1. Introduction and Who Guideline applies to

This guideline has been developed to deliver safe and appropriate empirical use of antibiotics for Adult patients on the Critical Care Units at University Hospitals of Leicester NHS Trust. The guideline applies to adult inpatient and should be used in conjunction with the Antimicrobial Prescribing Policy.

The recommendations within this guideline provide targeted empirical regimens covering likely pathogenic organisms for defined infections and aim to promote the evidence based use of antimicrobials, minimise the effect of antimicrobials on the patient's normal bacterial flora and adverse effects.

2. Guideline Standards and Procedures

2.1 General information

Please see separate guidelines for the treatment of neutropenic sepsis, and septic patients NOT on an intensive care unit.

IV Antibiotic therapy should be started within the first hour of the recognition of severe sepsis, after appropriate cultures have been taken.

In cases of sepsis in immunocompetent adults empirical therapy based upon the likeliest of sources of bacteraemia is necessary.

Appropriate microbiological specimens should always be taken before starting antibiotics. This should include two sets (four bottles) of blood cultures taken from separate sites (20ml/set). Recent microbiology results (where available) should be reviewed to identify if the patient is at risk of sepsis with a more resistant organism, which may not respond to standard first line therapy.

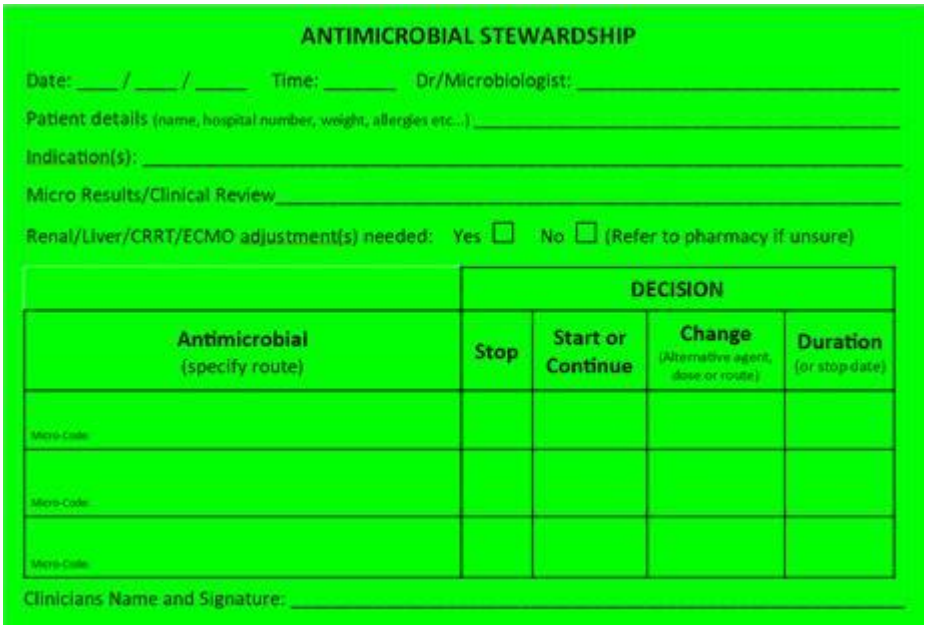
Vancomycin and once daily gentamicin must be prescribed on their dedicated prescription charts. Information around assays, dosing information and adjustments can be found on these charts and on the antimicrobial webpage.

- Patients with renal and/or liver impairment may need dose adjustments
    - Appendix 1 contains information for liver/renal dose adjustments for antifungals
    - Patients in acute renal/liver failure are likely to need full dosing of antimicrobials during for the first 24 to 48 hours of therapy and may need dose adjustments thereafter.
- Information on antimicrobials for patients who are breast feeding can be found on
    - https://www.sps.nhs.uk/articles/ukdilas/ for UK Drugs in Lactation Advisory Service (UKDILAS)
    - Contacting Medicines information on 0116 2586491
- Information for obstetric and gynaecological infections can be found on the
    - Antimicrobial website.
    - http://www.uktis.org/ for teratology information
    - Discussion with medical microbiologist and obstetrics may be warranted.
- In hours please contact the ICU ward pharmacy team to answer/coordinate your query in the first instance
- Out of hours assistance with difficult queries can be sought by the oncall pharmacist via switch board

Dosage recommendations for antimicrobials in patients undergoing CVVHDF can be found in the trust policy “Antimicrobial Dosing Guidelines for Adults receiving CVVHDF” Trust Reference: C23/2019.

A daily review of antimicrobial therapy must be conducted on each patient in a critical care setting in line with trust guidelines. Where a more formal review with a microbiologist has occurred documentation should be made on the green review stickers. See example in figure 1.

Information regarding antimicrobial assays for gentamicin, tobramycin, amikacin, vancomycin, teicoplanin, flucytosine, itraconazole, posaconazole and voriconazole can be found on the antimicrobial website on the intranet.



ANTIMICROBIAL STEWARDSHIP

Date: ____ / ____ / _____ Time: _____ Dr/Microbiologist: _____

Patient details (name, hospital number, weight, allergies etc...): _____

Indication(s): _____

Micro Results/Clinical Review _____

Renal/Liver/CRRT/ECMO adjustment(s) needed: Yes ☐ No ☐ (Refer to pharmacy if unsure)

	DECISION			
Antimicrobial (specify route)	**Stop**	**Start or Continue**	**Change** (Alternative agent, dose or route)	**Duration** (or stop date)
Micro-Code:				
Micro-Code:				
Micro-Code:				

Clinicians Name and Signature: _____

Figure 1: Sample Antibiotic Review Sticker.

2.2 Specific Antibiotic Advice

Quinolone (e.g. ciprofloxacin) warnings:

- Tendon Damage (rare) – Contraindicated with a history of tendon disorders related to quinolone use. Caution in people over 60 years, solid organ transplant, renal impairment or concomitant corticosteroids. Stop quinolone treatment immediately if tendonitis suspected.
- Aortic Aneurysm and Dissection (small increased risk) – Use with caution in patients at risk of aortic aneurysm and dissection (includes connective tissue disorders). Urgent review if sudden-onset severe abdominal, chest or back pain develops.
- Valve Prolapse (small risk) – use with caution in patients with congenital or pre-existing heart valve disease. Connective tissue disorders or other risk factors or conditions predisposing to heart valve regurgitation. Patients should seek immediate medical attention if they experience a rapid onset of shortness of breath, swelling of ankles, feet or abdomen or new-onset heart palpitations.
- Musculoskeletal and Neurological effects (very rare) – Stop treatment at the first signs of muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy and other CNS effects. Avoid using in patients who have experienced adverse effects from quinolones previously. Caution in people with a history or predisposition to seizures.

2.3 Antifungals Advice

Invasive Fungal Infections (IFIs) are increasing due to increasing immunocompromised and ICU patient numbers. Antifungal therapy may be indicated in patients with persistent sepsis despite antibiotic cover.

Patients with suspicion of IFIs, will need to be assessed by:

- Undertaking appropriate radiological scans and
- Collecting samples from the anatomical site of infection for culture and
- Where relevant collecting serum samples for:
    - Galactomannan for suspected invasive aspergillus infection and/or
    - Beta-D Glucan for suspected invasive candida infections
- Where relevant collecting deep respiratory samples i.e. BAL, NIBL, ET aspirates for:
    - Galactomannan for suspected invasive aspergillus infection

Please ensure the request reasons and sample origin site are clearly indicated when sending samples.
Non inclusion of request reason may result in the samples not being processed

With the exception of PO fluconazole (or IV if the patient is unable to take enterally), course durations of more than 7 days and for all other antifungals will require appropriate **microbiology verification codes** whilst on ICU.

Recommendations for antifungal use in patients with renal or liver impairment can be found in appendix 1

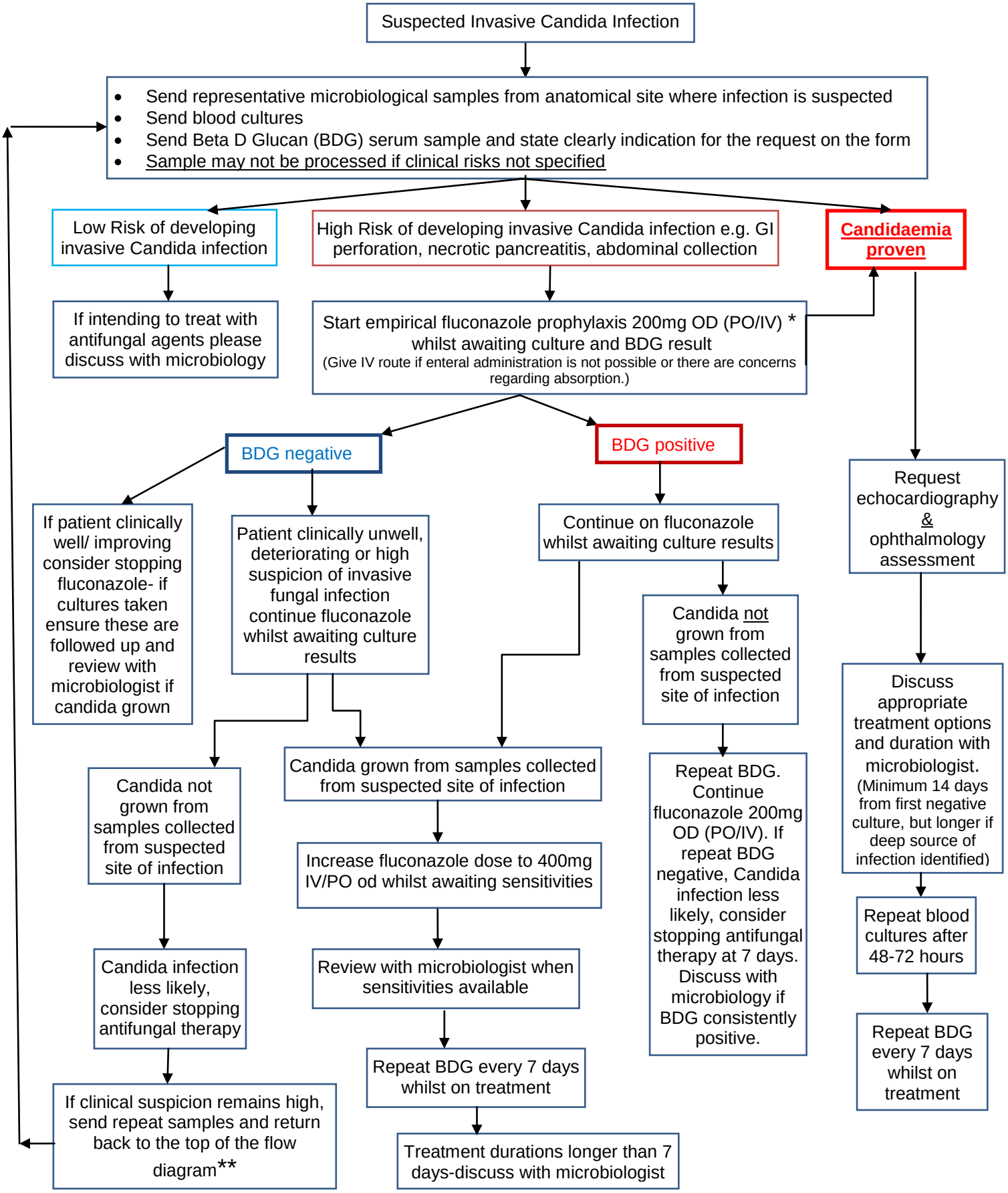
Requests for Isavuconazole will require a Blueteq number. Instructions for accessing and processing Blueteq numbers can be found on the intranet or by following the attached link:
Blueteq information

2.3.1 Candidaemia

Risks factors for developing Candidaemia

- Neutropenia
- Use of broad spectrum antibiotics after several days
- Indwelling intravenous catheters e.g. TPN use
- HIV/AIDS
- Gastrointestinal tract surgery including perforations, complex intra-abdominal collections, or peritonitis with faecal contamination
- Advanced vasculitic diseases on immunosuppression

Treatment guideline for suspected invasive Candida infection including Candidaemia (candida in blood culture)



Ongoing review with microbiology input if on antifungal treatment for more than 7 days, or if ongoing clinical concern.

*There may be some circumstances where fluconazole is a less appropriate empirical choice, e.g. prior treatment with azoles, known colonisation with non-susceptible Candida species, other clinical risk factors or contraindications and clinically significant interactions.

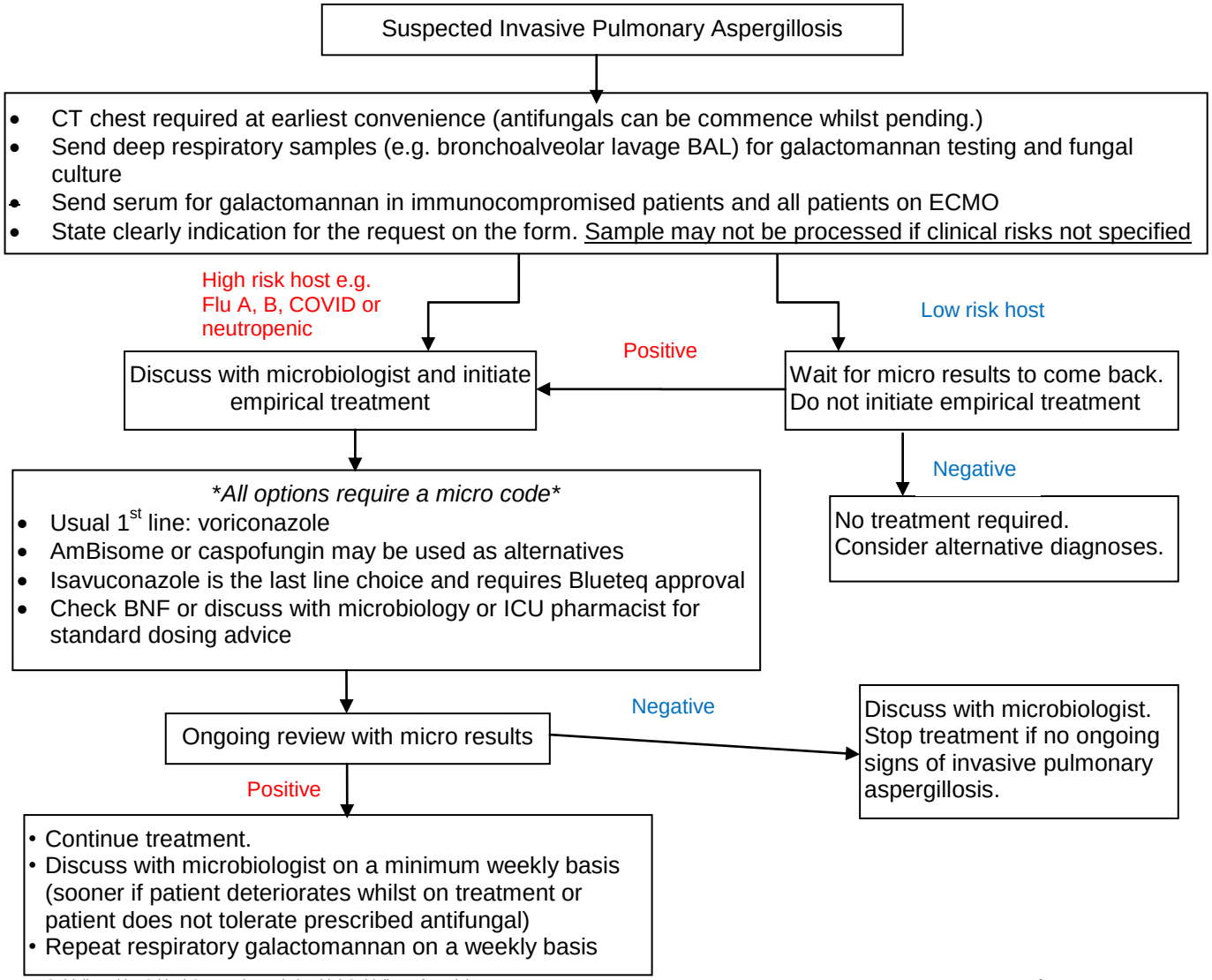
** If candida not grown from samples collected from the suspected infection site but clinical suspicion remains high send repeat microbiological samples from anatomical site where infection is suspected, send blood cultures and send BDG serum sample and state clearly the indication for the request on the form (sample may not be processed if clinical risks not specified).

2.3.2 Systemic Aspergillus Infections

Risks factors for developing Aspergillosis

- COVID patients
- Influenza patients
- Neutropenia
- Acute Leukaemia
- Organ Transplant recipient
- Chronic Granulomatous Disease
- Pre-existing lung disease
- Extracorporeal Membrane Oxygenation (ECMO)

Treatment guideline for suspected Invasive Pulmonary Aspergillosis



For further information on contraindications, cautions, drug interactions and adverse effects refer to the British National Formulary (**www.bnf.org**) or the Medicines Compendium (**www.medicines.org.uk**).

Abbreviations used:
OD: Daily
BD: Twice daily
TDS: Three times a day
QDS: Four times a day

Guidance on Initial Antimicrobial Therapy by Body Site

ONLY APPLICABLE TO INTENSIVE CARE PATIENTS (CRITICAL CARE).

Contact a microbiologist after 5 days if extended duration indicated or patient does not clinically improve.

Infection	Standard Regimen	Alternative Regimen	Comments
Acute sepsis: source unknown	Meropenem IV 1g TDS *Discuss continuation with microbiology after 24h of empirical therapy (if after 5pm, please contact micro after 9am the following day so that recent results can be viewed)* *If documented anaphylaxis to penicillins, or meropenem allergy, then consult microbiology.*		If unrelenting septic shock: Stat Gentamicin IV 7mg/kg <u>If not responding to therapy</u>: discuss with microbiology
Respiratory			
Severe Community Acquired Pneumonia (CURB-65 3-5)	Co-amoxiclav IV 1.2g TDS *and* Clarithromycin IV 500mg BD	Levofloxacin PO/NG/IV 500mg BD	Review atypical cover on sensitivity and culture results. Consider stepdown oral therapy when appropriate.
Hospital Acquired Pneumonia	<u>First line</u> Co-Amoxiclav 1.2g TDS. <u>Second line</u> If patient not responding can consider Piperacillin/Tazobactam IV 4.5g TDS	Levofloxacin PO/NG/IV 500mg BD	
Ventilator-associated Pneumonia	Piperacillin/Tazobactam IV 4.5g TDS	Meropenem IV 1g TDS	
Aspiration only	No Antibiotics		
MRSA Pneumonia	Linezolid PO/NG/IV 600mg BD	If no response discuss with microbiology	Oral therapy has excellent bioavailability and can be used if patient reliably absorbing. Treatment course duration: minimum 14 days.
Pulmonary or Extrapulmonary TB	Discuss with chest physician or ID physician.		Ensure discussions re: suitability of routes and access to visual acuity and audiometry testing are considered. Separate agents are often required.

Abdominal			
Infection	Standard Regimen	Alternative Regimen	Comments
Clostridium difficile associated diarrhoea	see *Clostridium difficile* guide on website regarding treatment options		
Biliary Sepsis	Ciprofloxacin PO/NG 500mg BD *plus* Metronidazole PO/NG 400mg TDS		<u>Oral Therapy has Good Bioavailability</u> First-line oral therapy should be used if oral/NG route available and patient reliably absorbing. Ciprofloxacin and Metronidazole tablets can be crushed and dispersed in water for NG administration if needed.
Biliary Sepsis <u>if enteral route unavailable</u>	Piperacillin/Tazobactam IV 4.5g TDS	Ciprofloxacin IV 400mg BD *plus* Metronidazole IV 500mg TDS. If patient is not responding after 48 hours, review with microbiologist	Second-Line IV therapy choice only if PO/NG route not available or GI absorption unreliable (e.g. high NG aspirates) Consider adding fluconazole: • 200mg OD IV prophylaxis *or* • 400mg OD IV treatment
Acute or Necrotising Pancreatitis	Meropenem IV 1g TDS	According to culture and sensitivities	No antibiotics indicated in pancreatitis unless CT evidence of <u>necrotising</u> pancreatitis Consider adding fluconazole • 200mg OD IV prophylaxis *or* • 400mg OD IV treatment
Peritonitis	Piperacillin/Tazobactam IV 4.5g TDS	Meropenem IV 1g TDS	Consider adding fluconazole • 200mg OD IV prophylaxis *or* • 400mg OD IV treatment

Other			
Infection	Standard Regimen	Alternative Regimen	Comments
Necrotising Fasciitis	Piperacillin/Tazobactam IV 4.5g TDS *and* Clindamycin IV 1.2g QDS	Meropenem IV 1g tds *and* Clindamycin IV 1.2g QDS	*Consider Immunoglobulin in Group A Streptococcal infection and complete immunoglobulin patient request and registration forms as specified on immunoglobulin page of INsite.*
	Surgical debridement is essential. *Samples must be marked as urgent and transported to laboratory rapidly.* • *Phone x16520 (8am – 8pm) or* • *On-call micro tech via switch (8pm – 8 am) so that sample can be processed urgently*		
MRSA blood stream infection	Vancomycin Load and dose according to vancomycin chart and renal function	Discuss with microbiologist	Aim for vancomycin target level of 15 to 20 mg/L for 14 days
Meningitis / Meningococcaemia	see *Bacterial meningitis and meningococcal septicaemia in adults guideline* on website regarding treatment options		Ensure public health notified. Refer to antimicrobial website for further advice, contact tracing and precautions
Viral Encephalitis	Aciclovir IV 10mg /kg every 8 hours Based on Ideal body weight	Discuss with microbiologist/virologist	Treatment course duration: 21 days. Discuss with virologist.

Table 1: ICU antimicrobial recommendations: Note above regimens do not need a microcode.

3. Education and Training

None additional

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Adherence to guideline in terms of choice and duration of antimicrobial therapy and obtaining samples before commencing antimicrobial therapy	Annual Trust Wide Antimicrobial Prescribing Audit	Antimicrobial Pharmacists	Annual	CMGS and TIPAC

5. Supporting References (maximum of 3)

Chatelon et al (2019). Choosing the right antifungal agent in ICU patients. Advances in Therapy. Volume: 36, Pages: 3308-3320

6. Key Words

List of words, phrases that may be used by staff searching for the Guidelines on PAGL. If none – state none. Antifungal, Critical Care, Candida, Aspergillus, Antibiotic, Antimicrobial, Antiviral.

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Antimicrobial Working Part review	**Policy and Guideline Committee Review**

Details of changes made during review March 2021:

- Amending guideline to Category C template, with rewording of introduction
- Reference to Antimicrobial Dosing Guidelines for Renal Impairment or CVVHDF In Adults C23/2019
- Reference to vancomycin and once daily gentamicin
    - Specific prescription charts,
    - Appropriate associated dosing and
    - Monitoring throughout document
- Separation of Hospital Acquired Pneumonia from Ventilator Associated Pneumonia, with modification of treatment choice
- Combined TB with Extra Pulmonary TB treatment choice. Additional Comments of route of treatment access and visual acuity documented
- Amendments to Biliary Sepsis treatments, first-line oral choices and second-line IV
- Reference to trust Clostridium difficile guidelines
- Reference to trust Bacterial meningitis and meningococcal septicaemia in adults guideline
- Fluconazole indications additional instructions
- Removal of line catheter related blood sepsis treatment option
- Addition of general information around antifungals on critical care, including Appendix 1 for renal or liver impairment doses

Details of changes made during review June 2021:

- Treatment guidelines for Candida and Aspergillus fungal infections
- Updated key word list
- Added information pertaining to lactation and teratology
- Columns in table of choice changed to standard regimen and alternative regimen
- Updated choice of therapy and recommendations in necrotising facititis

Appendix 1

Overview of pharmacokinetics of antifungals in patients with renal or liver failure.

Notes:

- If renal function declines with AmBisome or LFTs rise with azoles or echinocandins antifungal treatment may need adjusting as these may be a contributing cause. Please discuss with Microbiology, Antifungal stewardship team or Pharmacy team.
- For doses in CVVHDF see separate trust guidance.

Drug	Renal Impairment	Chronic Liver Impairment	Suggestions
AmBisome ♠ (Liposomal Amphotericin)	If possible use alternative due to nephrotoxicity. Unless benefit outweighs risk. No dosage adjustment	No dosage adjustment	Test dose of 1mg over 10 minutes required due to potential for anaphylactoid reactions. Monitor patient for 30 minutes and if no reaction proceed to give full dose – see Medusa for additional information.
Fluconazole	Dose reduction by 50% for GFR 11–50 ml/min	No dosage adjustment but may choose alternative agent if LFTs markedly raised. Discuss with microbiologist in this case.	• Obese critically ill: actual body weight • ICU patient: enhanced doses • Strong inhibitor of CYP3A4 and 2C9
Voriconazole ♠	No dose adjustment Consider Sulfobutylether-β-Cyclodextrin (SBECD) accumulation during intravenous infusion	Mild to moderate hepatic impairment: Normal loading doses then 50% dose reduction Severe impairment: Not been studied. Caution advised. Discuss with microbiology for alternatives	• Strong inhibitor of CYP2C0 and 2C19 • Moderate inhibitor of CYP3A4 • TDM recommended, see antimicrobial website for further information
Isavuconazole ♠	No dose adjustment	Enhanced serum levels, no dosage reduction required	• Moderate inhibitor of CYP3A4, P-glycoprotein, and BRCP • Blueteq approval needed for IFI
Posaconazole ♠	No dose adjustment for oral route	No dose adjustment. Potential for enhanced serum levels. TDM essential.	• Strong inhibitor of CYP3A4 causing drug–drug interactions. • TDM recommended, see antimicrobial website for further information
Caspofungin ♠	No dose adjustment	Enhanced exposure in moderate hepatic impairment: dosage reduction, discuss with pharmacy to ensure dose reduction does not cause underexposure in critically ill patients	
Anidulafungin ♦	No dose adjustment	Slightly lowered serum concentrations but no dosage adjustment recommended	Not stocked at UHL, patients from other NHS trusts will need discussion with Microbiology for alternatives
Micafungin ♠	No dose adjustment	Slightly lowered serum concentrations	Potential risk for liver tumours: use only if other antifungals are not appropriate

Reference/Adapted from: Chatelon et al (2019). Choosing the right antifungal agent in ICU patients. *Advances in Therapy*. Volume: 36, Pages: 3308-3320

Key: ♠= microcode required, ♦ = not stocked at UHL