

New anti-microbials

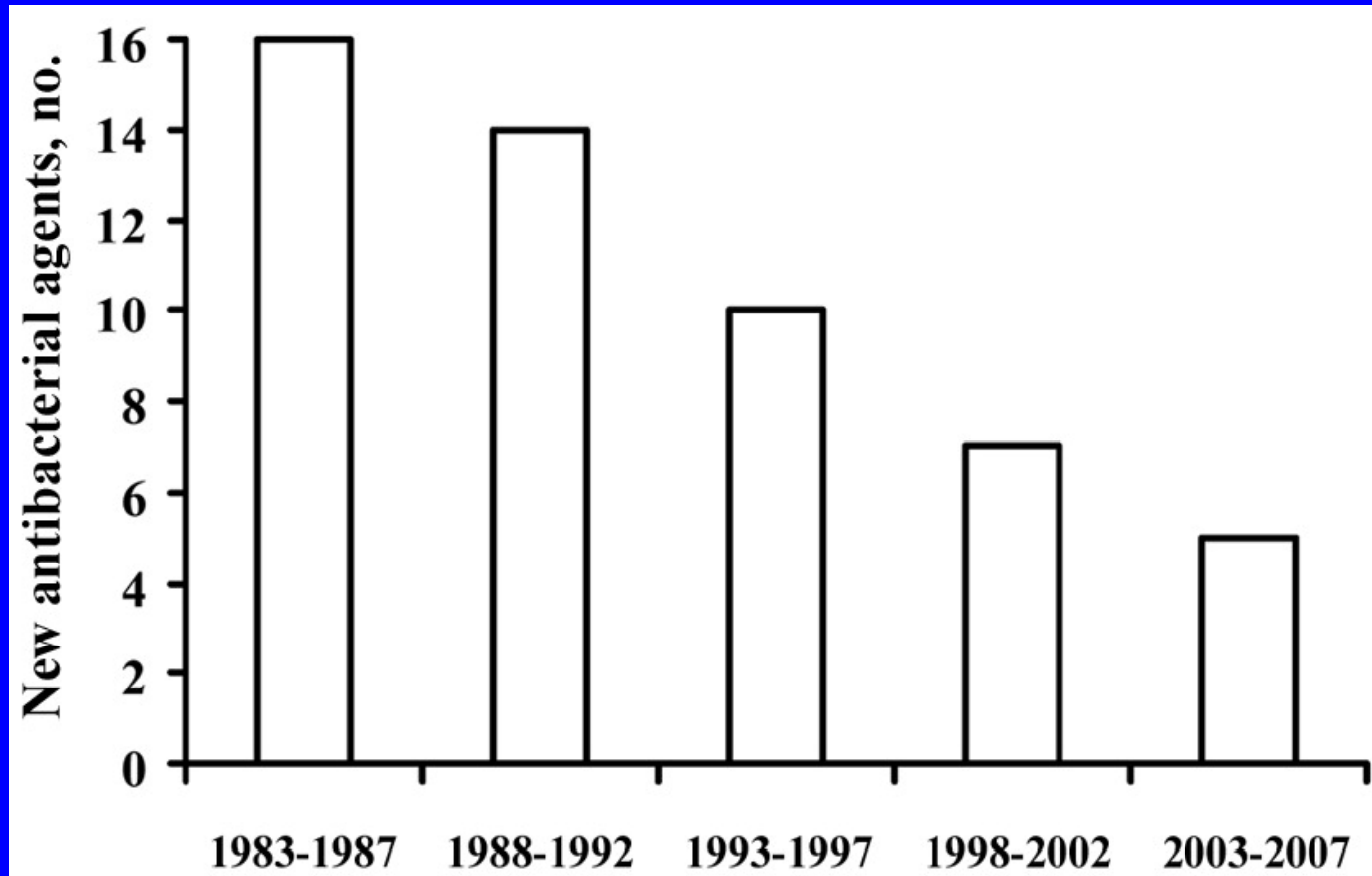
Kevin B. Laupland MD, MSc, FRCPC
Departments of Critical Care Medicine
and Medicine, University of Calgary

Disclosures

- Unrestricted research funding grants from Merck, GSK, Pfizer, and Wyeth
- Honorarium/travel support from Merck, CSL Behring, Pfizer, Wyeth, and Astellas

The need for new anti-microbials

- Emergence of resistance ESKAPE (IDSA; CID 2009;48:1-12) or should it be ESKÆPE?
 - *Enterococcus faecium*
 - *Staphylococcus aureus*
 - *Klebsiella pneumoniae*
 - *Acinetobacter baumannii*
 - (*Escherichia coli*)
 - *Pseudomonas aeruginosa*
 - *Enterobacter* species
- Toxicity/intolerance/efficacy



New antibacterial agents approved in the United States, 1983–2007.

From CLIN INFECT DIS 48(1):1-12.

© 2008 by the Infectious Diseases Society of America. All rights reserved.



CHICAGO JOURNALS

Anti-bacterials

- Quinupristin/dalfopristin (Synercid 1999-12-10)
- Moxifloxacin (Avelox 2000-10-19)
- Gatifloxacin (Tequin 2001-01-09)
- Linezolid (Zyvoxam 2001-04-02)
- Ertapenem (Invanz 2003-05-12)
- Telithromycin (Ketek 2003-05-28)
- Gemifloxacin (Factive 2004-03-09)
- **Daptomycin (Cubicin, 2007-09-24)**
- **Ceftobiprole (Zeftera 2008-06-26)**
- **Tigecycline (Tygacil 2008-10-23)**
- **Doripenem (Doribax 2009-09-02)**

Daptomycin

- Acidic cyclic lipopeptide natural antibiotic
- Broad spectrum Gram-positive agent
- Developed in 1980's but abandoned due to problems with myopathy at high doses
- Reintroduced at lower doses (4-6 mg/kg) without significant problems
- Bactericidal, IV only, caution and dose adjustment with renal dysfunction

Clinical data

- Many clinical trials done or underway in soft tissue infection, bloodstream infections, endocarditis, bone and joint infection (Livermore DM *JAC* 2008;62:S341-349)
- Non-inferior to vancomycin for *S. aureus* bacteremia and right sided endocarditis (Fowler et al *N Engl J Med* 2006;355:653-65)
- Inferior for pneumonia (pulmonary surfactant inactivates; Pertel P et al. *CID* 2008; 46:1142–51)

Daptomycin

- Option for MRSA bacteremia where vancomycin fails or patient is intolerant
- Role in enterococcal endocarditis/MRSA bone and joint infections?

Ceftobiprole

- Cephalosporin with potent activity against MRSA (and VISA) and resistant *S. pneumoniae*; *E. fecalis* but not *E. faecium*
- Ceftazidime/cefepime-like activity against Gram-negatives (no ESBL, caution with AmpC's, poor *Acinetobacter* species) and anaerobes
- Bactericidal, IV only, renal dose adjustment

Clinical data

- Skin and soft tissue infection
 - 95% each cure rate vs. vancomycin for Gram-positives (Noel et al *AAC* 2008;52:37-44)
 - 87% ceftobiprole vs 100% vancomycin + ceftazidime (non-significant; Noel et al *CID* 2008;46:647-55)
- CAP ceftobiprole vs ceftriaxone/linezolid
- HAP ceftobiprole vs ceftazidime/linezolid (abstracts)

Ceftobiprole

- Many attractive features but needs a track record and studies have not included serious invasive infections

Tigecycline

- Glycylcycline related to minocycline
- Side chain added to overcome resistance
- Bacteriostatic, IV only
- Concentrates in most tissues except bone and joint fluid
- *In vitro* activity ESKÆPE except *Pseudomonas aeruginosa*

Clinical data

- Several trials comparable efficacy for skin and soft tissue infections vs. imipenem or vancomycin/aztreonam (Ellis-Grosse et al *CID* 2005;41S341-343 and Babinchak et al *CID* 2005;41S354-367)
- Community acquired pneumonia vs. levofloxacin 90% vs 87% (Bergallo et al *DMID* 2009;1:52-61)
- Inferior to imipenem in VAP (Maroko et al ICAAC 2007)
- Observational studies 70% cure resistant Gram-negatives (Kelesidis et al *JAC* 2008;62:895-904)

Tigecycline

- Not for bacteremia, may be inferior for pneumonia
- Not tested in severe ICU infections
- Unlikely role as a first line agent
- Polymicrobial multi-drug resistant infections?

Doripenem

- Similar or better *in vitro* activity as imipenem against susceptible Gram-positives; meropenem against Gram-negatives
- Resistance is generally a class effect
- Well tolerated (no seizures)
- IV, bactericidal, renal dose adjustment

Clinical trials

- Intrabdominal infections 87% clinical cure with each of meropenem and doripenem (Lucasti *et al Clin Ther* 2008; 30:868-83)
- Urinary tract infections 82% post therapy microbiological test of cure doripenem vs 83% levofloxacin (Naber *et al Int J Antimicrob Agents* 2007;29:S212)
- Clinical cure rates 68% doripenem vs. 64% imipenem for VAP (Chastre *et al. Crit Care Med* 2008; 36:1089)

Doripenem

- ? CNS or other severe infections
- What role will it have
 - MIC data vs. clinical data
 - Track record with current carbapenems
 - Pricing vs. older/generic drugs

Anti-fungals

- Caspofungin (Cancidas 2001-07-19)
- Voriconazole (Vfend 2004-08-20)
- **Posaconazole (Posanol 2007-03-26)**
- **Micafungin (Mycamine 2007-05-22)**
- **Anidulafungin (Eraxis 2007-11-14)**

Posaconazole

- Expanded spectrum triazole
- *Candida* spp., *Aspergillus* spp. and enhanced activity against molds including Zygomycetes
- Drug interactions and risk for hepatotoxicity like voriconazole; PO only
- Prophylaxis of invasive disease in high risk leukemia patients; no comparative data for treating serious infections

Echinocandins

- Developed in the 1970's introduced clinical practice 1990's
- Caspofungin, micafungin, anidulafungin
- Glucan synthase inhibitors, interrupt synthesis of 1,3 beta-glucan needed to form cell wall
- Broad anti-*Candida* (less with *C. parapsilosis*), *Aspergillus* spp., but less active Zygomycetes
- Limited CNS penetration and no activity with *C. neoformans*
- Interactions caspofungin»micafungin»anidulafungin

The Pipeline

- Iclaprim
- Ceftaroline
- Oritavancin
- Dalbavancin
- Telavancin
- Garenoxacin

Conclusions

- There are some new agents that each have certain merits but none are wonder-drugs
- Clinical studies need to include severe disease
- The pipeline is fairly dry