Antimicrobial Stewardship

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Challenges to the implementation of antimicrobial stewardship in immunocompromised hosts

1. Physician perceptions and attitudes—"my patient is sicker than yours"
2. Wide range of possible infectious etiologies with diagnostic uncertainty
3. Impaired inflammatory responses
4. Difficulty in making an early diagnosis
5. Urgency for empiric effective antimicrobial therapy
6. Significant drug toxicities and potent drug interactions
7. Prolonged exposure to prophylactic antibiotics may lead to antimicrobial resistance
8. Increasing antimicrobial resistance with limited therapeutic options to appropriately treat empirically or documented infections
9. Difficulty with distinguishing rejection and graft versus host disease from infections
10. Difficulty in controlling the source of infection due to issues, such as thrombocytopenia, limiting surgical interventions
11. Prolonged duration of immunosuppressed state increases the risk for uncommon presentations of common and uncommon infections
12. Duration of antimicrobial therapy not clearly defined in many infections for these patients

Increased risk of infection by antibiotic-resistant organisms with the use of fluoroquinolones

Organisms	References
Gram-positives	
MRSA	Graffunder & Venezia,[31] 2002 Campillo et al,[32] 2001 Weber et al,[33] 2003
VRE	Liu et al,[34] 2012 Bodro et al,[35] 2013
Streptococcus viridans	Prabhu et al,[36] 2005
Gram-negatives	
Fluoroquinolone-resistant *Pseudomonas aeruginosa* and *Enterobacteriaceae*	Yoo et al,[37] 1997 Rangaraj et al,[38] 2010
ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*	Lautenbach et al,[39] 2001 Paterson et al,[40] 2000 Garnica et al,[41] 2013
Other non-fermenting gram-negative organisms (*Acinetobacter spp, Stenotrophomonas*)	Irfan et al,[42] 2008
Anaerobes	
C difficile	Golledge et al,[43] 1992 Weiss,[44] 2009 Pepin et al,[29] 2005

Opportunities for antimicrobial stewardship in immunocompromised hosts

- Produce and distribute to health care providers updated antimicrobial susceptibility trends for common organisms
- Formulary review
- Preprescription authorization
- Postprescription review and feedback
  - Monitoring drug interactions
  - Renal dosing optimization
  - Streamlining and discontinuation of unnecessary antimicrobials
- Antifungal stewardship
- Antiviral stewardship
- Develop multidisciplinary protocols, algorithms, and guidelines for the diagnosis, management, and prophylaxis of common infections
- Discuss microbiology, antibiotic use, and infection-related outcome data in multidisciplinary committees

Day 1

Initial Evaluation: Determining Risk for MDR-GN Pathogens, Infection Source and Severity of Illness

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Obtain:
- Patient history (prior infection, microbiology/colonization, recent antimicrobial use, recent hospitalization, co-morbidities, travel history)
- Physical examination
- Imaging, based on suspected source
- Cultures and RTD, if available

Determining Empiric Treatment [14,16]

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Assess <u>severity</u> of infection:
- Critically ill patients with sepsis/septic shock: More emphasis on broader-spectrum therapy
- Stable patients: Depending on other factors, narrower-spectrum therapy might be appropriate

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Assess <u>risk factors</u> for MDR-GN:
- Previous colonization/infection in the last 6 months with MDR-GN organism
- Broad-spectrum antimicrobial therapy during previous 30 days
- Age >70 years
- Bedridden
- History of prolonged or recent hospitalization and/or long-term care facilities
- Indwelling devices
- Immunosuppression
- Recent travel to an areas with high endemic rates of MDR-GN

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Assess <u>local resistance rates:</u>
- Review antibiogram data, including unit-specific data if available

Day 2-3 (variable)

Determining Definitive Treatment and Duration of Therapy

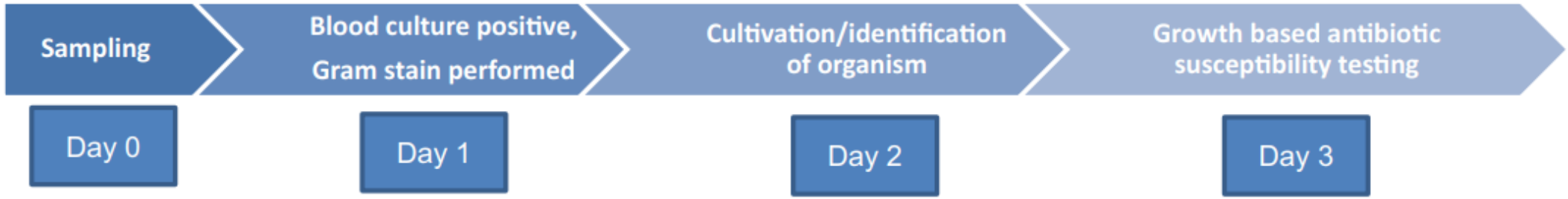
- Evaluate changes in clinical status
- Review microbiology tests, +/- biomarkers
- Determine if antibiotics can be stopped
- If antibiotic continuation indicated, consider pathogen, source of infection, comorbidities and drug interactions when selecting agent
- When possible, choose a single active agent with the narrowest spectrum that covers the causative pathogen, has the lowest probability of development of resistance, and a favorable side effect profile
- Plan for shortest indicated duration of therapy
- Monitor for clinical improvement, antibiotic-related side effects, laboratory parameters and ensure antibiotic dose optimization

Upon discharge

Hospital Discharge and Transition-of-Care

- Utilize multidisciplinary team to facilitate transition, when available
- Ensure the antibiotic can be reliably and safely administered outside of the hospital
- Schedule appropriate laboratory and radiographic monitoring in the outpatient setting
- Establish follow-up (e.g. with Infectious Diseases physician)
- Educate patient and caregiver regarding treatment plan

Timeline for Traditional Identification and Antibiotic Susceptibility Testing



Characteristics of Rapid Diagnostic Tests for Pathogens in Blood and Respiratory Specimens

Rapid diagnostic tests [52-54]	Resistance genes/organisms	Sample type	Day on which results available and time required to run assay
Genotypic susceptibility			
Multiplex PCR			
FilmArray® Blood Cultures Identification 2 (BCID2, Biofire®)	Identification of multiple bacteria, 7 yeasts and resistance genes: CTX-M, IMP, KPC, NDM, OXA-48 like, VIM, mcr-1, mecA/C, mecA/C and MREJ, vanA/B	Positive blood culture	Day 1, 1 hour
DNA Microarray			
Verigene® Gram-Negative (Luminex®)	Identification of 9 bacteria and resistance genes: CTX-M, KPC, IMP, NDM, OXA, VIM	Positive blood culture	Day 1, 2.5 hours

Magnetic resonance method after DNA hybridization			
T2Bacteria® (T2 Biosystems®)	Identification of 5 bacteria	Whole blood	Day 0, 3-5 hours
Multiplex PCR and DNA microassays			
GenMark ePlex® (GenMark Diagnostics, Inc.)	Identification of 21 bacteria, and resistance genes: CTX-M, IMP, KPC, NDM, OXA, VIM	Positive blood culture	Day 1, 1.5 hour
Fluorescence in-situ hybridization			
Gram-Negative QuickFISH (OpGen®)	Identification of *E. coli, P. aeruginosa*, and *K. pneumoniae*	Positive blood culture	Day 1, 0.3 hour

Rapid phenotypic susceptibility testing			
Time-lapse imaging of bacterial cells on dark-field microscopy. Antimicrobial susceptibility based on morphokinetic cellular analysis.			
Accelerate Pheno™ (Accelerate Diagnostics)	Identification of 16 bacteria and 2 yeasts with susceptibility results	Positive blood culture	Day 1, 1.5 hours (organism identification); 7 hours (susceptibility results)
Rapid identification			
Matrix-assisted laser desorption/ionization time-of-flight			
MALDI/TOF (Biomerieux, Bruker)	Identification of vast array of bacterial and fungal microbes	Positive blood culture	Day 1, 0.5 hour
Non-blood systems			
Multiplex PCR			
FilmArray® pneumonia panel (BioFire®)	Identification of 18 bacteria, 8 viruses, resistance genes: CTX-M, IMP, KPC, NDM, OXA-48 like, VIM, mecA/C, MREJ	Direct from respiratory culture	Day 0, 1 hour
Unyvero lower respiratory tract panel (OpGen®)	Identification of 19 bacteria, 1 fungi, resistance genes: CTX-M, KPC, NDM, OXA-23, OXA-24, OXA-48, OXA-58, TEM, VIM, mecA	Direct from respiratory culture	Day 0, 5 hours