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Empiric Management of Common Infections in Solid Organ Transplant Patients

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SHS + UHN ASP ANTIMICROBIAL STEWARDSHIP PROGRAM

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab Michener Institute

Mount Sinai Hospital
Sinai Health System
Joseph & Wolf Lebovic Health Complex

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Index: Infectious Syndromes & Management

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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

1 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?

2 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

⚠ Reasonable to wait for results before starting treatment if patient:
- ☑ is hemodynamically stable AND
- ☑ has fever as the only symptom AND
- ☑ does not have identifiable source or focus of infection

3 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

2a. Bloodstream Infection

Legend: ☑ Required ☐ As clinically indicated

Bloodstream infection (BSI) identified

Investigate possible source of BSI

If patient has **SEPSIS**, go to **Figure 3**

Bloodstream infection without sepsis

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

or

Source of infection **unknown**

Syndrome/souarce specific treatment:

- **Abdominal**
- **Central line**
- **Respiratory**
- **Urinary**

Blood culture gram stain

Gram positive

vancomycin 1g IV Q12H

or

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

or

If patient has history of carbapenem-resistant *Enterobacteriaceae*:
Consult Transplant Infectious Diseases

Yeast

Candidemia

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

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2b. Candidemia

Legend: ☑ Required ☐ As clinically indicated

Yeast was identified in blood culture

Is fluconazole contraindicated OR did patient receive fluconazole prophylaxis?

Yes to either

micafungin*
100 mg IV once daily

*Or other echinocandin as per hospital formulary

No to both

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

§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

Legend: ☑ Required ☐ As clinically indicated

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

Definitive diagnosis:

- ☐ Bloodstream infection with no other source except central line
- ☐ Concordant organism from central **and** peripheral specimens
- ☐ **DTP*** (differential time to positivity): organism growth detected in central line specimen at least 2h before peripheral specimen

****DTP** contact microbiology lab for this information*

Negative at 72h

Discontinue **vancomycin**

5 Remove central line if no longer needed.
Infectious indications for removing central line:

- **Bloodstream infections** due to *Candida spp.*, *Mycobacteria spp.*, *Staphylococcus aureus, S. lugdenesis*, *Pseudomonas aeruginosa*, and other Gram-negative organisms
- Persistent **positive blood culture 72h after initiation of antimicrobials** irrespective of pathogens isolated (e.g. coagulase negative staphylococci, enterococci, viridans group Streptococcus, *Corynebacterium spp.*, *Bacillus spp.*) with no other source of infections identified
- Ongoing or worsening **signs of infection due to suspected central line infections** despite 48-72h of appropriate antimicrobials
- **Complications** (septic thrombophlebitis, endocarditis, possible metastatic seeding e.g. osteomyelitis)
- Extensive **cellulitis** around IV sites (greater than 2 cm), from catheter exit site, along the subcutaneous tract of tunneled catheter
- Relapse or recurrent central line infections **after antimicrobial course** is completed

Follow **Figure 2a** for recommendations on specific antimicrobial based on gram stain

Repeat blood cultures if patient has ongoing signs of infections despite therapy

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.

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3. Sepsis

Legend: ☑ Required ☐ As clinically indicated

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 mmgHg

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

or

Source of infection **unknown**

Syndrome/source specific treatment:

- **Abdominal**
- **Central line**
- **Respiratory**
- **Urinary**

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)

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

Tailor antimicrobial therapy based on investigations, culture and susceptibility results

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4. Pneumonia in Solid Organ Transplant

Legend: ☑ **Required** ☐ **As clinically indicated**

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 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 transpalnt recipient**

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

or

If patient has **NO history of infection or colonization** in the **previous 90 days**

Consider if patient has any of the following:

- ☐ Admission ≥ 48 hours prior to symptoms
- ☐ Medical care (hemodialysis , wound care, chemotherapy) within the previous 30 days
- ☐ Hospitalization in an acute care hospital ≥ 2 days within the prior 90 days

If yes to any of the above

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

If none of the above applies

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.

Continue next page for tailored treatment for pneumonia

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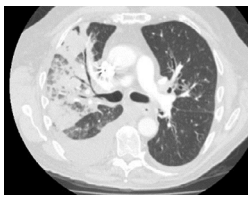
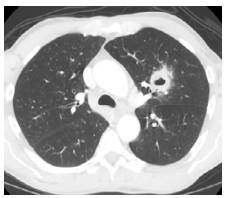
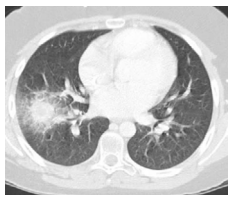
4. Pneumonia in Solid Organ Transplant Recipients

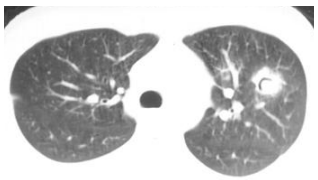
1 Chest Imaging

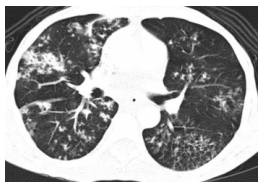
Hover mouse over image to enlarge

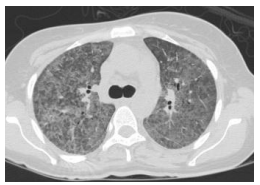

Consolidation

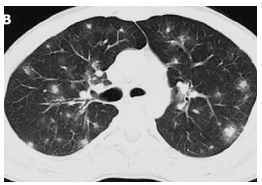

Lung cavity

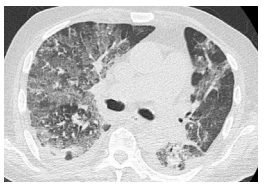

Halo sign


Air crescent sign


Tree in bud


GGO


Lung nodules


Interstitial infultrates

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

or

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

5a. Intra-abdominal Infections

Legend: ☑ **Required** ☐ **As clinically indicated**

Heart/lung transplant: **Go to Figure 5b.**

Early (within 1 month) post liver / kidney / pancreas transplant: **Go to Figure 5c.**

Late (>1 month) post liver / kidney / pancreas transplant: **Go to Figure 5d.**

Patient is pre-liver transplant

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

☑ 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

or

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:

piperacillin-tazobactam 4.5g IV Q8H +

If patient fails to respond to piperacillin-tazobactam alone:

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.

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5b. Intra-abdominal Infections

Legend: ☑ **Required** ☐ **As clinically indicated**

Pre-liver transplant: **Go to Figure 5a.**

Early (within 1 month) post liver / kidney / pancreas transplant: **Go to Figure 5c.**

Late (>1 month) post liver / kidney / pancreas transplant: **Go to Figure 5d.**

Patient received heart and/or lung transplant

Possible etiologies are:

- Pancreatitis
- Perforation
- Cholecystitis
- *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

or

C.difficile:

vancomycin 125mg PO Q6H + if symptoms are severe **add** **metronidazole** 500mg IV Q8H

or

Empiric therapy for **other etiologies:**

ceftriaxone 1g IV Q24H + **metronidazole** 500mg IV Q12H

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

- ☑ **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

→ *C.difficile* First Episode Algorithm

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

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5c. Intra-abdominal Infections

Legend: ☑ Required ☐ As clinically indicated

Pre-liver transplant: **Go to Figure 5a.**

Heart/lung transplant: **Go to Figure 5b.**

Late (>1 month) post liver / kidney / pancreas transplant: **Go to Figure 5d.**

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

or

No history of pseudomonal infections:

ertapenem 1g IV Q24H + ***vancomycin** 1g IV Q12H

or

***C.difficile* infection:**

vancomycin 125mg PO Q6H + if symptoms are severe **add metronidazole** 500mg IV Q8H

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

daptomycin 6 mg/kg IV Q24H

- ☑ **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

→ *C.difficile* First Episode Algorithm

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

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5d. Intra-abdominal Infections

Legend: ☑ Required ☐ As clinically indicated

Pre-liver transplant: **Go to Figure 5a.**

Heart/lung transplant: **Go to Figure 5b.**

Early (within 1 month) post liver / kidney / pancreas transplant: **Go to Figure 5c.**

Late (>1month) Liver, kidney and/or pancreas transplant

Possible etiologies are:

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

1 Investigations:

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

Laboratory:
- ☑ CBC

Microbiology:
- ☑ Blood culture
- ☑ Stool for *C. difficile* PCR toxin gene

2 Empiric therapy:

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

meropenem 1g IV Q8H

or

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

ertapenem 1g IV Q24H

or

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

→ *C.difficile* First Episode Algorithm

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

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6a. Urinary Tract Infection (UTI)

Click on orange button to see details

Definitions of Urinary Tract Infection

Urinary tract infection suspected

Patient has symptoms

Patient had kidney transplant within past 2 months, OR a stent is in place

ertapenem
1g IV Q24H

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

daptomycin
6 mg/kg IV Q24H

or

Patient did **not** have kidney transplant within past 2 months, AND does **not** have a stent in place

ceftriaxone
1g IV Q24H

Treat for 7 - 14 d or consult Transplant Infectious Diseases

or

Patient does NOT have symptoms

Patient had kidney transplant within the past 2 months, OR has stent in place

Select antibiotic based on urine culture and susceptibility results, for 5 - 7d of treatment.

or

Patient did **not** have kidney transplant within past 2 months, AND does **not** have a stent in place

Asymptomatic bacteriuria: No treatment

For Candiduria, go to Figure 6b

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 0.5×10^9 cells/L

Legend: ☑ Required ☐ As clinically indicated

1 Yeast isolated in urine

2 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
    - **Susceptible** to fluconazole → **fluconazole** 400 mg IV/PO, for 7 - 14 days
    - **Not susceptible** to fluconazole → **Consult** Transplant Infectious Diseases
  - **No** → **No treatment**

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

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7a. Diabetic Foot Infections

Legend: ☑ Required ☐ As clinically indicated

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

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7b. Diabetic Foot Infections

Legend: ☑ Required ☐ As clinically indicated

3 Initiate empiric therapy based on severity assessment

Patient has mild infection

- **cefazolin** 1-2g IV Q8H
- or
- **cephalexin** 500mg PO QID

or

Patient has moderate infection

- **ceftriaxone** 1g IV Q24H
- \+
- **metronidazole** 500mg IV/PO Q12H

or

Patient has severe infection

- **piperacillin-tazobactam** 4.5g IV Q8H
- or
- **meropenem** 1g IV Q8H
- \+
- **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

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

8. Frequently Asked Questions and Bibliography

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,

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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.

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