Scourge and Re-scourge of Pertussis

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***Bordetella pertussis* (whooping cough)**

- Highly contagious respiratory disease
- Severe debilitating cough illness (100 day cough) in persons of all ages
- Highest morbidity and mortality
- Estimated > 300,000 deaths/year
- Poorly controlled despite high vaccine coverage
- First Us pertussis vaccine for adolescents and adults (Tdap) licensed in 2005
- Adolescents and adults waning immunity-(5-10 years) giving it to our kids

Antigenic and biological active components

- Pertussis Toxin (PT)
    - Major virulence factor
    - Immunogenic and protective
    - Elicits lymphocytosis
    - In all acellular pertussis vaccines
- Filamentous hemagglutinin (FHA)
    - Adhesion to ciliated epithelial cells
    - Immunogenic but not completely protective
- Pertactin-cell surface protein
    - Enhances cell binding and entry
- Trachael Cytotoxin
    - Major reason for cough
    - Cough can not be treated with antibiotics
- Adenylate Cyclase
    - Inhibitsl local immune response
- Dermanecrotic toxin
    - Cell damage and death

Picture of Pertussis in the ED

- Lymphocytosis
- Fever usually minimal throughout course
- Characteristic Cough-toxin mediated/antibiotics do not modify the cough

Clinical Stages and Clinical Course

- Catarrhal-watery eyes, low grade fever, malaise, runny nose, 3 weeks after cough onset
    - 1-2 weeks
- Paroxysmal-bursts of coughing during a single exhalation followed by inspiratory whoop sound,
    - 1-6 weeks
- Convalescent-weeks-months paroxysms gradually improve

Infant Pertussis

- Young infants-highest rate of disease
- Atypical symptoms: apnea (sometimes with seizures), sneezing, gagging, choking, vomiting

Pertussis among Adolescents and Adults

- Disease often milder than in infants and children
- Persons with mild disease can transmit
- Difficult to diagnose infection
- Pertussis immunity wanes 5-10 years after childhood vaccine series

Complicated Pertussis Laboratory Diagnosis

- Stage of Disease
- Antibiotic administration wipes out B. pertussis
- Vaccination status
- Quality/timely collection of clinical specimens
    - Nasopharyngeal aspirate, nasopharyngeal swab
    - Swabs not cotton or calcium aliginate for PCR
- Transport
    - Regan Lowe, BG transport
    - PCR-universal transport media
- Culture
    - Gold Standard
    - 100% specific but low sensitivity
    - Highest yield in young patients, unvaccinated patients, patients early in cough illness prior to antimicrobials
    - Slow incubation time-up to 10 days
    - Freshly Prepared Regan-Lowe Media
- Identification
    - FA Testing
    - Biochemical not recommended
    - MALDI-TOF
- PCR
    - Primary diagnostic test
    - Potentially more sensitive than culture
    - Rapid
    - Disadvantages
        - Affected by disease phase and antibiotics
        - No national standard protocol
        - Potential for false positives

PCR Assays-Multiplex

- Focus-www.focusdx.com/
- Biofire-bioMerieux-www.biofiredx.com
- Vergene-Nansophere-www.nanosphere.us/
- Gen-Mark-e-Sensor-www.genmarkdx.com

PCR Assays-Single

- Illumingene-Meridian BioScience/www.MeridianBioscience.com
    - LAMP Molecular Technology
    - Provides Results in less than 1 hour: test and treat the same day
- Amplivue-Quidel-www.Quidel.com
    - Helicase-dependent amplification assay

The Reds, the Blacks and the Ugly!!AFB/Mycology Case Studies

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Rapid Growing Mycobacteria (RGM's)

- Do not stain well with Kinyoun
- Very susceptible to decontamination
- Reservoirs
    - Soil, water, dust
    - Extended habitats-grow in water including distilled water
    - Components of biofilms
    - In artificial water supplies
- Isolation of RGM's does not imply disease

Case 1: *Mycobaterium goodii* isolated from a pocket formed around a dysfunctional pacemaker.

M. goodii

- Belongs to *M. smegmatis* group
- Recognized in 1999
- Associated with community acquired wound infections, respiratory and nosocomial infections
- Nosocomial outbreak of wound infections associated with surgical implants, (2004), pacemaker infections
- Treatment-*M. smegmati*s group= general lack of susceptibility to clarithromycin

Case 2: *M. porcinum* from a patient with several year history of bronchiectasis and cough

M. porcinum

- First recognized as a human pathogen in 2004
- Emerging rapid grower
- In M. fortuitum group
- Wound infections, IV catheter-related infections, osteomyelitis
- Can be drinking water contaminant serving as a long term reservoir

Common Infections associated with the Following RIGM's

- Localized post-traumatic wound infections
- Catheter infections
- Surgical wound infections especially following augmentation mammoplasty, cardiac surgery
- Post traumatic or postsurgical corneal infections

M. fortuitum group
M. chelonae group
M. abscessus group

- M. abscessus ss abscessus group most drug resistantMycobacteria/inducible macrolide resistance

M. smegmatis group
M. mucogenicum group

Identification of RGM's

- More than 70 species
- Biochemical identification-forget it
- Molecular Sequencing
    - 16S RNA
    - rpoB-based gene sequencing
    - MALDI-TOF

Treatment of RGM's

- General lack of susceptibility to clarithromycin
- Duration of therapy: success depends on nature and severity of disease
- Localized infections: oral-single dose drug therapy for 4-6 months
- More severe: debridement, combination of oral and IV antimicrobials and then oral therapy for 6 months

Important to correctly identify and perform susceptibility testing on RGM's to predict antibiotic susceptibility and patient outcome

Dematiacious Fungi

- > 150 species and 70 genera
- Histology important in identification
    - Fontana-Mason stain: stain specific for melanin
    - Differentiated based on histologic findings
- Identification based on phenotypic studies
- Reference for dematiaceous fungi
    - Revankar, SG and Sutton, DA 2010, Clinical Microbiology Review 23:884-928

General Comments about Dematiaceous Fungi

- Common in environment
- Often isolated in laboratory but only 10% are likely to have clinical significance
- Clinical diease is uncommon

Clinical Syndromes of Dematiaceous Fungi

- Eumycetoma
    - Deep subcutaneous tissue infections of lower extremities, draining sinus tracts
- Chromoblastomycosis
    - Production of sclerotic bodies in subcutaneous tissue, tropical areas
- Phaehyphomycosis-reserved for everything else
    - Generic name that encompasses pathologic conditions associated with dematicaeous fungi

Disseminated Phaehyphomycosis

- *Scedosporium prolificans* is by far most common cause
- Primary Risk Factors
    - Immunocompromise of any kind
    - Known malignancy, neutropenia, HIV, Bone marrow transplant, solid organ transplant, cardiac hardware
- Body sites involved
    - Blood, lung, heart, skin, brain, kidney
- Overall Mortality 79%

Antimicrobial Testing Updates: What's New and What's Coming

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New Antibiotics

- 3 for MRSA
- 3 for ESBL and CRE in Gram negative rods
- Expensive
- Shorter course of therapy
- Unusual dosing regiments like single dose or weekly

Tedizolid (Sivextro™, Cubist)-Released June 2014

- Second generation linezolid (oxazolidinones)
- IV and PO
- Cellulitis drug
- For Gram positive cocci including MRSA and VRE
- More active than Linezolid about 4x and safer

Oritavancin (Orbactive™)-Released August 2014

- A lipoglycopeptide similar to vancomycin
- Skin and skin structure infections-1200 mg single-dose
- For Gram positive bacteria-MRSA and VRE

Dalbavancin (Dalvance™)-Released May 2014

- Vancomycin analog
- IV-2 doses (1,000 mg followed by 500 mg dose one week later)
- Approved for skin and skin structure infections
- Gram positive bacteria

Ceftaroline fosamil (Teflaro)-Released 2010

- 5th generation cephalosporin
- Skin and soft tissue infections
- Community acquired pneumonia
- Inhibits MRSA, MRSE, Pencillin R S. pneumoniae and E. faecalis
- Gram positive activity like vancomycin
- Gram negative activity like Ceftriaxone (Rocephin)
- Not active against ESBL, CRE or nonfermentors

Avibactam

- Best of all the beta-lactamase inhibitors
- Irreversible binding of enzyme
- Extends the spectrum of other drugs
- Inhibits ESBL's and KPC's

Ceftaroline-avibactam

- Avibactam extends spectrum for Ceftaroline to include ESBL's and KPC's
- Lowers MIC of ceftaroline against enterics at least 2X

Ceftolozane/tazobactam

- Phase III trials completed-submitted to FDA
- Most potent Gram negative cephalosporin seen
- Inhibits 98% Pseudomonas aeruginosa
- Active against ESBL's not CRE
- IV
- Reserve for serious Pseudomonas infections

Updates on Susceptibility Testing CLSI

- Table 1-Drugs recommended for testing
    - Cefazolin tested on urine isolates from uncomplicated UTI predicts other oral cephalosporins
    - Cefoxitin surrogate test for Oxacillin Resistance in staphylococci. Detects Mec A better than oxacillin
    - Doripenem added to carbapenem box in Group A for Acinetobacter
    - Minocycline is added to Group B for Acinetobacter
        - More active than tetracycline or doxycycline so if it is on your formulary you should test it rather than the others
- Table 2
    - For all disk diffusions testing;no more than 6 disks on a 100mm plate, disks should be 24 mm apart
    - Cefazolin predicts oral cephalosporins better than Cephalothin for urine cultures
    - For Acinetobacter and carbapenem comment specifies the dosing that interpretation refer to
    - Deleted vancomycin disk for staphylococci

- Susceptible Dose Dependent Category-SDD
    - New category of interpretation for Enterobacteriaceae and Cefepime
    - SDD replaces Intermediate
    - Four different dosing regimens for different infections
    - This is first drug CLSI is connecting dosing to MIC

Old Breakpoints	**Proposed Breakpoints**
S = ≤ 8	S = < 2
I= 16	SDD = 4-8
R= > 32	R = > 16

- Under SDD if MIC is 4 or 8 bump up to higher dosing
- Problem whether Doctors and pharmacists knowing how to interpret SDD result
- Need to have discussion with Pharmacy about SDD concept and result