4 mg/kg/day	• 20-29: 7.5 mg/kg/dose every 48 hours • 10-19: 4 mg/kg/dose every 48 hours	3 mg/kg/dose every 72 hours
Amoxicillin	no adjustment	no adjustment	usual dose every 12 hours	usual dose every 24 hours
Amoxicillin/ Clavulanate	no adjustment	no adjustment	½ dose, usual frequency	½ dose every 24 hours
Amphotericin B	no adjustment	no adjustment	no adjustment	no adjustment
Ampicillin	no adjustment	no adjustment	usual dose every: 6 hours (adults); 8 hours (children)	usual dose every: 12 hours (adults); 24 hours (children)
Cefazolin	no adjustment	no adjustment	usual dose every 12 hours	usual dose every 24 hours
Cefotaxime	no adjustment	usual dose every 8 hours	usual dose every 12 hours	usual dose every 24 hours
Ceftazidime	no adjustment	usual dose every 12 hours	usual dose every 24 hours	½ dose every 24 hours
Ceftriaxone	no adjustment	no adjustment	no adjustment	max. daily dose: 2 g (usual frequency)
Ciprofloxacin	no adjustment	no adjustment	usual dose every 24 hours	½ dose every 24 hours
Clindamycin	no adjustment	no adjustment	no adjustment	no adjustment
Cloxacillin	no adjustment	no adjustment	no adjustment	no adjustment
Colistin	no adjustment	no adjustment	usual dose every 24 hours	½ dose every 24 hours

Cotrimoxazole	no adjustment	no adjustment	½ dose, usual frequency	½ dose every 24 hours – avoid if possible
Doxycycline	no adjustment	no adjustment	no adjustment	no adjustment
Fluconazole	no adjustment	½ dose, usual frequency	½ dose, usual frequency	½ dose, usual frequency
Gentamycin[2]	• >80: no adjustment • 60-79: 4 mg/kg/day • 50-59: 3.5 mg/kg/day	• 40-49: 3.5 mg/kg/day • 30-39: 2 mg/kg/day	• 20-29: 4 mg/kg/dose every 48 hours • 10-19: 3 mg/kg/dose every 48 hours	2 mg/kg/dose every 72 hours
Levofloxacin	no adjustment	• adults: usual dose every 48 hours • children: no adjustment	• Adults 20-29: same dose as for 30-49 • Adults 10-19: 750 mg (loading dose), then 500 mg every 48 hours • children: ½ dose every 24 hours	• adults: 750 mg (loading dose), then 500 mg every 48 hours • children: ½ dose every 48 hours
Linezolid	no adjustment	no adjustment	no adjustment	no adjustment
Meropenem	no adjustment	usual dose every 12 hours	½ dose every 12 hours	½ dose every 24 hours
Penicillin G	no adjustment	½ dose, usual frequency	½ dose, usual frequency	½ dose every: 6 hours (adults); 8 hours (children)
Piperacillin/ Tazobactam	no adjustment	• >40 adult: no adjustment • 30-39 adult: 2.25 mg usual freq.; • 30-49 children: 40 mg (Pip.)/kg/dose every 6 hours	• 20-29 adults: 2.25 mg every 6 hours • 10-19 adults: 2.25 mg every 8 hours • 10-29 children: 40 mg(Pip.)/kg/dose every 8 hours	• adults: 2.25 mg every 8 hours • children: 35 mg (Pip.)/kg/dose every 8 hours
Teicoplanin[3]	no adjustment	From 5th dose on: usual dose every 48 hours	From 5th dose on: usual dose every 48 hours	From 5th dose on: usual dose every 72 hours
Tigecycline	no adjustment	no adjustment	no adjustment	no adjustment
Vancomycin[3]	no adjustment	• 40-49: usual dose every 24 hours • 30-39: usual dose every 36 hour	• 20-29: usual dose every 48 hours • 10-19: usual dose every 72 hours	½ dose every 72 hours

1) If on dialysis, aim to give recommended doses immediately after each session (according to recommended intervals in the table).
2) If available, adjust Aminoglycoside doses according to blood drug levels (see Annex 1.3 - TDM); if not possible, close monitoring to side effects and avoid if nephrotoxicity.
3) Vancomycin should be used in renal insufficiency without therapeutic drug monitoring (TDM, see Annex) only if absolutely no other alternative is available – preference for Teicoplanin.

References

1) European Society for Pediatric Infectious Diseases. Bone and Joint Infection. Practice Guidelines. 2017.

2) Berbari EF et al. 2015 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the Diagnosis and Treatment of Native Vertebral Osteomyelitis in Adults. Clin Infect Dis. 2015 Sep 15;61(6):e26-46.

3) Osmon DR et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013 Jan;56(1):e1-e25.

4) Lima AL et al. Recommendations for the treatment of osteomyelitis. Braz J Infect Dis. 2014 Sep-Oct;18(5):526-34.

5) Korean Society for Chemotherapy. Clinical guidelines for the antimicrobial treatment of bone and joint infections in Korea. Infect Chemother. 2014 Jun;46(2):125-38.

6) Lorrot M et al. Antibiotic therapy of bone and joint infections in children: proposals of the French Pediatric Infectious Disease Group. Arch Pediatr. 2017 Dec;24(12S):S36-S41.

7) Nicole Le Saux. Saux NL. Canada Pediatric Society - Position Statement: Diagnosis and management of acute osteoarticular infections in children. Pediatrics & Child Health, 2018, 336–343.

8) Saavedra-Lozano J et al. Bone and Joint Infections. Pediatr Infect Dis J. 2017 Aug;36(8):788-799.

9) Esposito S et al. Italian guidelines for the diagnosis and infectious disease management of osteomyelitis and prosthetic joint infections in adults. Infection. 2009 Dec;37(6):478-96.

10) Liu C et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011 Feb 1;52(3):e18-55.

11) Kolinsky DC et al. Musculoskeletal Infections in the Emergency Department. Emerg Med Clin North Am. 2018 Nov;36(4):751-766.

12) Spellberg B et al. Systemic antibiotic therapy for chronic osteomyelitis in adults. Clin Infect Dis. 2012 Feb 1;54(3):393-407.

13) Conterno LO et al. Antibiotics for treating chronic osteomyelitis in adults. Cochrane Database Syst Rev. 2013 Sep 6;(9):CD004439.

14) Chiappini E et al. Septic arthritis in children in resource limited and non-resource limited countries: an update on diagnosis and treatment. Expert Rev Anti Infect Ther. 2016 Nov;14(11):1087-1096.

15) Geurts J et al. Treatment strategies for chronic osteomyelitis in low- and middle-income countries: systematic review. Trop Med Int Health. 2017 Sep;22(9):1054-1062.

16) Sendi P et al. The use of rifampin in staphylococcal orthopedic-device-related infections. Clin Microbiol Infect. 2017 Jun;23(6):349-350.

17) Rieg S et al. Combination antimicrobial therapy in patients with Staphylococcus aureus bacteremia-a post hoc analysis in 964 prospectively evaluated patients. Clin Microbiol Infect. 2017 Jun;23(6):406.e1-406.e8.

18) Makridis KG et al. Management of infection after intramedullary nailing of long bone fractures: treatment protocols and outcomes. Open Orthop J. 2013 Jun 14;7:219-26.

19) Simpson AH et al. Current treatment of infected non-union after intramedullary nailing. Injury. 2017 Jun;48 Suppl 1:S82-S90.

20) Metsemakers WJ et al. Infection after fracture fixation: Current surgical and microbiological concepts. Injury. 2018 Mar;49(3):511-522.

21) Zimmerli W. Clinical presentation and treatment of orthopedic implant-associated infection. J Intern Med. 2014 Aug;276(2):111-9.

22) Fang C et al. Infection after fracture osteosynthesis - Part I: Pathogenesis, diagnosis and classification. J Orthop Surg (Hong Kong). 2017 Jan;25(1):2309499017692712.

23) Fang C et al. Infection after fracture osteosynthesis - Part II: Treatment. J Orthop Surg (Hong Kong). 2017 Jan;25(1):2309499017692714.

24) Bonnevialle P. Operative treatment of early infection after internal fixation of limb fractures (exclusive of severe open fractures). Orthop Traumatol Surg Res. 2017 Feb;103(1S):S67-S73.

25) Wintenberger C et al. Proposal for shorter antibiotic therapies. Med Mal Infect. 2017 Mar;47(2):92-141.

26) Keren R et al. Comparative effectiveness of intravenous vs oral antibiotics for post-discharge treatment of acute osteomyelitis in children. JAMA Pediatr. 2015 Feb;169(2):120-8.

27) Zaoutis T et al. Prolonged intravenous therapy versus early transition to oral antimicrobial therapy for acute osteomyelitis in children. Pediatrics. 2009 Feb;123(2):636-42.

28) Peltola H et al. Short- versus long-term antimicrobial treatment for acute hematogenous osteomyelitis of childhood: prospective, randomized trial on 131 culture-positive cases. Pediatr Infect Dis J. 2010 Dec; 29(12): 1123-8.

29) Bernard L et al. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomized, controlled trial. Lancet. 2015 Mar 7;385(9971):875-82.

30) Li YD et al. Appropriate duration of post-surgical intravenous antibiotic therapy for pyogenic spondylodiscitis. BMC Infect Dis. 2018 Sep 17;18(1):468.

31) Tone A et al. Six-week versus twelve-week antibiotic therapy for nonsurgically treated diabetic foot osteomyelitis: a multicenter open-label controlled randomized study. Diabetes Care 2015; 38:302-307.

32) Peltola H et al. Prospective, randomized trial of 10 days versus 30 days of antimicrobial treatment, including a short-term course of parenteral therapy, for childhood septic arthritis. Clin Infect Dis. 2009 May 1;48(9):1201-10.

33) Jagodzinski NA et al. Prospective evaluation of a shortened regimen of treatment for acute osteomyelitis and septic arthritis in children. J Pediatr Orthop. 2009 Jul-Aug;29(5):518-25.

34) Lota-Tamayo J et al. Short- versus long duration levofloxacin plus rifampicin for acute staphylococcal prosthetic joint infection managed with implant retention: a randomized clinical trial. Int J Antimicrob Agents. 2016 Sep;48(3):310-6.

35) Belthur MV et al. Prospective evaluation of a shortened regimen of treatment for acute osteomyelitis and septic arthritis in children. J Pediatr Orthop. 2010 Dec;30(8):942.

36) Chaussade H et al. Antibiotic therapy duration for prosthetic joint infections treated by Debridement and Implant Retention (DAIR): Similar long-term remission for 6 weeks as compared to 12 weeks. Int J Infect Dis. 2017 Oct;63:37-42.

37) Pääkkönen M et al. Does Bacteremia Associated with Bone and Joint Infections Necessitate Prolonged Parenteral Antimicrobial Therapy? J Pediatric Infect Dis Soc. 2015 Jun;4(2):174-7.

38) National Institute for Health and Care Excellence. Diabetic foot problems: prevention and management. NICE guideline. Published: 26 August 2015.

39) National Institute for Health and Care Excellence. Pressure ulcers: prevention and management. Clinical guideline. Published: 23 April 2014.

40) Lipsky BA et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012 Jun;54(12):e132-73.

41) Nicksic PJ et al. Management of the Pressure Injury Patient with Osteomyelitis: An Algorithm. J Am Coll Surg. 2017 Dec;225(6):817-822.

42) Aragón-Sánchez J et al. Modern management of diabetic foot osteomyelitis. The when, how and why of conservative approaches. Expert Rev Anti Infect Ther. 2018 Jan;16(1):35-50

43) Tschudin-Sutter S et al. Validation of a treatment algorithm for orthopedic implant-related infections with device-retention-results from a prospective observational cohort study. Clin Microbiol Infect. 2016 May;22(5):457.e1-9.

44) Keller SC1 et al. Role of Suppressive Oral Antibiotics in Orthopedic Hardware Infections for Those Not Undergoing Two-Stage Replacement Surgery. Open Forum Infect Dis. 2016 Aug 30;3(4):ofw176.

45) Pappas PG et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Feb 15;62(4):e1-50.

46) Li HK et al. Oral versus Intravenous Antibiotics for Bone and Joint Infection. N Engl J Med. 2019 Jan 31;380(5):425-436.

47) Stevens DL et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52.

48) Mermel LA et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009 Jul 1;49(1):1-45.

49) Alothman AF et al. Clinical practice guidelines for the management of invasive Candida infections in adults in the Middle East region: Expert panel recommendations. J Infect Public Health. 2014 Feb;7(1):6-19.

50) Crump JA et al. Epidemiology, Clinical Presentation, Laboratory Diagnosis, Antimicrobial Resistance, and Antimicrobial Management of Invasive Salmonella Infections. Clin Microbiol Rev. 2015 Oct;28(4):901-37.

51) D'Angelo RG et al. Treatment options for extended-spectrum beta-lactamase (ESBL) and AmpC-producing bacteria. Expert Opin Pharmacother. 2016;17(7):953-67.

52) Garnacho-Montero J et al. Managing Acinetobacter baumannii infections. Curr Opin Infect Dis. 2019 Feb;32(1):69-76.

53) Rodríguez-Baño J et al. Treatment of Infections Caused by Extended-Spectrum-Beta-Lactamase-, AmpC-, and Carbapenemase-Producing Enterobacterales. Clin Microbiol Rev. 2018 Feb 14;31(2).

54) Shin B et al. Antibiotic resistance of pathogenic Acinetobacter species and emerging combination therapy. J Microbiol. 2017 Nov;55(11):837-849.

55) Karaiskos I et al. Combination therapy for extensively-drug resistant gram-negative bacteria. Expert Rev Anti Infect Ther. 2017 Dec;15(12):1123-1140.

56) Kullar R et al. When sepsis persists: a review of MRSA bacteremia salvage therapy. J Antimicrob Chemother. 2016 Mar;71(3):576-86.

57) Lee AS et al. Methicillin-resistant Staphylococcus aureus. Nat Rev Dis Primers. 2018 May 31;4:18033.

58) Lewis PO et al. Treatment strategies for persistent methicillin-resistant Staphylococcus aureus bacteremia. J Clin Pharm Ther. 2018 Oct;43(5):614-625.

59) Kariuki S et al. Antimicrobial resistance and management of invasive Salmonella disease. Vaccine. 2015 Jun 19;33 Suppl 3:C21-9.

60) Zmora N et al. Open label comparative trial of mono versus dual antibiotic therapy for Typhoid Fever in adults. PLoS Negl Trop Dis. 2018 Apr 23;12(4):e0006380.

61) Harris PNA et al. Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients with E coli or Klebsiella pneumoniae Bloodstream Infection and Ceftriaxone Resistance: A Randomized Clinical Trial. JAMA. 2018 Sep 11;320(10):984-994.

62) Yahav D et al. Seven versus fourteen Days of Antibiotic Therapy for uncomplicated Gram-negative Bacteremia: a Non-inferiority Randomized Controlled Trial. Clin Infect Dis. 2018 Dec 11. doi: 10.1093/cid/ciy1054.

63) Holland TL et al. Effect of Algorithm-Based Therapy vs Usual Care on Clinical Success and Serious Adverse Events in Patients with Staphylococcal Bacteremia: A Randomized Clinical Trial. JAMA. 2018 Sep 25;320(12):1249-1258.

64) Chotiprasitsakul D et al. Comparing the Outcomes of Adults with Enterobacterales Bacteremia Receiving Short-Course Versus Prolonged-Course Antibiotic Therapy in a Multicenter, Propensity Score-Matched Cohort. Clin Infect Dis. 2018 Jan 6;66(2):172-177.

65) Mercuro NJ et al. Retrospective analysis comparing oral stepdown therapy for Enterobacterales bloodstream infections: fluoroquinolones versus β-lactams. Int J Antimicrob Agents. 2018 May;51(5):687-692.

66) Kutob LF et al. Effectiveness of oral antibiotics for definitive therapy of Gram-negative bloodstream infections. Int J Antimicrob Agents. 2016 Nov;48(5):498-503.

67) Lo CL1 et al. Fluoroquinolone therapy for bloodstream infections caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae. J Microbiol Immunol Infect. 2017 Jun;50(3):355-361.

68) Cheng L et al. Piperacillin-Tazobactam versus Other Antibacterial Agents for Treatment of Bloodstream Infections Due to AmpC β-Lactamase-Producing Enterobacterales. Antimicrob Agents Chemother. 2017 May 24;61(6).

69) Thompson CN et al. Treatment Response in Enteric Fever in an Era of Increasing Antimicrobial Resistance: An Individual Patient Data Analysis of 2092 Participants Enrolled into 4 Randomized, Controlled Trials in Nepal. Clin Infect Dis. 2017 Jun 1;64(11):1522-1531.

70) Khan AM et al. Neonatal and Perinatal Infections. Pediatr Clin North Am. 2017 Aug;64(4):785-798.

71) Shane AL et al. Neonatal sepsis. Lancet. 2017 Oct 14;390(10104):1770-1780.

72) Hsu AJ et al. Treatment of multidrug-resistant Gram-negative infections in children. Clin Infect Dis. 2014 May;58(10):1439-48.

73) Moxon CA et al. Beta-lactamases in Enterobacterales infections in children. J Infect. 2016 Jul 5;72 Suppl:S41-9.

74) Harris PN et al. Carbapenems versus alternative antibiotics for the treatment of bloodstream infections caused by Enterobacter, Citrobacter or Serratia species: a systematic review with meta-analysis. J Antimicrob Chemother. 2016 Feb;71(2):296-306.

75) Harris PNA et al. Risk factors for relapse or persistence of bacteremia caused by Enterobacter spp.: a case-control study. Antimicrob Resist Infect Control. 2017 Jan 21;6:14.

76) McKamey L et al. Assessing antimicrobial stewardship initiatives: Clinical evaluation of cefepime or piperacillin/tazobactam in patients with bloodstream infections secondary to AmpC-producing organisms. Int J Antimicrob Agents. 2018 Nov;52(5):719-723.

77) Moy S et al. Treatment Outcomes in Infections Caused by "SPICE" (Serratia, Pseudomonas, Indole-positive Proteus, Citrobacter, and Enterobacter) Organisms: Carbapenem versus Non-carbapenem Regimens. Clin Ther. 2017 Jan;39(1):170-176.

78) Iversen K et al. Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis. N Engl J Med. 2019 Jan 31;380(5):415-424.

79) Gupta K et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011; 52:e103–120.

80) Hooton TM et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clin Infect Dis. 2010 Mar 1;50(5):625-63.

81) Miller JM et al. A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2018 Update by the Infectious Diseases Society of America and the American Society for Microbiology. Clin Infect Dis. 2018 Aug 31;67(6):e1-e94.

82) Subcommittee on Urinary Tract Infection. Reaffirmation of AAP Clinical Practice Guideline: The Diagnosis and Management of the Initial Urinary Tract Infection in Febrile Infants and Young Children 2-24 Months of Age. Pediatrics. 2016 Dec;138(6).

83) National Institute for Health and Care Excellence. Public Health England. Pyelonephritis (acute): Antimicrobial Prescribing. October 2018.

84) National Institute for Health and Care Excellence. Public Health England. Urinary Tract Infection (Catheter-Associated): Antimicrobial Prescribing. November 2018.

85) National Institute for Health and Care Excellence. Public Health England. Urinary Tract Infections in Under 16s: Diagnosis and Management. August 2007 (update October 2018).

86) National Institute for Health and Care Excellence. Public Health England. Prostatitis (acute): Antimicrobial Prescribing. October 2018.

87) National Institute for Health and Care Excellence. Public Health England. Fever in Under 5s: Assessment and Initial Management. May 2013.

88) Bonkat G et al. EAU Guidelines on Urological Infections. European Association of Urology. 2017.

89) Stein R et al. Urinary tract infections in children: EAU/ESPU guidelines. Eur Urol. 2015 Mar;67(3):546-58.

90) Ammenti A et al. Febrile urinary tract infections in young children: recommendations for the diagnosis, treatment and follow-up. Italian Society of Pediatric Nephrology. Acta Paediatr. 2012 May;101(5):451-7.

91) Bataglia M et al. Racommandazioni in Tema di Diagnosi, Trattamento e Profilassi delle Infezioni delle Vie Urinarie. A cura del Comitato Linee Guida della Società Italiana di Urologia. Versione 1. 2015.

92) de Cueto M et al. Executive summary of the diagnosis and treatment of urinary tract infection: Guidelines of the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC). Enferm Infecc Microbiol Clin. 2017 May;35(5):314-320.

93) Kranz J et al. The 2017 Update of the German Clinical Guideline on Epidemiology, Diagnostics, Therapy, Prevention, and Management of Uncomplicated Urinary Tract Infections in Adult Patients: Part 1. Urol Int. 2018;100(3):263-270.

94) Kranz J et al. The 2017 Update of the German Clinical Guideline on Epidemiology, Diagnostics, Therapy, Prevention, and Management of Uncomplicated Urinary Tract Infections in Adult Patients. Part II: Therapy and Prevention. Urol Int. 2018;100(3):271-278.

95) Caron F1 et al. Practice guidelines for the management of adult community-acquired urinary tract infections. Med Mal Infect. 2018 Aug;48(5):327-358.

96) Choe HS et al. Summary of the UAA-AAUS guidelines for urinary tract infections. Int J Urol. 2018 Mar;25(3):175-185.

97) Kang CI et al. Clinical Practice Guidelines for the Antibiotic Treatment of Community-Acquired Urinary Tract Infections. Infect Chemother. 2018 Mar;50(1):67-100.

98) Beahm NP1 et al. The assessment and management of urinary tract infections in adults: Guidelines for pharmacists. Can Pharm J (Ott). 2017 Jul 31;150(5):298-305.

99) Robinson JL et al. Urinary tract infections in infants and children: Diagnosis and management. Paediatr Child Health. 2014 Jun;19(6):315-25.

100) South Australia expert Advisory Group on Antimicrobial Resistance (SAAGAR). Empirical Treatment of Bacterial Urinary Tract Infections (adults) Clinical Guideline. October 2017.

101) Okarska-Napierała M et al. Urinary tract infection in children: Diagnosis, treatment, imaging - Comparison of current guidelines. J Pediatr Urol. 2017 Dec;13(6):567-573.

102) Concia E et al. Clinical evaluation of guidelines and therapeutic approaches in multi drug-resistant urinary tract infections. J Chemother. 2017 Dec;29(sup1):19-28.

103) Bader MS et al. An update on the management of urinary tract infections in the era of antimicrobial resistance. Postgrad Med. 2017 Mar;129(2):242-258.

104) Strohmeier Y et al. Antibiotics for acute pyelonephritis in children. Cochrane Database Syst Rev. 2014 Jul 28;(7):CD003772.

105) Lewis-de Los Angeles WW et al. Trends in Intravenous Antibiotic Duration for Urinary Tract Infections in Young Infants. Pediatrics. 2017 Dec;140(6). pii: e20171021.

106) Johnson JR et al. Acute Pyelonephritis in Adults. N Engl J Med. 2018 Jan 4;378(1):48-59.

107) Schroeder AR et al. Intravenous antibiotic durations for common bacterial infections in children: when is enough? J Hosp Med. 2014 Sep;9(9):604-9.

108) Molyneux EM et al. The outcome of non-typhoidal salmonella meningitis in Malawian children, 1997-2006. Ann Trop Paediatr. 2009 Mar;29(1):13-22.

109) Wen SC et al. Non-typhoidal Salmonella infections in children: Review of literature and recommendations for management. J Paediatr Child Health. 2017 Oct;53(10):936-941.

110) Cohen R et al. Bacterial meningitis antibiotic treatment. Arch Pediatr. 2017 Dec;24(12S):S42-S45.

111) Costerus JM et al. Community-acquired bacterial meningitis. Curr Opin Infect Dis. 2017 Feb;30(1):135-141.

112) Patel NA et al. Systematic review and case report: Intracranial complications of pediatric sinusitis. Int J Pediatr Otorhinolaryngol. 2016 Jul;86:200-12.

113) Pai S et al. Pseudomonas aeruginosa meningitis/ventriculitis in a UK tertiary referral hospital. QJM. 2016 Feb;109(2):85-9.

114) Durrmeyer X et al. Stratégies thérapeutiques des méningites néonatales à Escherichia coli. Arch Pediatr. 2012 Nov;19 Suppl 3:S140-4.

115) Felsenstein S et al. Clinical and microbiologic features guiding treatment recommendations for brain abscesses in children. Pediatr Infect Dis J. 2013 Feb;32(2):129-35.

116) Gallegos C et al. Delayed Cerebral Injury in Adults with Bacterial Meningitis: A Novel Complication of Adjunctive Steroids? Crit Care Med. 2018 Aug;46(8):e811-e814.

117) Tunkel AR et al. 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis. Clin Infect Dis. 2017 Feb 14.

118) National Institute for Health and Care Excellence. Public Health England. Meningitis (bacterial) and meningococcal septicemia in under 16s: recognition, diagnosis and management. June 2010

119) New South Wales Government. Ministry of Health. Infants and Children: Acute Management of Bacterial Meningitis: Clinical Practice Guideline. Document Number GL2014_013. 15-Jul-2014.

120) Le Saux N et al. Guidelines for the management of suspected and confirmed bacterial meningitis in Canadian children older than one month of age. Paediatr Child Health. 2014 Mar;19(3):141-52.

121) Tunkel AR et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004 Nov 1;39(9):1267-84.

122) van de Beek D et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect. 2016 May;22 Suppl 3:S37-62.

123) McGill F et al. The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults. J Infect. 2016 Apr;72(4):405-38.

124) Boyles TH et al. Guidelines for the management of acute meningitis in children and adults in South Africa. South Afr J Epidemiol Infect 2013;28(1):5-15.

125) Keddy KH et al. Clinical and Microbiological Features of Salmonella Meningitis in a South African Population, 2003-2013. Clin Infect Dis. 2015 Nov 1;61 Suppl 4:S272-82.

126) Gilchrist JJ et al. Invasive Nontyphoidal Salmonella Disease in Africa. EcoSal Plus. 2019 Jan;8(2).

127) Bretonnière C et al. Rifampin use in acute community-acquired meningitis in intensive care units: the French retrospective cohort ACAM-ICU study. Crit Care. 2015 Aug 26;19:303.

List of Tables and Figures