Empiric Management of Common Infections in Solid Organ Transplant Patients

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Version date: August 1, 2017.
Approved by UHN Pharmacy & Therapeutics: September 11, 2017
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1. **Approach to Fever and Infections**

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1. Approach to Fever and Infections in a Solid Organ Transplant Patient

Eligible patients for this set of guidelines:
Solid organ transplant recipients and patients awaiting transplant.

Legend:  
✓ Required  
☐ As clinically indicated

### Key questions to ask regarding patient history

- Has the patient received organ transplant?
- Which type of transplant and how long ago?
- Was there any mismatch in transplant serology?
- Was there a history of rejection?
- Did patient receive T-cell depleting therapy for induction or treatment of rejection?
- Are there any recent changes to patient’s immunosuppressive therapy?
- Any recent sick contact, new sexual contact or exposure to animals?
- Any travel in the last 3 months?
- Did patient receive antibiotics in the last 3 months?
- Is the patient on antimicrobial prophylaxis?
- Is the patient on dialysis?

### Risk factors common to all SOT patients

- Technical or anatomical abnormalities
- Implanted devices, e.g. ventricular assistive device
- Environmental exposure: community and hospital-associated
- Instrumentation, e.g. drainage catheters, stents, or endotracheal tubes

### Initial investigations and tests for all patients with suspected infections

In addition to routine investigations on admission, e.g Complete Blood Count:

- Blood cultures - one from CVC lumen(s) if present and one from a peripheral site
- Blood CMV PCR (exception: D-neg/R-neg history)

Kidney transplant patients with stent in place
- Include urine culture in routine investigations

Syndrome / symptom-specific investigations:

- **Respiratory tract infection**
  - Chest X-ray
  - Consider chest CT if chest X-ray is abnormal
  - Nasopharyngeal swab for respiratory viruses
  - Legionella urinary antigen

- **Intraabdominal infection**
  - Abdominal ultrasound or CT
  - *C. difficile* toxin gene PCR as appropriate

- **Urinary tract infection (UTI): concurrently order**
  - Urine culture AND
  - Urinalysis

Reasonable to wait for results before starting treatment if patient:
- is hemodynamically stable
- has fever as the only symptom
- does not have identifiable source or focus of infection
If patient has SEPSIS, go to Figure 3

Bloodstream infection (BSI) identified

Bloodstream infection without sepsis

Patient has a suspected or known source of infection

Source of infection unknown

Syndrome/source specific treatment:
- Abdominal
- Central line
- Respiratory
- Urinary

Blood culture gram stain

Gram positive
- vancomycin 1g IV Q12H
- If patient has history of vancomycin-resistant enterococci infection or colonization: daptomycin 6 mg/kg IV Q24H (consider higher doses for persistent bacteremia)

Gram negative
- meropenem 1g IV Q8H
- If patient has history of carbapenem-resistant Enterobacteriaceae: Consult Transplant Infectious Diseases

Yeast
- Candidemia

Legend:
- Required
- As clinically indicated

Consult clinical pharmacist renal dose adjustment and drug interactions of antimicrobials but do not delay the first dose.
2b. Candidemia

Yeast was identified in blood culture

Is fluconazole contraindicated OR did patient receive fluconazole prophylaxis?

Yes to either

micafungin* 100 mg IV once daily

No to both

fluconazole 800 mg IV/PO§ x 1 dose, then 400 mg IV/PO§ once daily

*Or other echinocandin as per hospital formulary

§Do not use PO if patient is haemodynamically unstable or unable to tolerate oral intake

Perform the following tasks concurrently:

Is this a central venous catheter (CVC)-related bloodstream infection?
Remove CVC when safe to do so. See also Figure 2c

Consults:
- Transplant ID
- Ophthalmology

Repeat blood cultures daily after initiation of antifungal therapy until first negative result.

Consider diagnostic imaging to rule out any occult source (e.g. abscesses)

Tailor antifungal based on culture and susceptibility

Duration of therapy: Minimum 14 days after documented clearance of Candida spp. from bloodstream, in the absence of complications or dissemination attributable to candidemia.

Consult clinical pharmacist renal dose adjustment and drug interactions of antimicrobials but do not delay the first dose.
2c. Management for Central Line Infections

**1.** Obtain blood cultures **before** initiation of antimicrobials: Paired specimens from central venous catheters + peripheral vein

**2.** Culture exudates at exit sites, insertion sites, tunnel catheter tract, or pocket of implanted cardiovascular device if present

**3.** Empiric therapy for suspected central line infections: **vancomycin 1g IV Q12H**

**4.** Cultures are:

- Positive
- Negative at 72h

**Definitive diagnosis:**
- Discontinue vancomycin

**Legend:** [ ] Required [ ] As clinically indicated

**5.** Persistent bacteremia/fungemia or ongoing signs of infection:

- Reassess antimicrobials and organism susceptibilities to ensure there is no mismatch
- Rule out complications (e.g. with echocardiogram), and metastatic infections
- Remove central line if not already done
- Consult Transplant Infectious Diseases

**Duration of therapy:** Depends on the organism and whether the suspected source of infection, i.e. central line, is removed. Consult Transplant Infectious Diseases as needed.
3. Sepsis

1. Assess sepsis criteria

**Definition:**
Suspected infection AND organ dysfunction

- Consider sepsis if patient meets 2 or more of the following “quick SOFA” (qSOFA) criteria:
  - Respiratory rate ≥ 22 breaths/minute
  - Altered mental status
  - Systolic BP ≤ 100 mmHg

2. If patient meets criteria for sepsis

- **Consult** Intensive Care or Critical Care Response Team
- **Consult** Transplant Infectious Diseases

Initiate empiric therapy while awaiting consultation

3. Initiate empiric therapy

Patient has a **suspected or known source** of infection

Syndrome/source specific treatment:
- Abdominal
- Central line
- Respiratory
- Urinary

or

Source of infection unknown

**Legend:**
- ✓ Required
- ☐ As clinically indicated

- **meropenem** 1g IV Q8H
- **vancomycin** 1g IV Q12H

or

If patient has history of vancomycin-resistant enterococci infection or colonization:

- **meropenem** 1g IV Q8H
- **daptomycin** 6mg/kg IV Q24H (consider higher doses for persistent bacteremia)

Tailor antimicrobial therapy based on investigations, culture and susceptibility results

⚠️ Consult clinical pharmacist for renal dose adjustment and drug interactions of antimicrobials but do not delay the first dose
4. Pneumonia in Solid Organ Transplant

Pneumonia suspected

1. Complete investigations from Figure 1

2. Admit or treat as outpatient?

Consider admitting patient if...
At least one of the following applies:
- Patient is NOT a heart and/or lung transplant recipient
- Patient has had an increase in oxygen requirement
- Patient meets 2 or more of qSOFA criteria, indicating possible sepsis
  ▶ Respiratory rate ≥ 22 breaths/minute
  ▶ Altered mental status
  ▶ Systolic BP ≤100 mmHg

Treat as an outpatient ONLY IF...
All of the following apply:
- patient is NOT a heart and/or lung transplant recipient
- does not meet any of the clinical criteria

These guidelines do not replace clinician’s judgement to admit patient

3. Previous infection or colonization with multidrug resistant organisms

- If patient has had infection or colonization in the previous 90 days or is a lung transplant recipient
- If patient has NO history of infection or colonization in the previous 90 days

Initiate empirical antimicrobials which must be active against previously isolated organism(s) from respiratory specimens

Consider history of S. aureus (incl. MRSA), *Pseudomonas spp.*, *Stenotrophomonas spp.*, other multidrug resistant gram negative organisms, mycobacterial infections (tuberculosis and non-tuberculosis), *Aspergillus spp.* and other molds

If yes to any of the above

- ceftriaxone 1g IV Q24H
- azithromycin 500mg IV/PO Q24H

* Routine coverage for atypical bacteria has not proven to be of benefit. In Ontario, June to October is the highest risk when azithromycin should be considered.

If none of the above applies

- piperacillin-tazobactam 4.5g IV Q8H
- azithromycin 500mg IV/PO Q24H

Continue next page for tailored treatment for pneumonia
4. Pneumonia in Solid Organ Transplant Recipients

1. Chest Imaging

Hover mouse over image to enlarge

- Consolidation
- Lung cavity
- Halo sign
- Air crescent sign
- Tree in bud
- GGO
- Lung nodules
- Interstitial infiltrates

Consult Transplant Infectious Diseases for complicated pneumonia (e.g. empyema), fungal pneumonia and mycobacterial infections

Consult Respirology for bronchoscopy

2. Modifications

Modify empiric regimen based on specific culture and susceptibility results, and other investigations:

If positive for Influenza:
- **oseltamivir** 75 mg PO BID

or

If positive for *Legionella* spp.:
- **azithromycin** 500 mg IV/PO Q24H

or

If positive for Respiratory Syncytial Virus (RSV) or Cytomegalovirus (CMV):
- Consult Transplant Infectious Diseases

Tailor antimicrobial therapy when culture and susceptibility results become available

Consider IV to PO switch when appropriate to complete course of treatment

Duration of therapy:
- Bacterial: 7 days or as per Transplant Infectious Diseases
- Fungal: As per Transplant Infectious Diseases
- Influenza and RSV: 5 days and consult Transplant Infectious Diseases

Consult Transplant Infectious Diseases if patient may be allergic to the recommended antimicrobials

Consult clinical pharmacist for renal dose adjustment and drug interactions
If possible etiology is spontaneous bacterial peritonitis (SBP) following upper GI bleed:

1. **Empiric therapy:**
   - If patient does NOT have history of multidrug-resistant gram negative organisms:
     - **ceftriaxone** 1g IV Q24H and reassess on Day 3
   - or
     - **ertapenem** 1g IV Q24H and reassess on Day 3

2. **Assess if ongoing prophylaxis is necessary**
   - Widespread use of quinolones to prevent SBP in high-risk subgroups of patients, frequent hospitalizations and exposure to broad-spectrum antibiotics are associated with more gram-positives and extended spectrum beta-lactamase producing *Enterobacteriaceae* in SBP

If possible etiology is acute liver failure:

1. **Investigation:**
   - Blood culture
   - Urine culture
   - Ascitic fluid for culture, susceptibility, and cell count
   - Stool for *C. difficile* toxin gene PCR

2. **Empiric therapy:**
   - If patient fails to respond to piperacillin-tazobactam alone:
     - **piperacillin-tazobactam** 4.5g IV Q8H
     - **add *vancomycin*** 1g IV Q12H

     *If patient has history of vancomycin-resistant enterococci infection or colonization, instead of vancomycin:
     - **add daptomycin** 6 mg/kg IV Q24H

Consult Transplant Infectious Diseases

Tailor antimicrobial therapy based on microbiology results

Consult clinical pharmacist for renal dose adjustment and drug interactions of antimicrobials but do not delay the first dose.
5b. Intra-abdominal Infections

Patient received heart and/or lung transplant

Possible etiologies are:

- Pancreatitis
- Cholecystitis
- Perforation
- *C. difficile* infection

1. Investigations:
   - Abdominal CT
   - CBC
   - Stool for *C. difficile* PCR toxin gene

2. Empiric therapy:

*Patient has pancreatitis:*

- Do not initiate prophylactic antibiotics

   - *C. difficile*:
     - Vancomycin 125mg PO Q6H
     - If symptoms are severe add:
       - Metronidazole 500mg IV Q8H

   or

   - Ceftriaxone 1g IV Q24H
   - Metronidazole 500mg IV Q12H
   - Daptomycin 6 mg/kg IV Q24H

   If patient has history of vancomycin-resistant enterococci infection or colonization, consider adding:

Consult clinical pharmacist for renal dose adjustment and drug interactions of antimicrobials but do not delay the first dose.

Consult Transplant Infectious Diseases
Consult Surgery as indicated for source control
Tailor antimicrobial therapy based on microbiology results
Consult *C. difficile* First Episode Algorithm as applicable

Legend:  
- ✓ Required
-  As clinically indicated
5c. Intra-abdominal Infections

**Early (within 1 month) post-liver, kidney, pancreas transplant**

Possible etiologies are:
- Surgical site infection
- Abdominal wall abscess
- Retroperitoneal abscess
- Appendicitis
- Diverticulitis
- Peritonitis
- *C. difficile* infection

### 1. Investigations:

**Diagnostic imaging:**
- Abdominal ultrasound
- Abdominal CT if ultrasound is abnormal

**Laboratory:**
- CBC

**Microbiology:**
- Blood culture
- Collection (drainage) specimen for culture and sensitivity
- Stool for *C. difficile* PCR toxin gene

### 2. Empiric therapy:

#### History of infections due to *P. aeruginosa*:

- Meropenem 1g IV Q8H
- *Vancomycin* 1g IV Q12H

*If patient has history of vancomycin-resistant enterococci infection or colonization, instead of vancomycin IV:

- Daptomycin 6 mg/kg IV Q24H

#### No history of pseudomonal infections:

- Ertapenem 1g IV Q24H
- *Vancomycin* 1g IV Q12H

#### *C. difficile* infection:

- Vancomycin 125mg PO Q6H
- If symptoms are severe add metronidazole 500mg IV Q8H

**Consult** Transplant Infectious Diseases
**Consult** Surgery as indicated for source control
**Tailor** antimicrobial therapy based on microbiology results
**Consult** *C. difficile* First Episode Algorithm as applicable

⚠️ Consult clinical pharmacist for renal dose adjustment and drug interactions of antimicrobials but do not delay the first dose.
5d. Intra-abdominal Infections

Possible etiologies are:

- Common bile duct strictures or dilation
- Hepatic abscess
- Hepatic artery thrombosis
- Cholangitis
- Appendicitis
- Diverticulitis
- *C. difficile* infection

**Investigations:**

1. **Diagnostic imaging:**
   - Abdominal ultrasound
   - Abdominal CT if ultrasound is abnormal

2. **Laboratory:**
   - CBC
   - Blood culture
   - Stool for *C. difficile* PCR toxin gene

**Empiric therapy:**

History of infection due to **multidrug-resistant gram negative bacilli including *P. aeruginosa***:

- **meropenem**
  - 1g IV Q8H

History of infection due to **extended spectrum beta-lactamases gram negative bacilli but not *P. aeruginosa***:

- **ertapenem**
  - 1g IV Q24H

History of infection due to **no history** infection from multidrug-resistant gram negative bacilli:

- **piperacillin-tazobactam**
  - 4.5g IV Q8H

*If patient has history of vancomycin-resistant enterococci infection or colonization, consider adding:*

- **daptomycin**
  - 6 mg/kg IV Q24H

Consult clinical pharmacist renal dose adjustment and drug interactions of antimicrobials but do not delay the first dose.

Legend:

- [ ] Required
- [ ] As clinically indicated
6a. Urinary Tract Infection (UTI)

**Tailor antimicrobial based on culture and susceptibility results**

Consult clinical pharmacist for renal dose adjustment and drug interactions of antimicrobials but do not delay the first dose.
**6b. Candiduria**

**Definition:** Neutropenia = absolute neutrophil count less than or equal to 0.5x10^9 cells/L

1. **Yeast isolated in urine**
   - Remove stent and catheters if possible

3. **Does the patient have symptoms?**
   - Yes
     - Imaging (ultrasound) of kidneys to rule out abscess or fungal mass
     - If positive:
       - Consult Surgery
       - Consult Transplant Infectious Disease
   - No

   - Is patient undergoing a urologic procedure or is patient neutropenic?
     - Yes
       - Review susceptibility results
     - No
       - No treatment

**Consult** Clinical pharmacist for renal dose adjustment and drug interactions of antimicrobials but do not delay the first dose.
7a. Diabetic Foot Infections

1. Complete the following assessments and investigations:
   - **Laboratory investigations:**
     - CBC
     - C-reactive protein OR Erythrocyte sedimentation rate
   - **Microbiology:**
     - Tissue specimen from a cleansed infected wound for culture and sensitivity (do not send superficial swabs)
     - Purulent secretions or aspirate for culture and sensitivity
     - Screening for multidrug resistant organisms as per Infection Prevention and Control policies
   - **Diagnostic imaging studies:**
     - Lower extremity X-ray to rule in osteomyelitis
     - Lower extremity CT if X-ray inconclusive
     - MRI or bone / gallium scan if needed
   - **Vascular study:**
     - Assess vascularity of affected extremity
     - **Consult** Vascular Surgery

2. Assess severity of foot wound:
   - If patient has:
     - cellulitis/erythema limited to 2 cm from wound edge
     - localized tenderness and warmth
     - limited purulent discharge
     - superficial wound
     - Patient has mild infection
   - or
   - If patient has:
     - cellulitis/erythema beyond 2 cm from wound edge
     - localized tenderness and warmth
     - purulent discharge
     - infection involves deeper structure than skin
     - Patient has moderate infection
   - or
   - If patient has:
     - extensive or rapidly progressing cellulitis
     - infection involves deeper structure, plus necrosis, gangrene, ecchymoses, petechiae, or new anesthesia
     - sepsis or haemodynamic compromise
     - Patient has severe infection

3. Follow the appropriate path for empiric therapy management based on severity assessment

   Go to Figure 7b for recommended antimicrobials

Legend:
- **Required**
- **As clinically indicated**
7b. Diabetic Foot Infections

3 Initiate empiric therapy based on severity assessment

- **Patient has mild infection**
  - Cefazolin: 1-2g IV Q8H
  - **or**
  - Cephalexin: 500mg PO QID

- **Patient has moderate infection**
  - Ceftriaxone: 1g IV Q24H
  - **or**
  - Metronidazole: 500mg IV/PO Q12H

- **Patient has severe infection**
  - Piperacillin-tazobactam: 4.5g IV Q8H
  - **or**
  - Meropenem: 1g IV Q8H
  - **or**
  - Vancomycin: 1g IV Q12H

4 Modifications

- **Patient is colonized with MRSA**
  - Add vancomycin 1g IV Q12H

- **Patient is colonized with other multi-drug resistant (MDR) organism(s):**
  - Empiric therapy should be active against previously isolated MDR organism(s)
  - **Consult** Transplant ID

- **Osteomyelitis suspected:**
  - **Consult** Transplant ID
  - Duration of antimicrobial therapy minimum of 6 wks or as per Transplant ID

- **Poor vascularity:**
  - **Consult** Vascular Surgery if not already done
  - **Consult** Transplant ID
  - IV route for antimicrobials preferred

5 Other actions

- **Consult** wound care
- Tailor empiric therapy based on microbiology results
- Duration of therapy: 7-14 days (exception: min. 6 wks for osteomyelitis) or as per Transplant ID
- Switch from IV to PO route if appropriate to complete course of therapy

Legend:
- ☑️ Required
- ☐ As clinically indicated

⚠️ Consult clinical pharmacist for renal dose adjustment and drug interactions of antimicrobials but do not delay the first dose
1. How were these guidelines created?

Development of the guidelines were led by Dr. Shahid Husain (Transplant Infectious Diseases and SHS-UHN ASP) and Miranda So, PharmD (SHS-UHN ASP Pharmacotherapy Specialist). The recommendations are based on microbiology data from UHN's SOT patients, current literature and published guidelines. Earlier versions of this document were reviewed by clinicians from Multi-Organ Transplant (MOT), Transplant Infectious Diseases, Critical Care, General Infectious Diseases and SHS-UHN ASP. We incorporated their feedback where applicable. The final version is reviewed by MOT Pharmacy and Therapeutics (P&T) Subcommittee, and the institution's P&T.

2. Why are carbapenems and daptomycin recommended in the guidelines?

We reviewed historical SOT data from 2007-2012, and SOT antibiograms from 2013-2016 (courtesy of Dr. Sue Poutanen, Microbiologist and Infectious Diseases Specialist). We noticed an increase multidrug resistant gram-negative rods (e.g. E. coli, Enterobacter cloacae complex and Serratia marcescens), and vancomycin-resistant enterococci. Our recommendations aim to provide optimal spectrum of activities against most likely causative pathogens while investigations are being aggressively pursued. We emphasize tailoring therapy based on those results to minimize prolonged and unnecessary broad-spectrum antibiotics. We also encourage consultation with Transplant Infectious Diseases team where appropriate.

3. Why do you use qSOFA to assess if a patient may have sepsis?

The Sepsis-3 Consensus Guidelines recommend the use of Quick Sequential Organ Failure Assessment (qSOFA) as a bedside prompt to identify patients with suspected or documented infections and are at risk of poor outcomes outside the intensive care unit. It has been validated in a multi-centre study in 879 patients presenting to the emergency department. Compared with SIRS and severe sepsis criteria, qSOFA performed better at predicting in-hospital mortality. The hazard ratio of qSOFA score for death was 6.2 (95% CI, 3.8-10.3) vs 3.5 (95% CI, 2.2-5.5) for severe sepsis. We acknowledge that it has not been validated in the immunocompromised population.

4. What is the evidence behind your dosing suggestion for daptomycin?

The key indication in the guidelines for using daptomycin is for vancomycin-resistant enterococci (VRE). Recent data appeared to show that a higher dose may be needed, but the optimal remains unclear. Treatment effectiveness from cohort data may be dependent on the minimum inhibitory concentration of the isolate, and attainment of source control. Balancing the risk of adverse effects with higher doses and this off-label use (against VRE), we opted to recommend the standard dose while encouraging consultation with Transplant Infectious Diseases.

5. Why are the guidelines formatted this way?

From our previous work with UHN’s HealthCare Human Factors Engineering team, we learned that complex algorithms require designs that account for the interface with end-users to optimize usability. The design of the guidelines include use of hyperlinks and images, rather than simply text, boxes and arrows. Hyperlinks are embedded in all the orange buttons, which allow the end-user to self-direct to the most relevant sections at point of decision making. This format was used for several algorithms created by SHS-UHN ASP, including the High-Risk Febrile Neutropenia Protocol, Solid Tumor Febrile Neutropenia Protocol and C. difficile infection (First Episode) Algorithm. They are available at www.antimicrobialstewardship.com under “Best Practices”. We gratefully acknowledge the assistance of Ms. Rhea Pavan in formatting the guidelines.
8. Frequently Asked Questions and Bibliography


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