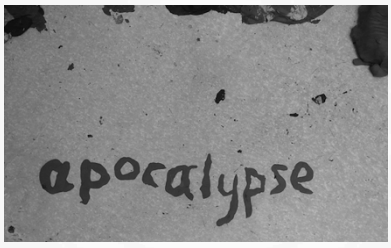
What's Hot in ID 2014

James S. Lewis II, Pharm.D., FIDSA
ID Clinical Pharmacy Coordinator
Oregon Health and Science University
Portland, OR

Objectives

- Describe highlights of the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and Infectious Diseases Society of America (IDSA) meetings.
- Recognize the strengths & limitations of emerging antibacterials
- List the conclusions of important infectious disease clinical trials presented over the past 12 months.
- Explain the impact of the new Clinical and Laboratory Standards Institute (CLSI) Candida breakpoints on echinocandin susceptibility.



http://www.wired.com/wiredscience/2013/07/carbapenem-resistance-worse/

Resistance Among Gram Negatives in U.S. Hospitals 2009-2012

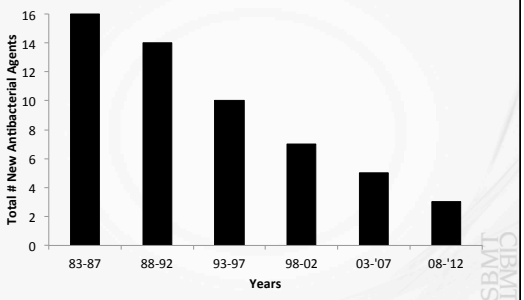
	% Resistance (n) in nonurinary isolates			
	ICU		Non-ICU	
Gram-negative	Ceftaz R	Imipenem R	Ceftaz R	Imipenem R
E. coli	11.0 (3084)	0.3 (3287)	6.9 (43445)	0.1 (47559)
K. pneumoniae	26.8 (1780)	11.5 (1907)	14.5 (16475)	5.8 (17228)
A. baumanii	60.1 (550)	52 (535)	35.4 (5532)	28.0 (4370)
P. aeruginosa	18.6 (2615)	23.2 (2689)	7.3 (35210)	8.4 (35810)

Shlaes DM, et al. *Antimicrob Agents Chemother* 2013;57:4605

Outbreak of NDM-1 in Denver, Colorado, 2012

- 8 pts with NDM-1 *Klebsiella* sp. in one hospital
- No obvious mode of spread; no direct link to India
- Prior to this, only 16 isolates in the U.S.
- In 2012, 4.6% of hospitals and 17.8% long term care facilities (LTCFs) reported having carbapenem resistant *Enterobacteriaceae* (CRE)
- MMWR Feb. 15, 2013 and March 8, 2013

The FDA Reboot of Antibiotic Development: Antimicrobial Agents Approved



Shlaes DM, et al. *Antimicrob Agents Chemother* 2013;57:4605

basilea
PHARMACEUTICA

PRESS RELEASE

Basilea's antibiotic ceftobiprole obtains regulatory approval in Europe for pneumonia

Basel, Switzerland, October 23, 2013 – Basilea Pharmaceutica Ltd. (SIX: BSLN) announced today the approval of its antibiotic ceftobiprole in Europe. Ceftobiprole is indicated for the treatment of hospital-acquired pneumonia (excluding ventilator-associated pneumonia) and community-acquired pneumonia in adults. Ceftobiprole has broad-spectrum activity against many pathogens that cause pneumonia including Gram-positive pathogens such as penicillin-resistant *Streptococcus pneumoniae* (PRSP), methicillin-resistant *Staphylococcus aureus* (MRSA) and various Gram-negative pathogens including *Pseudomonas* species.

Ceftolozane/Tazobactam

- Very active against *P. aeruginosa*
- Including ceftazidime and carbapenem resistant strains
- AmpC questions…
- More tazobactam than you are accustomed to
- Gram positive challenges
- And surprisingly…
- Completed phase 3 trials in
  - Urinary tract infections
  - Intra-abdominal infections

http://www.cubist.com/products/cxa_201: Accessed 12/18/13

ORIGINAL CONTRIBUTION

Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections

The ESTABLISH-1 Randomized Trial

- A cool study for a couple of reasons
- 1st – antibiotic stewardship
- 2nd – and from a more BMTish perspective…

Prokocimer P, et al. *JAMA* 2013;309:559-569

Audience Response Question 1

- Ceftolozane/tazobactam has excellent activity against which of the following organisms?
  - A: *Staphylococcus aureus*
  - B: Ceftazidime resistant *Pseudomonas aeruginosa*
  - C: *Bacteroides fragilis*
  - D: Carbapenem resistant *Enterobacteriaceae*

Famous ID Quote: "Resistant Bugs are Less Virulent"

- Carbapenem therapy in *P. aeruginosa* often leads to OprD deletion and carbapenem R
- Strains lacking OprD were
  - Better colonizers of mucosal surfaces
  - Disseminated to the spleen mice more effectively
  - More resistant to killing by human serum
  - Increased cytotoxicity against murine macrophages
  - Enhanced survival of *P. aeruginosa* in murine model

Skurnik D, et al. *Proc Nat Acad Sci* 2013;110(51):20747

ID Pharmacotherapy Paper of the Year

- First a refresher…
- Colistimethate sodium (CMS) = a long 4 letter word
- Nomenclature confusion
- Toxic
- Questionable efficacy
- Poor prodrug
- Good renal function = bad levels

Garonzik SM, et al. *Antimicrob Agents Chemother* 2011;55:3284

Meet Polymyxin B

- No scientific dosing guidelines in existence
- PK data from less than 20 patients
- One study with 9 adults but only 2 levels/pt
- Very very very limited data
- No urinary elimination data

Sandri AM, et al. *Clin Infect Dis* 2013;57:524

Switch and Switch Now?

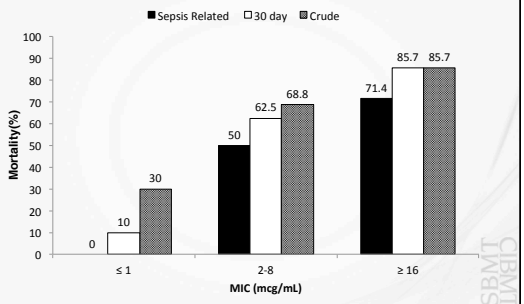
	Polymyxin B	Colistimethate Sodium
Prodrug	No	Yes – and a bad one
Protein binding	58%	??? - the concomitant presence of variable concentrations of CMS in plasma samples and other factors pose significant technical difficulties
Renally eliminated	No	Yes
Adjust dose for renal function	No	Yes
Therapeutic levels in patients with high CrCl	Yes	No
Dosing weight	Total body weight	the lower of either the actual or ideal
Loading dose required	Yes	Yes

Garonzik SM, et al. *Antimicrob Agents Chemother* 2011;55:3284
Sandri AM, et al. *Clin Infect Dis* 2013;57:524

Audience Response Question 2

- Which of the following is true about intravenous polymyxin B?
  - A: It is administered as a prodrug
  - B: It is eliminated renally and doses should be adjusted for renal function
  - C: It is readily dialyzed
  - D: It should be dosed on total body weight

A Bad Year for Cefepime (CPM): So it Kills People… Again…



Lee NY, et al. *Clin Infect Dis* 2013;56:488-95.

Cefepime MICs vs Outcome

- However… those are %S – of 33 people
- How many are in each arm?
- Issues with CPM patients in table 1:
  - Hospital stay before bacteremia 3X longer
  - Higher Pitt Bacteremia score (PBS)
  - PBS = 4 = 50% predicted mortality
  - In matched cohort use PBS ≥4. How much greater?
  - Matched cohort with PBS of ≥4 had a 5.9% mortality? REALLY?!?!?

Lee NY, et al. *Clin Infect Dis* 2013;56:488-95.

Cefepime: Package insert updated 4/2013

- Neurotoxicity
- Disturbance of consciousness, myoclonus, seizures, and nonconvulsive status epilepticus
- Most cases in renal impairment w/o dosage adjustment.
- Some cases in patients appropriately dosed
- Most cases reversible after d/c of cefepime and/ or hemodialysis.

http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a96295cf-e652-4f10-9e25-9f2a2cc036f6 – Accessed 12-18-13

Cefepime for AmpC producers

- The dogma of carbapenems
- Though shall not use a cephalosporin for a…
- But remember your pharmacology…
- In-vitro studies show very good AmpC stability
- Clinical outcomes somewhat lacking
- Somewhat odd definitions…
- But…

Tamma PD, et al. *Clin Infect Dis* 2013;57:781

30 Day All-Cause Mortality

Covariate	Odds Ratio (95% CI)	P Value
Cefepime	0.60 (.21-1.63)	.30
Cefepime Matched	0.63 (.23-2.11)	.36
ICU stay	2.60 (.88-7.68)	.08
McCabe score	2.63 (1.88-5.68)	.04
Immunocompromised	1.78 (.61-5.11)	.29
Mechanical ventilation	3.00 (1.01-8.95)	.04
Vasopressors	2.65 (.90-7.80)	.08

Tamma PD, et al. *Clin Infect Dis* 2013;57:781

Pip/Tazo and Extended Spectrum β-Lactamases (ESBLs): Test Tubes, Mice, and Now…

- Carbapenem vs Pip/Tazo in ESBL *E. coli* bacteremia
- Post hoc analysis of 6 prospective cohorts
- "…no trends favored the protective effect of carbapenems on mortality or length of stay."
- However…
- Mice and people >>> Test tubes?

Rodriguez-Bano J, et al. *Clin Infect Dis* 2012;54:167-74.

Carbapenemases Managed with Carbapenems – Clinical Data

- Case reports and retrospective data
- High mortality rates
- MICs and dosing often not reported
- Resistance, increasing age, comorbidities
- Better responses with lower MICs

Daikos GL & Markogiannakis A. *Clin Microbiol Infect* 2011;1135-41

So the Answer is… Combinations?

- *Klebsiella pneumoniae* carbapenemase (KPC) producing *K. pneumoniae* bacteremia
- Overall 30 day mortality = 41.6%
- Higher with monotherapy
- Septic shock, inadequate therapy, high APACHE III
- Combination therapy with tigecycline, colistin, and meropenem associated with lower mortality (OR: 0.11, CI = 0.02-0.69; P=.01)

Tumbarello M, et al. *Clin Infect Dis* 2012;55:943-50.

Case Closed?

- Meropenem + tigecycline + colistin in 16 patients
- 87.5% survival
- Meropenem 2gm Q8h 3h infusion in all patients "adjusted for renal function"
- "…monotherapy regimens utilizing drugs with substantial potency or PK shortcomings for blood stream infections (BSIs) may be associated with increased mortality"
- This means you tige and colistin!

Tumbarello M, et al. *Clin Infect Dis* 2012;55:943-50.

Outcomes of 36 BSIs Treated with Combinations that Included Meropenem

Mero MIC (mg/L)	Total	Nonsurvivors (%)	Survivors (%)
1	1	0	1 (100)
2	4	0	4 (100)
4	10	2 (20)	8 (80)
8	4	6 (35.2)	11 (64.7)
≥16	17	9 (25)	27 (75)

- So to review:
  - Colistin and tigecycline – bad PK/PD
  - Mortality with colistin + tige remained high
  - Add high dose, prolonged infusion mero and…

Tumbarello M, et al. *Clin Infect Dis* 2012;55:943-50.

Audience Response Question 3

- Blood stream infections with KPC producing organisms should be managed with combination therapy.

A: True
B. False

Fun with Fungus: CLSI Breakpoints (BPs) for Echinocandins Prior to 2011

- Anidulafungin, caspofungin, micafungin

  Susceptible $\leq$ 2 µg/ml

  Intermediate 4 µg/ml

  Resistant $\geq$ 8 µg/ml
- Based upon PK and clinical trials data

Echinocandin Breakpoints Changed in 2011

- To better detect known resistance mechanisms
  - Glucan synthase enzymes
  - Mutations in hot spot regions of *FKS1* and *FKS2*
- Markedly lowered MIC breakpoints and different by drug

Echinocandins – "Is that a Typo?"

			MIC Range (mcg/mL)	
Antifungal	**Species**	S	I	R
Micafungin	*C. albicans*	≤0.25	0.5	≥1
	C. glabrata	≤0.06	0.12	≥.25
	C. tropicalis	≤0.25	0.5	≥1
	C. krusei	≤0.25	0.5	≥1
	C. parapsilosis	≤2	4	≥8
	C. guillermondii	≤2	4	≥8

CLSI Document M27-S4 December 2012

Echinocandins – "That MUST be a Typo!"

			MIC Range (mcg/mL)	
Antifungal	**Species**	S	I	R
Anidulafungin	*C. albicans*	≤0.25	0.5	≥1
&	*C. glabrata*	≤0.12	0.25	≥0.5
Caspofungin	*C. tropicalis*	≤0.25	0.5	≥1
	C. krusei	≤0.25	0.5	≥1
	C. parapsilosis	≤2	4	≥8
	C. guillermondii	≤2	4	≥8

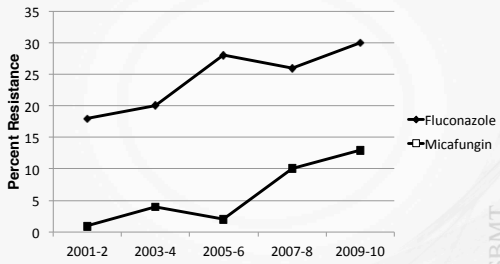
CLSI Document M27-S4 December 2012

C. glabrata: The Cockroach Strikes Back

- 293 instances of *C. glabrata* fungemia
- 2001-2010
- Fluconazole & echinocandin resistance
- Examined isolates for FKS mutations
- Evaluated data using new CLSI breakpoints

Alexander BD, et al. *Clin Infect Dis* 2013;56:1724

C. glabrata Resistance – Duke University Medical Center



Alexander BD, et al. *Clin Infect Dis* 2013;56:1724

Rapid Emergence of Echinocandin Resistance in *C. glabrata*

- *C. glabrata* from Hospital Day (HD) 15
  - Micafungin MIC = 0.015 mcg/mL
  - Caspofungin MIC = 0.06
  - Anidulafungin MIC = 0.06
- C. *glabrata* from HD 23
  - Micafungin MIC = 0.5 mcg/mL
  - Caspofungin = 1.0
  - Anidulafungin = 0.5

Lewis JS, et al. *Antimicrob Agents Chemother* 2013;57:4559

However… For *C. glabrata*

- "…PD targets needed for success in this model could be achieved based on MIC values of:
  - 0.25 mg/L for anidulafungin
  - 2 mg/L for caspofungin
  - 0.5 for mg/L micafungin"
- And these are the guys behind the new BPs!

Lepak A, et al. *Antimicrob Agents Chemother* 2012;56:5875-82.

The Gold Standard for *Candida* spp.?

All Organisms (N=958)	P	Odds Ratio	95% CI
Echinocandin – Mortality	.02	0.65	.45-.94
Echinocandin – Success	.01	2.33	1.27-4.35

- Do proposed new BPs overcall resistance?
- If you're already azole resistant… then what?
- A return to amphotericin?

Andes DR, et al. *Clin Infect Dis* 2012;54:1110-22.
Pfaller MA, et al. *J Clin Micro* 2008;46:551-9.

2012 European Candida Guidelines: Recommendations for Targeted Invasive Candidiasis Treatment in Patients with Malignancies

Drug	Strength
Caspofungin/Micafungin	A2
Anidulafungin	B2
Liposomal AmB 3mg/kg/d	B2
AmB Lipid Complex	C2
Fluconazole	C2
Voriconazole	C2

- Other points:
  - Posaconazole: no data
  - Differences in lipid AmB formulation recommendations
  - Echinocandin recommendation differences

Ullman AJ, et al. *Clin Microbiol Infect* 2012;18 (Suppl 7):53-67.

In Case You Forgot…

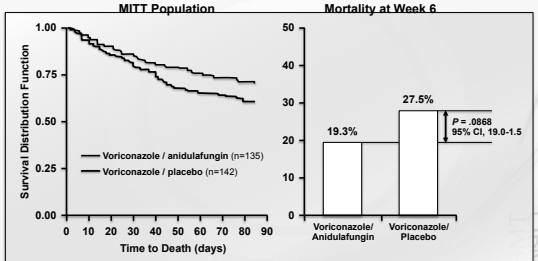
	Micafungin N=264	L-AmB N=267	P ≤ 0.05
Therapy D/C	4.9%	9.0%	=0.087
Infusion reaction	17.0%	28.8%	X
Back pain	0.4%	4.5%	X
LFTs	4.2%	1.9%	
Hypokalemia	6.8%	12.0%	
Creatinine ↑	10.3%	29.9%	X

Kuse ER et al. *Lancet* 2007; 369: 1519–27.

Audience Response Question 4

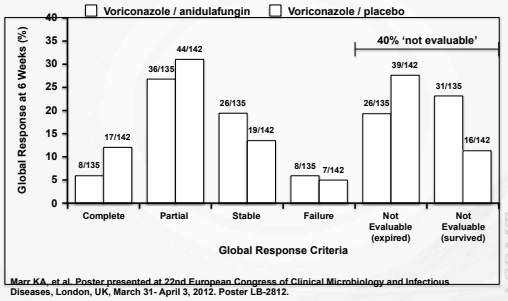
- The new CLSI breakpoints for *Candida* spp. and the echinocanins are designed to do which of the following?
  - A: Guarantee clinical and microbiologic failure when an organism is resistant
  - B: Ensure clinical success when an organism is susceptible
  - C: Detect FKS mutations in the glucan synthase genes of *Candida* spp.
  - D: What new breakpoints?

Voriconazole + Anidulafungin vs. Voriconazole Monotherapy for Invasive Aspergillosis: MITT Population



Marr KA, et al. Poster presented at 22nd European Congress of Clinical Microbiology and Infectious Diseases, London, UK, March 31- April 3, 2012. Poster LB-2812.

Voriconazole + Anidulafungin vs. Voriconazole Monotherapy for Invasive Aspergillosis: Some oddities



Marr KA, et al. Poster presented at 22nd European Congress of Clinical Microbiology and Infectious Diseases, London, UK, March 31- April 3, 2012. Poster LB-2812.

Voriconazole: Dosing and Bioavailability Questions

Probability of Achieving Different Voriconazole Trough Plasma Concentrations Targets with 200, 300, and 400 Twice-Daily Oral and Intravenous Dosing Regimens

VRC Trough Concentration Target (mg/L)	Probability, by Dosing Regimen and Route of Administration					
	200 mg Twice Daily		300 mg Twice Daily		400 mg Twice Daily	
	Oral (%)	Intravenous (%)	Oral (%)	Intravenous (%)	Oral (%)	Intravenous (%)
1	60	86	78	95	95	97
1.5[a]	49	**70**	**68**	**87**	**78**	92
2	35	56	55	77	67	86
4	11	22	22	43	35	56
4.5[a]	8	**18**	**19**	**37**	**29**	50
5	4.5	15	16	26	26	44

Pascual A, et al. *Clin Infect Dis*. 2012;55(3):381-390.

A Couple Words on *C. difficile* & Contact Precautions

- Wash your hands, don't use hand gels, etc.
- But wait…
- Asymptomatic carriers contributing to new cases?
- When it rains…
- Gowns and gloves don't prevent acquisition of multidrug resistant organisms?

Eyre DW, et al. *NEJM* 2013;369:1195
Curry SR, et al. *Clin Infect Dis* 2013;57:1094
Harris AD, et al. *JAMA* 2013;310:1571

Conclusions

- Bad bugs everywhere
- Few new antibiotics, especially on gram(-) side
- Polymyxin B looking better and better
- Echinocandin BPs and *C. glabrata*
- Combination therapy for invasive aspergillosis?