Antimicrobial Agent Update

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Which of the following is an approved indication for ceftaroline?

A. Acute bacterial skin and skin structure infection
B. Intraabdominal infection due to vancomycin resistant enterococci
C. Bacteremia due to methicillin-resistant Staphylococcus aureus
D. Hospital acquired pneumonia due to atypical pathogens
E. All of the above
Objectives

- Review antimicrobials
  - New antimicrobials
  - New indications
Where are all the new antibiotics?

- IDSA 2004 White Paper “Bad Bugs, No Drugs”
- Increasing microbial resistance
- Challenges to Antimicrobial approvals
- Cost of development
Table 1: Antibiotic Approvals (1983-Present)

Source: IDSA’s 2004 Bad Bugs, No Drugs report (modified)
Select New Antibacterial Agents Approved Since 1998

<table>
<thead>
<tr>
<th>Antibacterial</th>
<th>Year</th>
<th>Novel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifapentine</td>
<td>1998</td>
<td>No</td>
</tr>
<tr>
<td>Quinupristin/dalfopristin</td>
<td>1999</td>
<td>No</td>
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<tr>
<td>Moxifloxacin</td>
<td>1999</td>
<td>No</td>
</tr>
<tr>
<td>Gatifloxacin*</td>
<td>1999</td>
<td>No</td>
</tr>
<tr>
<td>Linezolid</td>
<td>2000</td>
<td>Yes</td>
</tr>
<tr>
<td>Cefditoran pivoxil</td>
<td>2001</td>
<td>No</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>2001</td>
<td>No</td>
</tr>
<tr>
<td>Gemifloxacin</td>
<td>2003</td>
<td>No</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>2003</td>
<td>Yes</td>
</tr>
<tr>
<td>Telithromycin*</td>
<td>2004</td>
<td>No</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>2005</td>
<td>No</td>
</tr>
<tr>
<td>Doripenem</td>
<td>2007</td>
<td>No</td>
</tr>
<tr>
<td>Telavancin</td>
<td>2009</td>
<td>No</td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>2010</td>
<td>No</td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>2011</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Spellberg *CID* 2004, modified
Bad Bugs Need Drugs

10x'20
Ten new ANTIBIOTICS by 2020

1 ceftaroline fosamil: Forest Laboraties, Inc.
Approved October 29, 2010
New Agents

- 2008 – No antimicrobial approvals
- 2009 – Telavancin
  - Coartem™ - Artemether and Lumefantrine- (new approval, not new drug)
  - Peramivir (investigational)
- 2010 – Ceftaroline
  - Tigecycline (new indication)
  - Doripenem (new dose availability)
  - Daptomycin (new IV push option)
- 2011 – Fidaxomicin
  - HCV: boceprevir, telaprevir,
  - HIV: rilpivirine, FTC/TDF/RPV (Complera™)
  - FQ- New black box warning regarding myasthenia gravis
- 2012 – HIV-emtricitabine/tenofovir new indication
Pipeline

- A few back to studies: Dalbavancin
- CDI agents
  - monoclonal antibody,
  - non-toxigenic C diff,
  - oxazolidinone with FQ moiety,
  - Lipoglycopeptide
- Ceftibiprole
  - Plays on existing drugs: Fluoroketolide, new B-Lactamase inhibitors in combination with existing cephalosporins
- No novel gram-negative drug for at least 10 years
- HIV – Gilead, “Quad” elvitegravir + cobicistat (CYP 3A4 inhibitor) + emtricitabine + tenofovir. Recommended for approval-JUST APPROVED
Antifungals - Echinocandins

- Anidulafungin, caspofungin, micafungin
- Have gotten cheaper in last few years
- All roughly equivalent in spectrum
  - Indications differ by agent (although similar activity)
  - Affects cell wall synthesis (unique to antifungals)
  - Once daily IV dosing
  - *in vitro* spectrum
    - Yeasts, moulds, salvage for aspergillosis
    - NO Cryptococcal Coverage, weak C. parapsilosis
Telavancin (Vibativ™)

- Lipoglycopeptide
- Approved September 2009
- Built on vancomycin
  - Cell wall and cell membrane active
- **Indication:**
  - Complicated skin and skin structure infection due to certain Gram positives including MRSA
- **Pending Indication:**
  - Pneumonia
- **Dosing**
  - 10mg/kg IV q24h
  - Renal dosing necessary
  - Dialysis dosing not yet established.
AEs

- Teratogenic (but preg cat c!) in some animals
- Nephrotoxicity
- QTc prolongation (looks less than FQ)
- Interference with INR, PT, PTT, without bleeding risk
- Nausea/vomitting, taste disturbance, foamy urine
- No increase in Red Man
- A-telavancin
- B-vancomycin

Images are Public Domain
Telavancin

- **Unique aspects**
  - Based on vancomycin, but varied mechanism
    - Cell Wall and Cell membrane active
  - Another option for MRSA activity, some VRE
  - IV only
  - No need to check levels
  - Looks to be more effective than vanc in skin, but results not statistically significant.
Ceftaroline (Teflaro), Forest Pharmaceuticals

- Cephalosporin ? Generation
- Approved 10/29/2010
- Indications:
  - Acute bacterial skin and skin structure infections (ABSSSI)
    - MRSA, MSSA, Strep, E coli, K pneumo, K oxy.
  - Community-acquired bacterial pneumonia (CABP)
    - MSSA, Pneumococcus (+/- bacteremia), H infl, K pneumo, K oxy, E coli
- Dosing
  - 600mg IV q12h over 1hr Crt Cl >50
  - 400mg IV q12h over 1hr Crt Cl >30-<50
  - 300mg IV q12h over 1hr Crt Cl >=15, <=30
  - 200mg IV q12h over 1hr ESRD, including HD.

Teflaro PI
Ceftaroline

Teflaro PI
Ceftaroline

- Binds PBP2a, PBP2x
- AEs
  - Well tolerated, no specific AE >5%
  - Nausea, diarrhea, rash, most common
  - No significant difference between ceftaroline and comparators, Vanc/Aztreonam, Ceftriaxone.
- Pregnancy B
- Minimal interactions with P450 drugs
- Excretion: Primarily kidneys, 64% in urine unchanged.
Ceftaroline—Unique Aspects

- IV Only
- No hepatic adjustment
- Dose have renal dosing recommendations
- Indicated for ABSSSI, CABP
- In vitro activity vs. MRSA
- Marginal at best for Enterococcus fecalis, Minimal if any for E faecium.
Tygacil (tigecycline)

- Minocycline with attachment at 9 position
- Broad Spectrum Gram Positive, Gram Negative, Anaerobic
- NO Pseudomonas, Proteus, Providencia, Morganella (MP3)
- Approved
  - Complicated Skin and Skin structure infection
  - Complicated Intraabdominal infection
  - CABP due to H. influenzae, Pneumococcus +/- bacteremia, legionella,
- NOT APPROVED
  - DM foot with osteomyelitis
    - Met endpoints for skin, but not osteo
- Good in vitro killing of MRSA and VRE
  - Approved MSSA, MRSA , VSE (cSSSI)
  - Approved MSSA, VSE (cIAI)
Tygacil (tigecycline)

- **New Black Box on All Cause mortality (2010)**
  - Higher mortality observed across all studies including phase IV
  - Subgroup, shows mostly in situations where drug used off label

- **Unique Aspects**
  - IV Only
  - Long Half-Life, still dosed twice daily
  - High tissue distribution, relatively low serum concentrations
    - May not be good for bacteremia
  - Broad Spectrum Non-Beta Lactam
    - May help consolidate therapy
    - Safe in Beta-Lactam allergic patients
Cubicin (daptomycin)

- Cyclic lipopeptide
- 8/03 Approved for Skin and Skin Structure (including MRSA) but only VSE
- 5/06 S. aureus BSI including Right Sided endocarditis (MSSA/MRSA)
- Daptomycin has NO lung penetration
Cubicin (daptomycin)

- Another alternative for MRSA
- Appears to have less renal dysfunction and reasonable tolerance compared with vancomycin
- No need to check levels
- Concern of Muscle toxicity, check CPK weekly
- NEW: 2 minute IV infusion/Push
Doribax (doripenem)

- **Approved**
  - Approved 10/07
    - Complicated intra-abdominal
    - Complicated UTI
  - Carbapenem
  - More similar in spectrum to meropenem and imipenem than to ertapenem
  - Has anti-pseudomonal coverage
    - May have better susceptibility patterns vs other carbapenems for PSA
  - Renal adjustment
Doribax (doripenem)

- **Unique Aspects**
  - IV Only
  - May have lower MICs and better PSA coverage than other carbapenems
  - Looks less likely to induce PSA resistance than other carbapenems
  - Like most of the carbapenems, covers acinetobacter
    - Not demonstrated to be any better vs. acinetobacter
  - NEW: 250mg now available.
MDX-066 (CDA-1) and MDX-1388 (CDB-1)

- Phase II Completed
- Human antibody-based monoclonal antibodies to neutralize CDTA/CDTB
  - Standard of care (metro vs. vanco) + MAb vs. placebo one time infusion.
  - Placebo recurrence rate 20%, consistent with literature
  - MAb recurrence rate reduced 70% compared with placebo (reduces recurrence to about 7%)
- Merck doing further development
OPT-80-fidaxomicin-Dificid

- APPROVED-5/2011
- NEJM 2/2011
  - 10 days OPT-80 vs. vancomycin PO
  - Similar Cure rates compared with vancomycin 92.1% vs 89.9%
  - Lower recurrence rates compared with vancomycin, 13.3% vs 24%
  - Global Cure rates higher compared with vancomycin, 77.7% vs. 67.1%

- Second Phase 3 data similar
- Newest data-Second Phase 3 trial
  - As above, but recurrence rate similar to vancomycin when dealing with epidemic strain
    - Recurrence trends toward favoring fidaxomicin, but not statistically significant.

Optimer Pharmaceuticals Press Release 11/10/2008
• L1-1642: Gerding G et al. Phase 3 trial of Fidaxomicin vs Vanc-
decreased cure rate for epidemic BI/NAP1/027 strain
  – Cure: Fidaxomicin-92%; Vanc-90%;
  – Cure if NAP1: Fidaxomicin: 86%; Vanc 85%
  – Recurrences overall: Fidaxomicin-13%; Vanc 24% (p=0.004)
  – Recurrences if NAP1: Fidaxomicin-24%; Vanc 24%
• Cure rate for NAP1 was less than other strains; recurrence rate for
  NAP1 with Fidaxomicin therapy was not better than vanc
• NAP1 strain is bad! OPT 80 has gained a name but lost some luster?
During 2 phase III RCTs, separate stratum of patients who had single prior CDI and recurred within 3 months

128 patients; FDX (66; 200 mg bid X 10), Vanc (62; 125 mg qid x 10); mean age 63; endpoint-recurrence in 4 weeks

Results:

- Recurrences in 4 weeks
  - Vanc: 35.5% (22/62)
  - FDX: 19.7% (13/66); 45% reduction (p=0.045)

- Recurrences in 2 weeks
  - Vanc 17 (27.4%); FDX 5 (7.6%)  p = 0.003

- Risk of recurrence 2.7 fold greater in patients > 75 yrs compared to 55 years

- FDX: negligible impact on fecal flora
OPT-80-fidaxomicin-Dificid

- New class of CDI Agent “Macrolide”
- No reported resistance in studies
- Minimal absorption
- Minimal impact on gut anaerobes
- PO only-10 day course
- Lower recurrence rates, especially with 1\textsuperscript{st} recurrent patients
- Expensive
- NTAP: $868 or 50% of difference between overage of DRG, whichever is less.
Anti-Hep C-Boceprevir

  - Boceprevir for untreated HCV Genotype 1
    - Gp 1: pegIFN-RBV + Placebo 44wks
    - Gp 2: peg IFN-RBV + boceprevir 24 wks
    - Gp 3: peg IFN-RBV + boceprevir 44wks
  - SVR non-black: Gp 1 40% vs Gp 2 67% vs Gp 3 68%
  - SVR black: 23% vs 42% vs 53%
  - Anemia 13% controls vs 21% boceprevir
Anti-Hep C

- 4/2011, Recommended for approval
- 5/2011, Telaprevir, boceprevir-APPROVED!
- Approval for recurrence/treatment
- New Agents for HCV
  - Combination with PEG-IFN, RBV
  - Anemia biggest AE
- Apparently better SVR than standard of care
- Cost? Role? Efficacy in HIV?
Rilpivirine—Edurant, Complera

- Another new NNRTI
- AE similar to other NNRTI
- Complera (TDF+FTC+Rilpivirine):
  - The second once-daily fixed combination triple drug
Elvitegravir, cobicistat, TDF, FTC

- Stribild – “Quad”
- Cobi (3A4 inh)-used to “boost” elvitegravir
Truvada (emtricitabine/tenofovir)

- Pre-exposure prophylaxis
  - iPrEx
    - Seronegative men/transgender women, high risk behavior
    - Monthly HIV testing, condom distribution, management of STI education, risk reduction counseling
    - 2499 enrolled 1251 Truvada, 1248 Placebo
    - 131 Seroconverted 48 vs. 83, risk reduction 42%
      - Risk reduction greatest with detectable intracellular tenofovir.
Truvada (emtricitabine/tenofovir)

- Partners PrEP
  - Serodiscordant heterosexual couples in Kenya/Uganda
  - Monthly HIV testing, Adherence counseling, preg testing
  - Uninfected partner 61-64% male
  - 4758 couples enrolled, TDF 1589, FTC/TDF 1583, Placebo 1586
  - 82 Seroconversions, 13 FTC (2 during preg treatment interruption)/TDF, 52 Placebo. 75% risk reduction, best in subjects with detectable plasma tenofovir, adherence key.
Truvada (emtricitabine/tenofovir)

- Must be taken daily
- Indicated for discordant heterosexual couples and MSM with high risk for HIV infection
  - Inconsistent condom use, STI, exchange of sex for…, drug use, incarceration, unknown HIV status of partner with any of previous
- Confirm HIV (-) and retest every 3 months.