UPDATE ON NOVEL ANTIMICROBIAL THERAPIES AND PNEUMONIA VACCINATION GUIDELINES

February 23rd, 2015

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OBJECTIVES

- Describe the new recommendations regarding pneumococcal vaccinations
- Explain the place in therapy of Rapivab and restrictions to its use at the institution
- Review the evidence behind Zerbaxa and identify its niche in therapy
- Understand the potential use of Dalvance and Orbactiv
- Assess the utilization of Sivextro and evidence supporting its efficacy

PNEUMONIA IMMUNIZATION

- Currently two pneumococcal vaccines available

- Pneumovax 23 (PPSV23)
  - Given IM or SQ
  - Chronic health condition, smoker, LTC resident
  - Broader target population

- Prevnar 13 (PCV13)
  - Given only IM and only once*
  - Immunocompromising condition, CSF leak, cochlear implant, asplenia
  - Serotype: 6A

Pneumovax 23[package insert].Whitehouse Station, NJ: MERCK& CO., INC.;2011.
Prevnar 13 [package insert]. Philadelphia, PA: Pfizer, Wyeth Pharmaceuticals, INC; 2010.

PNEUMONIA IMMUNIZATION

- ACIP initially recommended:
  - PCV13 for pts 19-64 YO w/immunocompromising condition(s)
  - PPSV23 for same pt population, pts w/chronic health condition, & pts ≥ 65 YO

- ACIP now recommend:
  - PCV13 for pts 19-64 YO w/immunocompromising conditions **+ pts ≥ 65 YO** (in series w/PPSV23)

"Current Pneumococcal Vaccine Recommendations". Centers for Disease Control and Prevention. http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html. 12/22/2014. Accessed on 02/10/15.

PNEUMONIA IMMUNIZATION

- Evidence behind recommendation:
- CAPiTA trial
  - N=85,000 adults ≥65 YO
  - 45.6% efficacy vs vaccine-type pneumo. PNA
  - 45% efficacy vs vaccine-type non-bacteremic pneumo. PNA
  - **75% efficacy vs vaccine type invasive pneumo. dx***
- Two randomized immunogenicity studies:
  - PCV13 induced immune response ≥ vs PPSV23
  - PPSV23 as initial dose in series elicited < antibody response vs PCV13

"Current Pneumococcal Vaccine Recommendations". Centers for Disease Control and Prevention. http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html. 12/22/2014. Accessed on 02/10/15.

PNEUMONIA IMMUNIZATION

- Pneumo. vaccine- naïve pt ≥ 65 YO:
  - PCV13 at ≥ 65 YO → 6-12 mo. → PPSV23
- Previously received PPSV23 at ≥ 65 YO:
  - PPSV23 already given → ≥ 1 yr → PCV13
- Previously received PPSV23 at < 65 YO + now ≥ 65 YO:
  - PPSV23 already given → ≥ 1 yr → PCV13 → 6-12 mo. → PPSV23 (≥ 5 yrs since first PPSV23*)

"Current Pneumococcal Vaccine Recommendations". Centers for Disease Control and Prevention. http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html. 12/22/2014. Accessed on 02/10/15.

RAPIVAB

- Peramavir- only IV neuraminidase inhibitor available
  - Others NAI's: tamiflu, relenza
- FDA approved for uncomplicated cases of influenza virus type A or B infection
- Outpt regimen: 600 mg IV x 1 dose infused over 15-30 min
- AE's: diarrhea, N/V, reduced neutrophil count

Rapivab [package insert]. Durham, NC: BioCryst Pharmaceuticals, INC. 2014.

RAPIVAB

- Inpt regimen: 600 mg IV daily x 5 days (off-label)
  - 10 days of tx studied but no clear benefit demonstrated

- Renal adjustment:
  - CrCl: $\geq$ 50 mL/min: 600 mg daily
  - CrCl: 30-49 mL/min: 200 mg daily
  - CrCl: < 30 mL/min: 100 mg daily
  - CRRT: 600 mg daily (off-label)

- CDC recommends peramivir for serious, complicated influenza cases in pts unable to benefit from PO NAI

Rapivab [package insert]. Durham, NC: BioCryst Pharmaceuticals, INC. 2014.

RAPIVAB

- Restriction criteria:
  - Influenza diagnosis: influenza (+) or prodrome of illness
    - (-) rapid influenza diagnostic test ≠ exclusion
  - ICU/critical care location
  - Unable to receive PO/PT tamiflu
    - ECMO/CRRT still obtain adequate absorption from PO
  - ID &/or critical care order only
- Duration of tx after 5 days to be evaluated
- IV to PO conversion evaluated daily

ZERBAXA

- Ceftolozane/tazobactam
  - Structurally similar to ceftazidime

- Indicated for treatment of complicated:
  - Intra-abdominal infections in combo w/flagyl
  - UTI's, including pyelonephritis

- Approved spectrum:
  - *Enterobacteriaceae*
  - *Pseudomonas aeruginosa*
  - *B. fragilis*
  - Some *streptococcus species*

Zerbaxa [package insert]. Lexington, MA: Cubist Pharmaceuticals, INC. 2014

ZERBAXA

- Renal dosing:
  - CrCl: > 50 mL/min: 1000 mg/500 mg IV Q8H over 60 min
  - CrCl: 30-50 mL/min: 500 mg/250 mg
  - CrCl: 15-29 mL/min: 250 mg/125 mg
  - HD: LD of 500 mg/250 mg, then 100 mg/50 mg

- Caveats of tx:
  - Convulsing-inducing effects < cefepime or ceftazidime
  - Minimal cross-resistance
  - Allergic cross-sensitivity
  - Susceptible to carbapenamases/some ESBL's

Zerbaxa [package insert]. Lexington, MA: Cubist Pharmaceuticals, INC. 2014

ZERBAXA

- ASPECT-cIAI trial
  - Zerbaxa & flagyl for 4-14 days non-inferior to meropenem for cure rate, 83%vs 87.3% in ITT population
- ASPECT-cUTI trial
  - Composite microbiological & clinical cure rates superior for zerbaxa vs levaquin for 7 day tx in MITT population
    - 76.9% vs 68.4%
- Phase III, open-label trial for VAP
  - Zerbaxa 3 g/1.5 g IV Q8H vs zosyn 4.5 g IV Q8H
  - Terminated after 4 months…

Zerbaxa [package insert]. Lexington, MA: Cubist Pharmaceuticals, INC. 2014

ZERBAXA

- Claim to fame: resistant *pseudomonas*/ESBL-producing GNB
  - In vitro susceptibility support MIC $\leq$ 8 mcg/mL
    - Variable susceptibility shown to ESBL-producing pathogens
    - MIC approved by FDA < than this for these pathogens*

- Niche: MDR or pan-resistant *Pseudomonas aeruginosa*
  - Pending e-test susceptibility
  - Case-by-case basis

Zerbaxa [package insert]. Lexington, MA: Cubist Pharmaceuticals, INC. 2014

LIPOGLYCOPEPTIDES

Dalvance

- Approved for: ABSSSI by gram +
- 1000 mg IV x 1, 1 wk later: 500 mg (over 30 min)
- Renally dose adjusted
- Concerns with therapy:
  - Reversible ALT elevation

Orbactiv

- Approved for: ABSSSI by gram +
  - *Enterococcus faecalis*
- 1200 mg IV x 1 (over 3 hr)
- Concerns with therapy:
  - CYP interactions
  - Interferes w/coagulation tests*

Dalvance [package insert]. Chicago, IL: Durata Therapeutics, US Limited 2014.
Vibativ [package insert]. South San Francisco, CA: Theravance, INC. 2009.

LIPOGLYCOPEPTIDES- DALVANCE

- Dalbavancin:
- Renal dose adjustment:
  - CrCL < 30 mL/min w/o HD: 750 mg IV x 1, 375 mg 1 wk later
  - HD: no dose adjustment necessary

- Pro's:
  - Long half-life: 346 hours
  - Dosing scheme
- Con's:
  - Only approved for SSSI's
  - Caution in mod-severe hepatic impairment (↓ AUC)

- Potential role: long-term tx of gram + infections
  - Osteo*

Dalvance [package insert]. Chicago, IL: Durata Therapeutics, US Limited 2014.

LIPOGLYCOPEPTIDES- ORBACTIV

- Oritavancin:

- Pro's:
  - Long half-life: 245 hours
  - One time dosing = convenient
- Con's:
  - Only approved for SSSI's
  - Drug interactions
  - Contraindicated w/UFH after 48h post administration
  - Risk of resistance?

- Potential role: to be determined

Vibativ [package insert]. South San Francisco, CA: Theravance, INC. 2009.

SIVEXTRO

- Tedizolid: second generation oxazolidinone
  - "Me-too" drug to linezolid
- FDA approved for treatment of ABSSSI's by gram +
- Approved spectrum:
  - *MSSA/MRSA*
  - *Streptococcus pyogenes*
  - *Streptococcus agalactiae*
  - *Streptococcus anginosus group*
  - *Enterococcus faecalis*

Sivextro [package insert]. Lexington, MA: Cubist Pharmaceuticals, INC. 2014

SIVEXTRO

- Dose: 200 mg PO or IV daily x 6 days
  - IV: PO conversion 1:1
  - Infused over 1 hr
- Caveats of tx:
  - After reconstitution only good for 24 hrs
  - Not studied in neutropenic pts
  - Myelosuppression similar to zyvox
  - Weak MAOI: not studied in pts on serotonergic agents

Sivextro [package insert]. Lexington, MA: Cubist Pharmaceuticals, INC. 2014

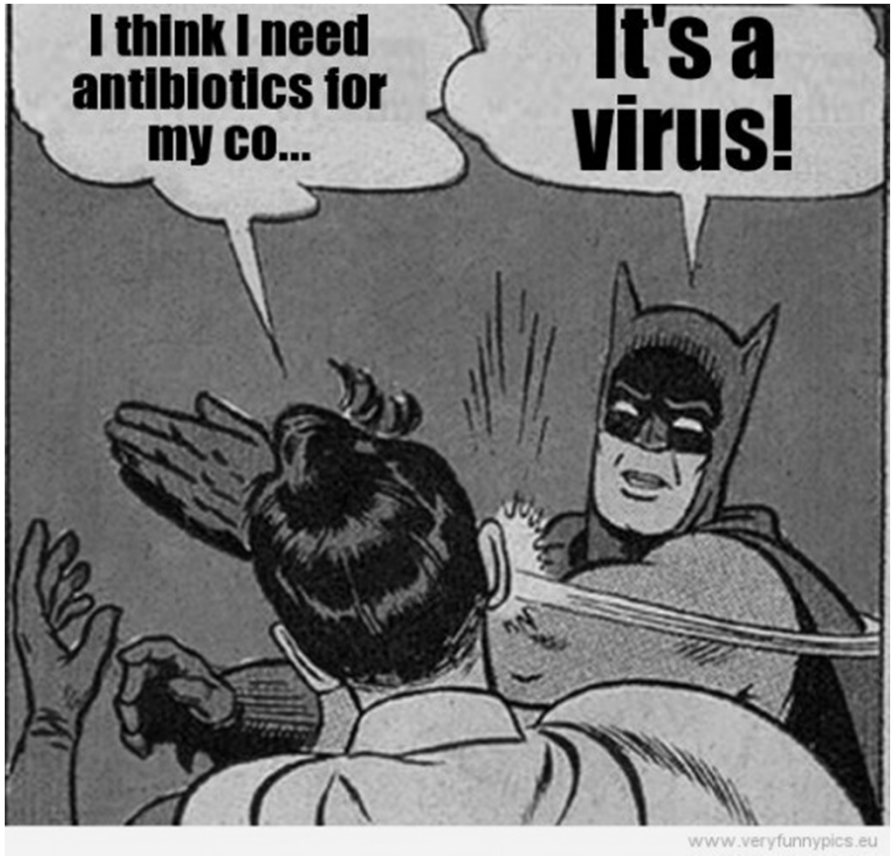
SIVEXTRO

- Two double-blind, non-inferiority trials, n = 1315
  - Study drug x 6 days vs linezolid x 10 days
  - Primary endpoint: early clinical response
    - Trial 1: 79.3% vs 79.1%
    - Trial 2: 85.2% vs 82.6%

- Bottom line:
  - Frequency & duration benefit
  - Potential use for linezolid-resistant pathogens
  - More data needed

Sivextro [package insert]. Lexington, MA: Cubist Pharmaceuticals, INC. 2014

?QUESTIONS?



http://veryfunnypics.eu/2013/01/24/everytime-i-go-to-the-doctor/