

2014 Infectious Diseases Review

Jill K. Leslie, PharmD, BCPS, BCOP
Clinical Pharmacy Specialist: Bone marrow transplant and
Hematology Services
Franciscan St. Francis Health
Indiana Blood and Marrow Transplant
Indianapolis, IN 46237

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Disclosures

None

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Objectives

- Summarize key findings from data published or presented regarding infections in hematopoietic cell transplant (HCT) patients
- Identify new challenges/issues in the field of infectious diseases
- Relate new challenges/issues in infectious diseases that may impact the care of immunocompromised hosts
- Describe new antimicrobials recently approved or that are in development


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Presentation Organization

- Viruses
- Bacteria
- Fungus
- Infection Control




Viruses



Parainfluenza Virus (PIV) Lower Respiratory Tract Disease After Hematopoietic Cell Transplant: Viral Detection in the Lung Predicts Outcome

- Retrospective review of 199 patients with laboratory confirmed parainfluenza virus and classified as lower respiratory tract disease (LRTD)
- LRTD were then classified into 3 groups: possible, probable, and proven
 - Possible = PIV in upper respiratory tract with pulmonary infiltrates with/without LRTD
 - Probable = PIV detected in lung with LRTD without new pulmonary infiltrates
 - Proven = PIV detected in the lung with new pulmonary infiltrates with/without LRTD symptoms

Seo S. Clinical Infectious Diseases. 2014;58(10):1357-68.



Parainfluenza Virus Lower Respiratory Tract Disease After Hematopoietic Cell Transplant: Viral Detection in the Lung Predicts Outcome

- Patient data collected 1990-2011
- Based on the proposed classification
 - 78 (39%) Possible
 - 19 (10%) Probable
 - 102 (51%) Proven
- The median time to PIV infection and PIV LRTD after transplant was 71.5 and 78 days

Shi S. Clinical Infectious Diseases 2014;58(10):1357-68.

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Parainfluenza Virus Lower Respiratory Tract Disease After Hematopoietic Cell Transplant: Viral Detection in the Lung Predicts Outcome

- Probabilities of overall survival and mortality from respiratory failure @ 90 days
 - Upper respiratory tract infection (URTI): PIV detected in nasopharyngeal or sputum with symptoms but no infiltrates
 - Overall survival: 91% URTI, 62% LRTD ($p < .001$)
 - Mortality from respiratory failure: 2.5% URTI, 28% LRTD, ($p < .001$)
- Probabilities of 90 day survival in LRTD: 87% possible, 58% probable, and 45% proven ($p < .001$)

Shi S. Clinical Infectious Diseases 2014;58(10):1357-68.

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Parainfluenza Virus Lower Respiratory Tract Disease After Hematopoietic Cell Transplant: Viral Detection in the Lung Predicts Outcome

- Conclusions
 - Patients with PIV detection in the lungs (proven/probable LRTD) had worse outcomes compared with PIV detection in nasopharyngeal samples
 - New LRTD definition could be useful for future outcome studies and need for validation for other viruses and immunocompromised settings


Shi S. Clinical Infectious Diseases 2014;58(10):1357-68.

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DAS181 (Fludase/Paradase)

- Investigational sialidase fusion protein
- Removes sialic acid-containing receptors from host respiratory epithelial cells, preventing both influenza and parainfluenza viruses from binding to the cells
- In development by Ansun Biopharma
 - Fludase-in Phase III trials
 - Paradase- in Phase II trials


www.ansunbiopharma.com, Accessed November 14, 2014



DAS181 for the treatment of parainfluenza virus (PIV) infections in 16 hematopoietic stem cell transplant recipients

- Clinical manifestations and outcomes: May –Dec 2013
- Parainfluenza classification
 - Proven: PIV in BAL and pulmonary infiltrates
 - Possible: PIV in NP swab and pulmonary infiltrates
 - URTI: PIV + but no infiltrates or hypoxia
- DAS181 adult dosing and administration
 - 10 mg dry powder inhaler (DPI)
 - 3.2-4.5 mg nebulized
 - Daily 5-10 days


ICAAC 2014 abstract T-2034a Salvatore M, et al. Weill Cornell, NY, Ansun Biopharma, CA.



DAS181 for the treatment of parainfluenza virus (PIV) infections in 16 hematopoietic stem cell transplant recipients

- Severity of illness: 7 proven, 7 possible, and 2 URTI **data presented in oral abstract slightly differs from published abstract*
- Symptoms: 16 cough, 11/16 dyspnea, 8/16 fever, 12/16 hypoxia, 3/16 mechanical ventilation, 14/16 pneumonia
- Thirteen patients had clinical improvement by end of treatment
- Reported Adverse Events: Headache (2), Dry mouth (1)
- Microbiologic clearance documented in 5/14 (36%), 30-days from the start of treatment
- Thirty-day mortality = 19%
- DAS181 may be safe and effective, further study needed

ICAAC 2014 abstract T-2034a Salvatore M, et al. Weill Cornell, NY, Ansun Biopharma, CA.



Successful Treatment of Parainfluenza Virus Respiratory Tract Infection with DAS181 in 4 Immunocompromised Children

- Patients
 - Three post allo BMT
 - Three considered to have lower respiratory tract disease
 - One prior treatment with ribavirin
- Patients were treated with either dry powder inhaler (1) 10 mg or nebulized solution (3) 0.14 mg/kg/day x 2 then 0.2 mg/kg/day x3
- All patients tolerated therapy and obtained undetectable viral loads

Waghmare A, J of Ped Infect Dis, 2014;3:5.

Additional Information: ICAAC Abstracts


- T-458 Oxygen requirements As Predictor For Mortality in Hematopoietic Cell Transplant Recipients With Parainfluenza Virus Infection. Seo S. Fred Hutchinson Cancer Research Ctr. Seattle WA.
 - A review of oxygen requirements in 177 patients with PIV infection. Delayed onset of oxygen requirement after diagnosis of PIV LTRD was associated with increased mortality
- V-1821 DAS181 Anti-viral Activities Against The Human Polyomaviruses JC and BK. Tran CS, et al. Boston MA.
 - *Cells were treated with DAS181 to evaluate activity against the viruses*

Audience Participation Question #1

AS is a 54 yof 42 days post alloHCT that presents to the outpatient BMT clinic with new cough, oxygen saturation of 88% on room air and new radiographic pulmonary infiltrates. A respiratory viral panel reveals parainfluenza virus, type 3.3 from a bronchial wash. Which of the following statements is TRUE?

- AS's infection can be classified as and upper respiratory tract infection
- Based on a proposed new classification, AS would have proven LRTD and be at risk for a worse outcome
- AS would NOT be a candidate for investigational DAS181

Respiratory Syncytial Virus (RSV)




An Immunodeficiency Scoring Index (ISI) to Predict Outcomes in Stem Cell Transplant Patients with RSV

Criteria	Score
ANC < 500 / μ L	3
ALC < 200 / μ L	3
Age > 40 y	2
Myeloablative Conditioning	1
GVHD (acute or chronic)	1
Corticosteroids (within 30 days)	1
Recent (within 30 days) engraftment or pre-engraftment alloHCT	1

At the time of diagnosis
 Low risk: 0-2 Moderate risk: 3-6 High risk: 7-12


Shah DP, et al. Blood 2014;123(21):3263-3268.



An Immunodeficiency Scoring Index (ISI) to Predict Outcomes in Stem Cell Transplant Patients with RSV

- Developed from 237 allogeneic stem cell transplants from 1996 -2009 with upper respiratory tract RSV
- URTI definition: respiratory symptoms with no hypoxemia or infiltrates seen on chest radiograph or CT scan at the time of diagnosis
- A weighted scoring index for RSV infection accounting for the number and magnitude of immunodeficiency indicators

Shah DP, et al. Blood 2014;123(21):3263-3268.



An Immunodeficiency Scoring Index (ISI) to Predict Outcomes in Stem Cell Transplant Patients with RSV

Pertinent findings

- There was a significant trend of increasing incidence of lower respiratory tract infection (LRTI) and RSV-associated mortality was observed as the risk increased from low to moderate to high
- Patients in the high-risk group had the greatest benefit of ribavirin-based therapy
- Data shared during ICAAC abstract 2029 demonstrated significant cost savings that can be achieved by using this index to guide which patients should receive inhaled ribavirin

Shah DP, et al. Blood 2014;123(21):3263-3268

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An Immunodeficiency Scoring Index (ISI) to Predict Outcomes in Autologous Hematopoietic Cell Transplant (Auto-HCT) Recipients with Respiratory Syncytial Virus (RSV) Infections

- Applied to auto-tpx between 1995-2013 with RSV upper respiratory tract infection
- Risk for progression to LRTI was determined in those who presented with URTI (n = 104); mortality was assessed for the entire cohort (n = 131)
- Patients were stratified to Low (0-2), Moderate (3-6), High (7-12) Risk groups
- Auto tpx patients had a max score of 10, see previous slide for index scoring

ICAAC 2014 abstract T-2029 Shah D, et al. MD Anderson, Houston, TX.

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An Immunodeficiency Scoring Index (ISI) to Predict Outcomes in Autologous Hematopoietic Cell Transplant (Auto-HCT) Recipients with Respiratory Syncytial Virus (RSV) Infections

- Results: there was a significant increased incidence of LRTI observed as the risk increased from low to moderate (HR: 5.2 [1.3-20.6]) to high (HR: 19.9 [3.3-119.7]) (P<0.0001)
- Higher mortality was observed in high risk group compared to the low and moderate risk groups (HR: 9.56 [1.59-57.3], P = 0.01)
- Observation: Aerosolized ribavirin for URTI did not impact progression to LRTI; however high mortality was observed in the high risk group that did not receive it

ICAAC 2014 abstract T-2029 Shah D, et al. MD Anderson, Houston, TX.

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Oral GS-5806

- Oral novel small molecule in development by Gilead Sciences
- GS-5806 is believed to block RSV replication by inhibiting RSV F-mediated fusion of RSV RNA
- Currently in Phase II clinical trials
- Oral GS-5806 Activity in a Respiratory Syncytial Virus Challenge Study. DeVincenzo JP, et al. *NEJM*.2014;37:711-22.

www.gilead.com accessed November 14, 2014

CIPM/TTR
JIM/RSV

Additional RSV papers/posters

- Impact of aerosolized ribavirin on mortality in 280 allogeneic haematopoietic stem cell transplant recipients with respiratory syncytial virus infections. Shah DS, et al. *J Antimicrob Chemother*.2013;68:1872-1880.
- Respiratory Syncytial Virus in Hematopoietic Cell Transplant Recipients: Factors Determining Progression to Lower Respiratory Tract Disease. Kim YJ, et al. *JID*. 2014;209:1195-204.
- Abstract T-459 ICAAC 2014: Outcomes of Respiratory Syncytial Virus (RSV) and Ribavirin in Hematopoietic Cell Transplant Recipients: A Retrospective Chart Review. Thanasombat E, et al. City of Hope, CA.

CIPM/TTR
JIM/RSV

Cytomegalovirus (CMV)

CIPM/TTR
JIM/RSV

CMV viral load (VL) predicts CMV disease non-relapse mortality (NRM) after hematopoietic cell transplantation in the preemptive therapy era

- Background: Data examining the association between specific viral load thresholds and clinical outcomes are lacking
- Retrospective cohort, 1st alloHCT 2007-2012
- Weekly plasma PCR testing, weekly until Day +100. Antiviral pre-emptive therapy (PET) was started for viral load of ≥ 125 IU/ml
- Total of 926 patients with 96 cases of CMV disease. Five hundred five patients started PET
- Viral load thresholds
 - 150, 250, 500, 750, and 1000 IU/mL

ICAAC abstract T-2034b Green ML, et al. Fred Hutchinson Cancer, Seattle WA.

CMV viral load (VL) predicts CMV disease non-relapse mortality (NRM) after hematopoietic cell transplantation in the preemptive therapy era

- Plasma viremia at any level was associated with a 6-fold elevation in the risk of CMV disease
- CMV VL ≥ 1000 IU/mL was associated with NRM (adj HR 2.45, $p < 0.001$)
- Conclusions: A clear relationship exists between CMV VL and both CMV disease and NRM in the PET era. Overall, these data establish the suitability of CMV VL as a primary endpoint in phase III clinical trials in the field of CMV drug and vaccine development

ICAAC abstract T-2034b Green ML, et al. Fred Hutchinson Cancer, Seattle WA.

Letermovir (Merck)

- Designed to inhibit human CMV viral terminase.
- Letermovir for Cytomegalovirus Prophylaxis in Hematopoietic-Cell Transplantation
 - Multicenter, randomized, double-blind, placebo-controlled, phase 2 clinical trial comparing 3 different doses (60, 120 and 240 mg) in allogeneic hematopoietic-cell transplant
 - Once a day for 12 weeks in CMV + patients (N=131)
 - Endpoints: Incidence and time to onset of all-cause failure of prophylaxis
 - Letermovir 240 mg significantly reduced the time to the onset of prophylaxis failure (*detectable CMV antigen or PCR at 2 time points*)

Chemaly KJ, et al. NEJM 2014;370:1781-9.

Additional Letemovir Information

- Vergheze PS. Letemovir Treatment of Human Cytomegalovirus Infection Antiinfective Agent. *Drugs Future*. 2013;38(5):291-298.
- Current clinical trials
 - NCT02137772-MK-8228 (Letemovir) Versus Placebo in the Prevention of Clinically-Significant Cytomegalovirus Infection in Adult, CMV-Seropositive Allogeneic Hematopoietic Stem Cell Transplant Recipients. Goal enrollment is 540 patients

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LIVINGS

Brincidofovir (CMX001)-Chimerix Inc.

- Oral lipid formulation of cidofovir
- Absorbed in the small intestines, long intracellular half life and no nephrotoxicity
- NCT01769170: A Study of the Safety and Efficacy of CMX001 for the Prevention of CMV Infection in CMV-seropositive HCT Recipients: SUPPRESS
 - Phase III trial
 - Estimated 450 adult patients
 - Powered to detect a relative 50% decrease in clinically significant CMV infection
 - Expected results mid-2015

<http://www.chimerix.com> accessed November 14, 2014
 <http://clinicaltrials.gov> accessed November 14, 2014

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Brincidofovir Clinical Trials

Completed

- NCT00793598: CMX001 in Post-transplant Patients with BK Virus Viruria (estimated 60 patients)
- NCT01241344: The Adv Halt Trial
 - Phase II Safety and Efficacy of Preemptive Treatment for the Prevention of Adenovirus. Enrollment 52 adults and children

Recruiting

- NCT02087306: Phase III, Open-labeled, Multicenter Study of the Safety and Efficacy of Brincidofovir Treatment of Early Versus Late Adenovirus Infection (estimated 20 patients adults and pediatrics)

<http://clinicaltrials.gov> accessed November 14, 2014

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LIVINGS

Additional CMV Articles

- Frequent Occurrence of Cytomegalovirus Retinitis (CMVR) During Immune Reconstitution Warrants Regular Ophthalmic Screening in High-Risk Pediatric Allogeneic Hematopoietic Stem Cell Transplant Recipients. *Hiwarkar P. CID.2014;58(12):1700-6.*
 - *CMVR developed in 13 of 56 (23%) of those with significant CMV viremia*
- Donor Cytomegalovirus Status Influences the Outcome of Allogeneic Stem Cell Transplant: A study by the European Group for Blood and Marrow Transplantation (EBMT). *Ljungman P. et al. CID.2014;59(4):473-81.*
 - *Reviewed allo BMT patients from 1992-2008. Confirmed the negative impact on overall survival if a CMV+ donor/CMV-recipient. For CMV+/recipient, data support selecting CMV+/donor in myeloablative conditioning regimens*

Additional CMV Abstracts

- T-1789 Evaluation of the Incidence of Cytomegalovirus (CMV) with Various Graft-Versus-Host-Disease (GVHD) Prophylactic Regimens. *Tollkuci EL. Rush Med Center, Chicago, IL.*
 - *Compared common GVHD prophylaxis regimens and incidence of CMV viremia/infection. Total of 72 patients included*
- T-461 Analysis of CMV Testing and Treatment Thresholds. *Acharya K. Medical College of Wisconsin*
 - *Retrospective evaluation of patients with CMV nucleic acid amplification test (NAAT) > 1000 copies*

Everolimus relationship with CMV

- Emerging solid organ transplant data regarding the use of m-tor inhibitor based prophylaxis regimens and the reduced incidence of cytomegalovirus infections
 - *Transpl ID.2013;15(2):150-62*
 - *Transplantation. 2012;94(12):1208-17.*
- Prospective evaluations planned
 - *NCT01927588 Evaluation of everolimus on CMV in renal transplant patients.*

Audience Participation Question #2

Which of the following compounds is NOT in development for viral infections?

- A. Letermovir
- B. GS-5806
- C. Brincidofovir
- D. Avibactam

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Additional viral abstracts and papers

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JMB/SS

The Long-Term Impact of Respiratory Viral Infections (RVIs) on Pulmonary Function in Allogeneic Hematopoietic Cell Transplant (Allo-HCT) Recipients

- Report of serial changes in pulmonary function (PF) from pre HCT to post-RVI from Aug 2004 –Jul 2013
- Included patients with RSV, Influenza and Parainfluenza
- A decline was defined as a change in FEV1 of 15% from prior pulmonary function test (PFT)
- Total of 310 single episodes and 100 with multiple episodes

ICAAC 2014 abstract T-2030 Azzi JM, et al. MD Anderson, Houston, TX

CIPIATTS
JMB/SS

The Long-Term Impact of Respiratory Viral Infections (RVIs) on Pulmonary Function (PF) in Allogeneic Hematopoietic Cell Transplant (Allo-HCT) Recipients

- Results

Episodes	FEV1 Decline (15% or more)
Single RVI	46/310 (15%)
Multiple RVI	25/100 (25%) p = 0.02

 - Incidence of bronchiolitis obliterans syndrome was not different between the two groups
 - No difference based on the three viruses, however the median decrease in FEV1 was greater in patients with multiple episodes of RVI or after a single RSV episode
- Conclusion: RVI after allo HCT has a negative impact on PF. Serial monitoring with PFTs may help identify patients that may benefit from early interventions

ICAAC 2014 abstract T-2030 Azzi JM, et al. MD Anderson, Houston, TX


Additional Viral ICAAC Abstracts

- T-469 Acute Kidney Injury in Hematopoietic Stem Cell Transplant Recipients with BK associated Hemorrhagic Cystitis. Fashanu A. Cleveland Clinic, OH
- T-457 Indicators of Early Mortality Among Immunocompromised Hosts with Community-Acquired Respiratory Viral Infections. Apewokin SK. Univ of Arkansas, AK

Influenza Articles

- Memoli MJ, et al. The Natural History of Influenza Infection in the Severely Immunocompromised vs Nonimmunocompromised Hosts. *CID*.2014;58(2):214-24.
- Diaz-Granados CA, et al. Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults. *N Engl J Med*.2014;371:635-45.


Bacteria



New Antibacterials- Approved

- Long acting lipoglycopeptides (\$\$\$\$)
- Dalbavancin (Dalvance) Durata Therapeutics
 - May 2014
 - Weekly dosing: 1000 mg IV followed by 500 mg (renal dose adjustment for creatinine clearance less than 30 mL/min).
 - Side effects: nausea (5.5%), headache (4.7%), diarrhea (4.4%)
- Oritavancin (Orbactiv) The Medicines Company
 - August 2014
 - Single Dose: 1200 mg IV over 3 hours
 - Artificially elevates aPTT for up to 48 hours and may prolong PT and INR for up to 24 hours
 - Contraindicated: Therapeutic unfractionated heparin
 - Warnings with warfarin


www.dalvance.com - Accessed January 15, 2015.
www.themedicinecompany.com - accessed January 22, 2015



New Antibacterials- Approved

- Oxazolidinone
 - Tedizolid (Sivextro) Cubist
 - June 2014
 - Dosing: 200 mg either PO or IV daily
 - Warning regarding “patients with neutropenia”: safety and efficacy not established
- Cephalosporin + beta-lactamase inhibitor
 - Ceftolozane-tazobactam (Zerbaxa) Cubist
 - FDA approval Dec. 2014
 - Dosing: 1.5 grams IVPB q 8 hours
 - Multi-drug resistant gram negative rod coverage: including carbapenem resistant

www.sivextro.com - accessed January 21, 2015
www.zerbaxa.com - accessed January 22, 2015



New Antibacterials- Awaiting Approval

- Avibactam products
 - Ceftazidime-avibactam (Forest/Actavis and Astra Zeneca)
 - FDA decision anticipated 1st quarter 2015
 - Will aid in the treatment of Carbapenem-resistant *Enterobacteriaceae* (CRE), Extended-spectrum beta-lactamase (ESBL) producing Gram-negative bacteria as well as multi-drug resistant *Pseudomonas aeruginosa*
 - Ceftaroline-avibactam
 - Aztreonam-avibactam

www.fda.gov/downloads/AdvisoryCommittees/ Accessed January 22, 2015
www.clinicaltrials.gov/ Accessed January 22, 2015

CLIMATE
LABS

Impact of Levofloxacin Prophylaxis on Rates of Bloodstream Infection and Fever and Neutropenia in Patients with Multiple Myeloma Undergoing Autologous Hematopoietic Stem Cell Transplantation

- Levofloxacin was administered to myeloma patients undergoing auto transplant but not the lymphoma patients
- Rates of bloodstream infections(BSI) and fever/neutropenia (FN) within 30 days post transplant were compared in the pre (2003-2006) and post (2006-2010) intervention group

ICAAC 2014 abstract T-1295 Satlin MI, et al. Weill Cornell Med Coll. NY.

CLIMATE
LABS

Impact of Levofloxacin Prophylaxis on Rates of Bloodstream Infection and Fever and Neutropenia in Patients with Multiple Myeloma Undergoing Autologous Hematopoietic Cell Transplantation

Myeloma	PRE	POST	Lymphoma	PRE	POST
BSI	41%	15% (P < 0.001)	BSI	43%	47% (P < 0.001)
FN	92%	61% (P < 0.001)	FN	99%	97% (P < 0.001)

Conclusion: Levofloxacin prophylaxis during neutropenia is associated with a decreased risk of BSI and FN in patients with MM undergoing autoHCT

ICAAC 2014 abstract T-1295 Satlin MI, et al. Weill Cornell Med Coll. NY.

CLIMATE
LABS

Fluoroquinolone Resistant Gram-negative Bacteremia (GNB) in Allogeneic Hematopoietic Cell Transplant Patients during an Era of Levofloxacin Prophylaxis

- Nine year retrospective cohort study, adults, 2003-2012
- Annual trends in incidence rate (IR) of GNB and fluoroquinolone (FQ) resistant and those with FQ-sensitive GNB
- Total of 2306 patients were included of which 283 had GNB. Overall annual trends were not statistically significant
- Conclusion: Rates of FQ-resistant GNB have not significantly changed

ICAAC 2014 abstract T-1288 Miles-Jay A. Seattle Cancer Center, WA.

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Impact of vancomycin-resistant enterococcus (VRE) screening on clinical outcomes in patients with hematological malignancies and hematopoietic cell transplantation with VRE bacteremia

- Reviewed VRE bacteremia in hematology and HCT from 2006-2011. Total of 96 patients
- Thirty-eight patients were known colonized with VRE, 28 were not colonized and 30 unknown colonization
- Results:
 - Time to start appropriate VRE therapy was delayed in the unknown colonization
 - Higher rates of septic shock, intubation, ICU admission and 30-day mortality were seen in patients not screened
 - No difference in mortality was found even with earlier initiation of appropriate VRE antibiotics in the known colonizers

ICAAC 2014 abstract T-1792 Yang X, et al. City of Hope

CIBMT
JMBSS

Adverse Survival Consequences of Daptomycin Non-susceptible Enterococcal (DNE) Blood Stream Infection in Immunocompromised Hosts

- Evaluate the impact of DNE on early mortality in immunocompromised hosts
- Patient who died within 15 days of cultures were compared those who survived past 15 days
- Total of 384 patients were included
- On a multivariable logistic regression analysis predictors of 15-day mortality: WBC, DNE, and elevated LDH. All $p < 0.05$

ICAAC 2014 abstract T-1788 Apevokin SK. Univ of Arkansas

CIBMT
JMBSS

Can the respiratory viral panel (RVP) reduce antibiotic use in hospitalized pediatric patients with cancer?

- Evaluation of the impact of a positive RVP on antibiotic duration and hospital length of stay (LOS) in pediatric patients
- Retrospective review of all patients admitted to the pediatric oncology unit from 10/2011 through 6/2013 with an RVP ordered within 24hrs of admission
- Total of 321 patients (50% solid tumor, 28% heme, 22% alloHCT)
 - Fifty percent had positive RVP (N=161)

ICAAC 2014 Abstract 2770 Palomino P, et al. Memorial Sloan Kettering, NY.

Can the respiratory viral panel (RVP) reduce antibiotic use in hospitalized pediatric patients with cancer?

- Negative binominal regression in univariate and multivariate models showed no association of a positive RVP on the duration of antibiotics (5 vs. 5 days) or LOS (5 vs. 6 days)
- Presence of febrile/neutropenia and/or other infection was associated with longer antibiotic duration (10 vs. 1 days, $p < 0.0001$) and hospital LOS (6 vs. 4 days, $p < 0.0001$)

ICAAC 2014 Abstract 2770 Palomino P, et al. Memorial Sloan Kettering, NY.

VRE papers


- Kaki R, et al. Vancomycin-Resistant Enterococcus (VRE) Transmission and Risk Factors in Contacts of VRE Carriers. *Infect Control Hosp Epidemiol.* 2014;35(7):876-879
- Knelson LP, et al. A Comparison of Environmental Contamination by Patients Infected or Colonized with Methicillin-Resistant Staphylococcus aureus or Vancomycin-Resistant Enterococci: A Multicenter Study. *Infect Control Hosp Epidemiol.* 2014;35(7):872-875
- Munita JM, et al. Failure of High-Dose Daptomycin of Bacteremia Caused by Daptomycin-Susceptible *Enterococcus faecium* Harboring LiaSR Substitutions. *CID.* 2014

Antimicrobial Resistance

- The Global Challenge of Carbapenem-Resistant Enterobacteriaceae in Transplant Recipients and Patients with Hematologic Malignancies. *CID.* 2014;58(9):1274-83

ICAAC 2014 Abstract 2770 Palomino P, et al. Memorial Sloan Kettering, NY.


Clostridium difficile



Risk Factors for Recurrent *Clostridium difficile* infection(CDI) in hematopoietic stem cell transplant recipients


- Two year retrospective case-control of recurrent and non-recurrent CDI at University of Michigan
- Overall, 13.4% incidence of CDI and a 23.3% recurrence rate
- Total of 22 recurrent CDI and 73 nonrecurrent CDI
- Neutropenia at the time of index case was found to be the only independent predictor of recurrent disease
- Traditional risk factors of recurrent infection did not predict relapse

Huang AM, et al. Transpl Infect Dis.2014;16:744-750




Additional Papers

- Kinnebrew MA, et al. Early *Clostridium difficile* Infection during Allogeneic Hematopoietic Stem Cell Transplant. *Plos ONE* 9(3): e90158.
- Dominguez SR, et al. High Colonization Rate and Prolonged Shedding of *Clostridium difficile* in Pediatric Oncology Patients. *CID*.2014;59(3):401-3.
- Jury LA, et al. Outpatient Healthcare Settings and Transmission of *Clostridium difficile*. *PLoS ONE* 8(7): e70175.




Intestinal microbiome



The effects of intestinal tract bacterial diversity on mortality following allogeneic hematopoietic stem cell transplantation

- Allogeneic patients were enrolled in fecal collection protocol
- Specimen collection time point: engraftment (within 7 days)
- Total of 80 patients included in the analysis from Sept. 2009-Aug. 2011
- Specimens were analyzed for microbial diversity and classified into three groups
 - High, intermediate, and low


Tauri Y, et al. Blood 2014;124(7):1174-1182.




The effects of intestinal tract bacterial diversity on mortality following allogeneic hematopoietic stem cell transplantation

- Results
 - High microbial diversity = 26 (32.5%),
 - Intermediate microbial diversity = 20 (25%)
 - Low microbial diversity = 34 (42.5%)
- Overall survival was significantly different between the 3 groups (P=0.019). Estimated overall survival at 3 years was 67% high, 60% intermediate, and 36% for low
- Bottom Line: Intestinal diversity is predictive of mortality in allogeneic stem cell transplant

Tauri Y, et al. Blood 2014;124(7):1174-1182.




Fungus



Antifungal Prophylaxis Associated with Decreased Induction Mortality Rates and Resource Utilized in Children with New-Onset Acute Myeloid Leukemia (AML)

- Retrospective cohort, newly diagnosed AML at pediatric institutions contributing to the Pediatric Health Information System
- Primary endpoint: inpatient death during induction
- Secondary endpoints: rate of antibacterial exposures, blood cultures, and chest CT scans
- All patients underwent induction therapy with ADE (cytarabine, daunorubicin, and etoposide)


Fisher BT, et al. Clinical Infectious Diseases. 2014;58(4):502-8.



Antifungal Prophylaxis Associated with Decreased Induction Mortality Rates and Resource Utilized in Children with New-Onset Acute Myeloid Leukemia (AML)

- Eight hundred seventy-one patients included in the final analysis of which 57% received antifungal prophylaxis (80% flu; 20% other)
- Results
 - Patients receiving any type of antifungal prophylaxis were at a significantly decreased risk of induction mortality (adjusted HR, 0.42; 95% CI, 0.19-0.90)
 - All secondary endpoints were met (less antibiotic days, fewer blood cultures and CT scans)

Fisher BT, et al. Clinical Infectious Diseases. 2014;58(4):502-8.



Posaconazole (PSC) Concentration in children receiving antifungal prophylaxis after allogeneic haematopoietic stem cell transplant (HCT)

- Patients received 4 mg/kg TID PSC suspension after HCT. Twelve patients were given cookies to improve resorption
- Total of 28 patients (age 2-16 years)
- Total of 196 serum concentrations
 - 59 samples below 500 ng/ml
 - 20 samples between 700-1000 ng/ml
 - 91 samples above 1000 ng/ml
- Conclusion: The majority of samples and the average concentration per patient did show a sufficient PSC concentration above 700 ng/ml in children after 12 mg/kg/day and cookies helped

ICAAC abstract A-722 Heinz WJ, Tuebingen, Germany

Posaconazole Tablet Formulation Therapeutic Drug Monitoring (TDM) and Toxicity Analysis

- Review of 45 patients
- Therapeutic serum concentrations (SC) were defined as: greater than 500 ng/ml for prophylaxis and greater than 700 ng/ml for treatment
- Results
 - Median SC = 1400 ng/ml (range 243-7060 ng/ml)
 - Eighty-two percent had a therapeutic concentration
 - Seven (20.5%) patients experienced QTc prolongation at least 10% increase from baseline
 - Ten (22.7%) patients experienced increase in liver function tests

ICAAC A-702 Pettit NN, Univ of Chicago Med, Chicago, IL

Clinical Experience Using Posaconazole (POS) Extended Release Tablet For The Prevention of Invasive Fungal Infections in Hematological Cancer Patients: Does One Size Fit All?

- Goal to determine the range of serum trough concentrations in hematological and stem cell transplant patients receiving posaconazole prophylaxis
- Goal serum concentration $\geq 0.7 \mu\text{g/mL}$
- Results (28 patient included)
 - Mean concentration = $1.19 \mu\text{g/mL}$
 - Seventy-one percent of patients achieved goal
 - Patients with diarrhea, BMI ≥ 30 or weighing ≥ 90 kg were more likely to have subtherapeutic concentrations

ICAAC M-1759 Miceli MH, Univ Michigan, Ann Arbor, MI

Audience Response Question # 3

You have been asked to develop recommendations for therapeutic drug monitoring in patients receiving posaconazole. Based on data presented, which of the following patient groups would you recommend therapeutic drug monitoring?

- A. Pediatric patients on posaconazole suspension that are unable to maintain oral intake
- B. Adult alloHCT with grade III or IV gastrointestinal GVHD
- C. Adult alloHCT with a BMI \geq 30
- D. All of the above

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Micafungin in Invasive Fungal Infections in Children With Cancer: National Study

- Objective: To evaluate the safety and efficacy of micafungin in pediatric patient from 2012 -2013
- Results
 - Hematopoietic stem cell transplant (HCT) (23/30 tx success)
 - Invasive fungal infection (IFI) = 26
 - Fever of unknown origin(FUO) = 4
 - Pediatric Heme/Onc (PHO) (59/63 tx success)
 - IFI = 36
 - FUO = 27
- Conclusion: Therapy with micafungin was safe and successful in a high rate of child with IFI/FUO in 69% HCT and 93% of PHO patients

ICAAC abstract G-1897 Shycynski J, et al. Poland

CIBMTR
LMBSS

Pharmacokinetics and Pharmacovigilance of Voriconazole in Children with Cancer

- Objective: to quantify the number of children who achieve adequate plasma drug levels (DL) with the recommended dose of 14 mg/kg/d (bid) during the first week of treatment
- Patients had invasive fungal infections based on EORTC. Starting IV dose = 14 mg/kg/d (bid), Oral = 10-14 mg/kg/d (bid). DL measured between 4-7 days of treatment
- Fourteen children were included, total of 68 voriconazole samples. Goal 1-5 mg/L
- Results/Conclusion:
 - 5/14 (35%) had initial DL < 1 mg/L
 - All patients with doses of 600 mg/d reached levels of > 2 mg/L
 - Fifty percent of children required a dose adjustment
 - DL monitoring is necessary in children

ICAAC abstract G-1898 Rabello M, et al. Santiago, Chile

CIBMTR
LMBSS

Isavuconazole (Astellas;Basilea)

- July 2014, New Drug Application filed
- Broad-spectrum triazole, prodrug
- Intravenous (cyclodextrin-free) and oral formulations
- Dosing: initial loading dose (200 mg 3 x day) followed by once daily dosing (200 mg)
- Active against: *Cryptococcus* sp., Mucorales, dimorphic fungi (*Blastomyces*, *Histoplasma*, and *Coccidioides*)

www.astellas.com accessed November 14, 2014
Infect Drug Resist 2013;6:169-174.

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ICAAC and IDSA Posters

- A Phase 3, Double-Blind, Non-Inferiority Trial Evaluating Isavuconazole (ISA) vs Voriconazole (VRC) for the Primary Treatment of Invasive Mold Infection (SECURE). Original data ECCMID; Barcelona, Spain: May 10-13, 2014
 - ICAAC M-1761 Outcomes by Minimum Inhibitory Concentrations(MICs)
 - ICAAC M-1757 Outcomes in patients with heme malignancies
 - ICAAC M-1756 Outcomes by malignancy status
- IDSA-824 Open Label Phase 3 Study of Isavuconazole (VITAL): Focus on Mucormycosis
 - Small numbers, only 11 of 35 were assessable for efficacy. Thirty-one percent complete partial response


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Additional Fungal Posters

- A-706 Relationship Between Voriconazole Concentrations and the Probability of Breakthrough Fungal Infections. Liverpool, UK
- M-1772 Aspergillus Specific PCR of Specimens more Adequately Representing the Infectious Localization such as Bronchoalveolar Lavage, Cerebrospinal Fluid or Tissue/Effusion Samples are Superior to Testing Concurrent Blood Samples in Immunocompromised Patients with Suspected Invasive Aspergillosis. Germany
- M-1787a (1→3)-β-Glucan Detection in Urine and Serum in patients with Underlying Hematological Malignancies. Hoenigl M. Univ Austria
- POA-003 Variability of Voriconazole Trough Concentrations in Allogeneic Hematopoietic Stem Cell Transplantation Patients: Impact of Genetic Factors and Comedications on Initial and Longitudinal Follow-up. Thiebaut-Bertrand A. Grenoble, France

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Infection Prevention



How Often is Central Line-Associated Blood Stream Infection (CLABSI) Identified as Catheter-Related Blood Stream Infection (CRBSI) In Cancer Patients? Challenging the New Guidelines

- Comparison of the definitions CLABSI (by CDC) and CRBSI by the Infectious Disease Society of America (IDSA) in cancer patients
- Retrospective review of 426 CLABSI cases between Jan 2013-March 2014
- One hundred fifty-eight patients who had either two simultaneously positive blood cultures drawn from CVC and peripheral site or positive blood culture and positive catheter tip

ICAC 2014 Abstract K-1668 Hamal ZA, et al. MD Anderson, Houston, TX




How Often is Central Line-Associated Blood Stream Infection (CLABSI) Identified as Catheter-Related Blood Stream Infection (CRBSI) In Cancer Patients? Challenging the New Guidelines

- Results: 72 of the 158 patients had definite CRBSI.
- Performance of CLABSI +/- Mucosal Barrier Injury (MBI) definition in identifying CRBSI

	CLABSI-MBI (%)	CLABSI-nonMBI (%)
Sensitivity	18 %	82%
Specificity	38%	62%
Positive Predictive Value	20%	64%
Negative Predictive Value	36%	80%


ICAC 2014 Abstract K-1668 Hamal ZA, et al. MD Anderson, Houston, TX



How Often is Central Line-Associated Blood Stream Infection (CLABSI) Identified as Catheter-Related Blood Stream Infection (CRBSI) In Cancer Patients? Challenging the New Guidelines

- Results:
 - CRBSI was identified more commonly in non-MBI CLABSI cases compared to MBI CLABSI (64% vs 20%, P < 0.0001)
 - Similarly, CRBSI occurred more frequently among non-neutropenic CLABSI cases compared to neutropenic CLABSI cases (66% vs 28%, P < 0.0001)
- Conclusions:
 - CLABSI definition has a low sensitivity, specificity and predictive values for catheter related bacteremia in cancer patients with MBI and/or neutropenia.
 - IDSA definition for CRBSI may be more accurate in identifying the catheter as being the source of BSI in neutropenic patient or those with MBI


ICAAC 2014 Abstract K1668 Hamal ZA, et al. MD Anderson, Houston, TX



Audience Response Question #4

True or False: The CLABSI definition set forth by the CDC is all encompassing that does not need improvement


A. True
B. False

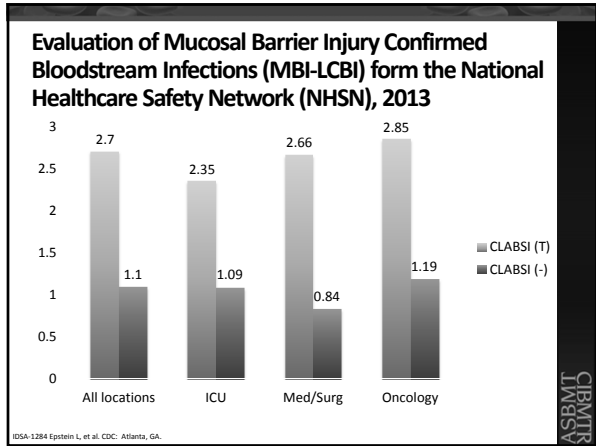


Evaluation of Mucosal Barrier Injury Confirmed Bloodstream Infections (MBI-LCBI) from the National Healthcare Safety Network (NHSN), 2013

- MBI-LCBI was introduced in 2013. Examine the impact of removing MBI-LCBI from CLABSI
- Data from Jan-June 2013 of facilities reporting at least 1 MBI-LCBI. CLABSI rates per 1000 central line days were determined with and without MBI-LCBI
- Total of 10452 CLABSIs reported with 703 (6.7%) meeting the MBI-LCBI criteria
- Most common organisms: *E. coli* (23%), *E. Faecium* (19%), and *K. pneum.* (8%)

ISA-1284 Epstein L, et al. CDC, Atlanta, GA





Questions
