Antimicrobial Resistance: When to Worry (or Not)

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Objectives

Describe the rates of resistance to various antibiotics in common infections.

Identify two to three suitable alternatives for these resistant organisms.
Recent newsflash

Scientists find superbug bacteria in World War I soldier who died of dysentery

Washington Post article @ washingtonpost.com
The Post Story

✓ Shigella-induced dysentery isolate from 1915

✓ DNA compared with 1954, 1984, 2002 isolates

✓ Researchers in the UK have studied evolution of this organism over a century

✓ The 1915 isolate resistant to PCN and many other antibiotics years away from their discovery
Introduction

Covered in this lecture

✓ *Clostridium difficile* infections
✓ *Propionibacterium acnes* infections
✓ *Pseudomonas aeruginosa* infections
✓ Methicillin-resistant *Staphylococcus aureus* infections (MRSA)
✓ Rifampin-resistant *Clostridium difficile* infections (“RRCD”)
Introduction

Other resistant bacteria of broader interest to all of medicine (not covered here)

- Vancomycin-resistant enterococcus (VRE); of particular interest *E. faecium* MDR
- Penicillin-resistant pneumococcus (many are MDR)
- Fluoroquinolone resistant *N. gonorrheae*
- Triple-rx resistant *H. pylori*
Introduction

Some background issues of bacterial resistance to various antibiotics

✓ Note “they” are generally “drug-bug” pairs (MRSA, VRE, TCN-resistant *P. acnes*)

✓ Through *conjugation*, etc. via *plasmids* can connect (share genetic material) → other species

✓ Reality is subsequent to drug-bug combo, often shared resistance = *MDR* (*multidrug* resistance)

✓ Resistance may occur within a few days of starting appropriate *rx* – pseudomonas, RRCD
Introduction

Antimicrobial resistance general tendencies

• Generally level of antimicrobial resistance varies widely from geographical locale to another
• Generally increased resistance occurs over time, comparing data from one site to itself
• Resistance can occur via “natural methods” of bacterial existence and replication
Introduction

Some reassurance

✓ No catastrophic resistance trends for drugs we use in Dermatology

✓ Much of the resistance occurs in absence of drug exposure
Some significant concerns

✓ Pharma antibiotic pipeline far from robust (7-10 day course po drugs less profitable vs chronic meds)

✓ Selected bacteria less pertinent to our field have become almost pan-resistant at times (eg VRE)

✓ Excessive use of antibiotics is a substantial factor (abx “stewardship” programs widespread now)
** In *Dermatology*, generally can **wait** for C&S; antibiotics possibly on hold for a few days (MRSA, pseudomonas rx)
Following two figures are from Todar “Online Textbook of Bacteriology”
Three mechanisms of antibiotic resistance in bacteria.
Mechanisms of horizontal gene transfer (HGT) in bacteria
**Clostridium difficile**

**Organism** *Clostridium difficile*

- = difficult to isolate and grow in culture originally
- Gram +, spore forming, toxin producing, non-invasive anaerobe
- CDAD = pseudomembranous enterocolitis = antibiotic-associated colitis = “C diff”
Clostridium difficile

**Risk factors** – not related to specific antibiotics

- Debilitated (1) advanced age 65+, (2) co-morbidities and/or hospitalized, (3) obesity
- Immunosuppression (1) cancer **chemo**, (2) SCT
- GI “disturbance” (1) gastric acid suppression, (2) GI surgery, (3) enteral feeding
- Perioperative abx especially if hospital is having an “outbreak”


**Clostridium difficile** *

Risk factors – antibiotic related (and another)

✓ Abx most likely (1) clindamycin, (2) beta-lactam broad spectrum, (3) fluoroquinolones

✓ Abx course (1) “long” duration, (2) broad spectrum rx, (3) multiple agents

✓ Risk highest in first month after rx (can be during, and up to 3 mos after rx)

✓ Risk for recurrences (1) age ≥ 75 y/o, (2) ≥ 10 stools daily, (3) Cr ≥ 1.2
Clostridium difficile *

Pathogenesis – toxins and spores/vegetative form

✓ C diff with no toxin = no disease minority of strains
✓ Newborns, neonates no receptors for toxin
✓ Outside colon → survives in spore form (resistant to heat, acid, antibiotics)
✓ Inside colon → functional vegetative, toxin producing forms, antibiotics can kill
**Clostridium difficile** *

Pathogenesis – spread, recurrence

- Usually (not always) requires **disruption** of intestinal **flora** by antibiotics
- Spread fecal-oral route (health care **providers, family, etc**)
- **C diff recurrence** largely due to **spores, not** vegetative form
- Normal flora – **Bacteroides spp.** provide **GI barrier** function, among other bacteria
**Clostridium difficile Toxins**

- Toxin A (enterotoxin) inflammatory, ↑ in mucosal secretion
- Toxin B (cytotoxin) 10x more potent than toxin A → mucosal damage
- Binary toxin (from NAP/BI/027) similar to iota toxin by *C. perfringens*
- NAP1/BI/027 strain – larger quantities of toxins A and B vs other strains
- Above toxins alter cytoskeleton, GTP signal transduction → cell retraction, induce apoptosis GI epithelium
- One marker is ↑ IL-8
More **virulent** strains of *C diff*

- **J strain** – especially **clindamycin** resistance epidemics 1980s and 1990s
- **NAP1/BI/027 strain** (hypervirulent) – largely **fluoroquinolone** resistance
- This latter strain gained prominence in early 2000s (~2001)
Clostridium difficile

Resistance trends

• Rise in refractory virulent strains, much due to NAP1/BI/027
• Rise in frequency and severity with low/absent host Ab to A toxin
Clostridium difficile *

Prevention/Rx “antibiotic stewardship”

• Abx most effective (1) metronidazole, (2) oral vancomycin, (3) rifamixin?

• Fecal transplantation = fecal bacteriotherapy (one RCT as of Feb 2014)

• Possible role of probiotics (can not “hurt”??)

Miscellaneous info

• Organism discovered 1935, first resistance noted 1970

• Uncertain if limit acne/rosacea abx to 3 months truly makes a difference??
Propionibacterium acnes

Organism *Propionibacterium acnes/spp.* = risk for invasive infections

Risk factors
✓ Clinically **significant infections** in setting of (1) surgery with **hardware**, (2) **CSF shunts**, (3) endovascular **devices** and/or **procedures**
*Propionibacterium acnes*

**Pathogenesis**

- *P. acnes* normal flora human skin and mucosal surfaces, *not* very pathogenic
- Difficult to determine if contaminant or true pathogen
- More likely pathogenic (1) pure culture multiple specimens, (2) deeper culture
- This organism is capable of adherence and biofilm formation
- Indolent growth, clinical sx of inflammation minimal, delayed months, even years
Propionibacterium acnes

Resistance trends
• “Increasing” but solid data on trend relatively hard to find

Prevention/Rx
• Benzoyl peroxide +/- tretinoin
• Hardware removal unless creates unstable spine, etc.
• Parenteral PCNs to rx invasive forms
Propionibacterium acnes

Miscellaneous info

✓ Resistance alone minor problem due to abx with anti-inflammatory effects

✓ Typically acne abx plus benzoyl peroxide smaller risk (BPO non-selective killing)
**Pseudomonas aeruginosa**

Organism *Pseudomonas aeruginosa*

Risk factors

- General risk factors (1) invasive devices, (2) bed ridden, (3) ICU stay, (4) DM, (5) recent surgery
- Key issue for above pneumonia and sepsis
- Prior antibiotics (1) fluoroquinolones, (2) cephalosporins – broad spectrum, (3) carbapenems (ertapenem), (4) amino-glycosides
- Likelihood that antibiogram predicts rx success decreases with length hospital stay
Pseudomonas aeruginosa

Pathogenesis

• Common intrinsic resistance or acquired resistance during treatment
• Multidrug resistant (MDR) organisms common = 3 or more drugs or drug families resistant
• Colistin often effective with these strains
Resistance trends

✓ Over 25 years (IU data) ~30% pseudomonas now resistant to fluoroquinolones

✓ Study of MDR 200 hospitals (1) 22% pneumonia isolates, (2) 15% bloodstream isolates

✓ Up to 10% resistance acquired during rx with anti-pseudomonal agents
Pseudomonas aeruginosa

Prevention/Rx

✓ Does not thrive in acidic environment (acetic acid soaks)
✓ Remove catheters, drain abscesses, remove obstructions
✓ Fluoroquinolones only reliable (mostly) oral rx for Pseudomonas infections
✓ Severe infection combination rx required (not by derm)
✓ **Fight urge** rx (+) Pseudomonas C&S in pt with leg ulcer
✓ **More logical to** rx (1) gram (–) toe web infect or (2) hot tub folliculitis
Lessons learned

✓ **Caution** with *empiric* rx

✓ **Should answer** two questions prior to *fluoroquinolone* rx

(1) Is the *Pseudomonas* a pathogen or contaminant in the clinical scenario?

(2) What are C&S results?
Methicillin-resistant *Staphylococcus aureus*

**Organism** - Methicillin-resistant *Staphylococcus aureus* = MRSA

**Risk factors for “HA” MRSA**

- HA = **Hospital acquired** ("health-care associated") severe, invasive disease
- Key factors (1) **prolonged** hospitalization/ICU/dialysis, (2) **antibiotic** use, (3) MRSA colonization/nearby **patients with MRSA**, (4) invasive devices
Methicillin-resistant *Staphylococcus aureus*

Risk factors for “CA” MRSA

✓ CA = **Community acquired** young, healthy pt, **no** recent health care exposure

✓ Line between these two is **increasingly blurred** (caution with generalizations)

✓ Risk factors (1) skin **trauma** multiple ways, (2) cosmetic **body shaving**, (3) HIV infection, (4) shared equipment, (5) incarceration, (6) **contact** pt with MRSA
Methicillin-resistant *Staphylococcus aureus*

Pathogenesis – molecular genetics

✓ If MRSA resistant to oxacillin/methicillin, then also co-resistant other β-lactams, macrolides, etc.
✓ MRSA requires presence *mec* gene (lacking *mec* gene then will be MSSA)*
✓ Mec encodes penicillin binding protein 2A (PBP2A produced via *mecA*, with much lower affinity PCNs); this can be diagnoses by PCR
 ✓ In contrast to PBP2A, PBP 1 through 4 have a high affinity for PCNs
**Methicillin-resistant *Staphylococcus aureus***

Pathogenesis – about *mec* and *fem*

- **Mec** gene has structural component (**mecA**) and 2 regulatory components
- Both resistance mechanism mec regulatory component (1) **mecR1-mecI** negative control; mec mutations → tremendous resistance, (2) β-lactamase genes
- Expression of MRSA via *fem* genes = factor essential for methicillin resistance)
**Methicillin-resistant *Staphylococcus aureus***

**Pathogenesis – about SCCmec**

- **Mec** gene part of *(SCCmec)* staphyloccal chromosomal cassette *mec*
- **HA-MRSA** – usually *SCCmec* types I, II, III
- **CA-MRSA** – usually *SCCmec* types IV, V *(were more uniquely abx sensitive)*
- Total *SCCmec* types I through XI – some strains have *bovine host reservoir*
Methicillin-resistant *Staphylococcus aureus*

Pathogenesis – about PVL gene

✓ Panton-Valentine leucocidin (**pvl**) toxin gene – **may** have **some correlation** with CA-MRSA (genes lukF-PV and lukS-PV)

✓ **Recent trend** ↑ **PVL toxin** producing MRSA commonly with **MDR sensitivities**
Methicillin-resistant *Staphylococcus aureus*

Resistance trends

- **Introduction of methicillin in 1959**, soon after resistant staph aureus noted
- Widespread outbreaks of MRSA initially in Europe early 1960s
- Largely believed that MRSA originally derived from “coag-negative staph”
- Mec gene similar in all staphylococcal species
Methicillin-resistant *Staphylococcus aureus*

**Prevention/Rx**

- If abscess – **I&D** (< 5 cm I&D or debridement alone may suffice)
- Almost always in dermatology can await **C&S** (problem is a Thursday or Friday clinic or hospital consult)
- Empiric antibiotic choice CA-MRSA (1) long-acting *tetracyclines*, (2) **TMP/SMX**, (3) clindamycin *fading somewhat*, (4) **linezolid** much more $$$
- **Parenteral** rx – extensive SSTI, fever, co-morbidities such as DM, HIV use IV **vancomycin** with back-up options daptomycin, linezolid
- Be aware of future possible role of teicoplanin and fidaxomicin (a macrolide)
Rifampin-resistant *Clostridium difficile*

**Organism** Rifampin-resistant *Clostridium difficile*

Roughly equal to “RRCD”

**Risk factors**

✓ Long-term rifampin use in TB *(perhaps also with 12 week hidradenitis use??)*

✓ Use of rifampin as monotherapy *(never wise)*
Rifampin-resistant *Clostridium difficile*

Pathogenesis

- Great majority resistant strains not previously exposed to rifamycins**
- Many of RRCD are BI/NAP1/027 ribotype (similar to *C diff* in general)
- Many of RRCD are *rpoB* gene positive
Rifampin-resistant *Clostridium difficile*

Resistance trends

✓ Traditionally thought that *C diff* virtually always sensitive to rifampin

✓ Another rifamycin, rifamixin (non-systemic) formerly even more reliable

✓ Some rifampin resistant *C diff* strains initially evident in long-term TB rx
Rifampin-resistant *Clostridium difficile*

- **Huang 2013 study** RRCD 2006-2007 (8%), 2007-2011 (17%) in US Texas

- Quotes another study RRCD “CA” 34%, “HA” 35% resistance

- **Miller 2011 study** RRCD Italy isolates 18.8%, Canada isolates 2.1%

- **Spigaglia 2011 study** 148 C diff strains resistant to at least one abx, 48% MDR to rifampin, erythromycin, clindamycin, moxifloxacin (of total 55% MDR) Italy

- **Huang 2010 study** – RRCD 29.1%, and 8.5% rifaximin resistant in China

- **Curry 2009 study** – about 50% RRCD, (1) 7 of 8 rifampin exposed pt isolates, (2) with 166 of 462 unexposed pt isolates in US Pennsylvania
Rifampin-resistant *Clostridium difficile*

**Prevention/Rx**

✓ Vancomycin, metronidazole **still DOC** for *C diff* (at least CA = community acquired)

✓ Rifampin has been used as **adjunct** for *C diff* in some settings, Cochrane review **no benefit**
# IUH Antibiogram Data MSSA & MRSA

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## IUH Antibiogram Data *Pseudomonas*

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*Combo with Pip/Taz, cefepime, meropenem respectively (excluding CF pt)*
Some Take Home Points

✓ The sky is not falling (at least not for outpt Dermatology)
✓ However wisdom is to wait for C&S when possible
✓ Realize acne regimens can be made relatively resistance proof with BPO (what about rosacea??)
✓ Antibiograms are a great tool for local sensitivity trends
✓ Brief courses of abx always lower priority pharma, while high prices for short courses abx lower priority insurers
✓ Government involvement in this problem is both good news & bad news (→ sequelae always cash and control)
✓ Overall UpToDate good source of info for this topic et al.
Many thanks!!