SASKPIC

‘Understanding the mechanisms of resistance in AROs and why that’s important’

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Objectives

• Why we care about ARO’s
• Mechanism of Action of beta-lactam and glycopeptide Antibiotics and the mechanism of resistance to these agents in:
  – MRSA
  – VRE
  – ESBL
  – CPO, CPE/CRE/CRO...what’s the difference?
• Bench to bed-side: Why do we care about just these organisms? Should we care about others?
• Horizontal Infection Control Strategies
Q. Where did antibiotic resistant organisms (ARO’s) come from?

• Bacteria have had mechanisms for resisting antibiotics LONG BEFORE WE invented antibiotics…probably, long before the existence of man!!!

• Naturally occurring compounds with antibiotic properties very common in the environment
  – Penicillin produced by the Penicillium a.k.a. bread mold
  – Vancomycin produced by Streptomyces bacterium found in soil

• Bacteria needed to have mechanisms encoded in their genes that would allow them to survive in the presence of these ubiquitous deadly compounds
Q. So why weren’t ARO’s a problem long long ago?

- Bacteria and their natural environmental predators were in a state of ‘amicable’ equilibrium

- Penicillin discovered by Alexander Fleming (1928)
  - Miracle cure for Staphylococcal skin and soft tissue infections
  - No side effects!
  - Mass produced and utilized during the first world war

- Since the advent of antibiotics, bacteria have been under greater and greater pressure to survive
Survival pressure

Natural Selection

Resistant bacteria

Antibiotics

Population of mainly susceptible bacteria

TIME

Population of mainly resistant bacteria
European study: 33,000 deaths a year from resistant infections

Filed Under: Antimicrobial Stewardship
Chris Dall | News Reporter | CIDRAP News | Nov 06, 2018
The villains of the IPC world

- MRSA: Methicillin Resistant *Staphylococcus aureus*
- VRE: Vancomycin Resistant *Enterococcus*
- ESBL: Extended Spectrum Beta-Lactamase producing Gram negative bacteria
- CPO: Carbapenemase Producing Organisms
  - CPE: Carbapenemase producing Enterobacteriaceae
  - CRO/CRE: Carbapenem resistant organisms/Enterobacteriaceae
Why do we care about these organisms in particular?

• Common and/or with limited/no treatment options available

• MRSA, ESBL and CPO are all resistant to the members of the most commonly used class of antibiotics known as the BETA-LACTAMS
  – Very important antibiotics due to their bactericidal action

• The genes responsible for resistance are carried on MOBLIE genetic elements as opposed to being located on the CHROMOSOME
In order to understand the mechanism of resistance, we must first look at mechanism of antibiotic action

- Beta-Lactams (Penicillin) and Glycopeptides (Vancomycin) disrupt the formation of the bacterial cell wall

- Cell death = bactericidal
IMPORTANT TO UNDERSTAND ABOUT B-LACTAMS

- Have a Beta-lactam ring
- Bind to transpeptidases a.k.a. Penicillin Binding Proteins (PBPs) = prevent cell wall formation
MRSA: *mec* genes

- Resistant to ALL beta lactams
- Vancomycin, Daptomycin and Linezolid are the only treatment options of severe infections
VRE: \textit{van} genes

- Vancomycin Sensitive Enterococcus

- VRE

- Linezolid, Daptomycin are treatment options of severe infections
ESBL and CPO

The image illustrates the interaction between β-lactamase and a β-lactam antibiotic molecule. β-lactamase breaks a bond in the β-lactam ring of penicillin to disable the molecule. Bacteria with this enzyme can resist the effects of penicillin and other β-lactam antibiotics.
ESBL and CPO: Beta-lactamases with different targets

• Extended Spectrum Beta-Lactamases (*SHV, TEM, CTX-M* genes)

![ESBL Examples](image)

• Carbapenemases (*NDM, VIM, IMP, OXA* genes)

![Carbapenemase Examples](image)
CPO: the SUPER villain

• These organisms tend to carry resistance genes to beta-lactams as well as OTHER ANTIBIOTIC CLASSES
  – Fluoroquinolones (ex. cipro, levo and moxifloxacin)
  – Aminoglycosides (ex. gent and tobramycin)
  – Macrolides (ex. eryhtro, azithro and clarithromycin)
  – Tetracyclines (ex. tetra, doxy and minocycline)
  – Sulfonamides (ex. trimetoprim-sulfamethoxazole)

• Frequently they are resistant to ALL AVAILABLE ANTIBIOTICS
Summary

• MRSA: modified Penicillin binding protein (PBP)
  – B-lactam can’t bind and inhibit PBP so cell wall synthesis continues

• VRE: modified protein chain of the peptidoglycan
  – Vancomycin can’t bind, but PBP can so cell wall synthesis continues

• ESBL and CPO: beta-lactamases
  – Beta-lactam antibiotics destroyed therefore can’t bind and inhibit PBP so cell wall synthesis continues
Q. What do you mean by mobile genetic elements?

- **Mobile genetic elements**: small circular (plasmid) or straight (transposon) piece of bacterial DNA that contains a resistance gene(s) and can replicate and move independently of the bacterial chromosome.
  - Can transfer between cells of **same** or **different** bacteria types
  - Usually carry resistance genes to multiple antibiotic classes

- **Chromosomal**: the resistance genes are integrated into the larger bacterial chromosome and are therefore, not easily transferable
Q. What are the implications of this difference?

• A. Theoretically, the number of bacteria that are affected and therefore the ease of spread of the resistance genes

• Plasmids can replicate independently of bacterial replication and transfer resistance genes to “ANY” bacterium whereas chromosomical resistance genes stay in that one bacterial species therefore resistance genes can be spread more **widely** by plasmids

• Analogy???
  – Tower of Babel
    • universal language spoken⇒transfer of ideas easy and widespread
    • different languages spoken⇒transfer of ideas impaired because can only communicate with individuals speaking same language
The worst case scenario...

• When MRSA acquires *Van* genes encoding for vancomycin resistance....VMRSA

• However, despite the frequency of MRSA and VRE co-colonization, VMRSA is still RARE!!
Examples of Chromosomally encoded beta-lactamases and other mechanisms of resistance

- “SPICE” organisms- have an AmpC gene in their chromosomal DNA (not mobile) that encodes a beta-lactamase that destroys penicillins and cephalosporins. It’s an ESBL look alike, but we do not implement isolation precautions!
  - Serratia
  - Providencia
  - Indole positive Proteus vulgaris
  - Citrobacter
  - Enterobacter

- Stenotrophomonas maltophilia- resistant to beta-lactams including Carbapenems and a number of other antibiotic classes
  - Carbapenem resistance is mediated via a Carbapenemase located on the chromosome
  - Would be considered a CPO, but we do not implement isolation precautions!

- Pseudomonas aeruginosa – oftentimes resistant to ALL available antibiotics including Carbapenems (seen especially in CF patients)
  - Carbapenem resistance may be mediated by plasmid borne carbapenemase → CPO → would isolate
  - Carbapenem resistance may be mediated by other mechanisms (chromosomal) besides a carbapenemase → CRO, but we do not implement isolation precautions!
Mechanisms of resistance to antibiotics

1. The antibiotic can’t get inside the cell
2. The antibiotic can’t bind to its target
3. The antibiotic is destroyed
4. The antibiotic is actively removed from the cell
CPO/CPE vs. CRO/CRE explained

• Both are resistant to Carbapenems

• CPO/CPE- resistance mediated by carbapenemase
  – May be plasmid or chromosomal

• CRO/CRE- resistance mechanism not defined, and may include, but is not limited to a carbapenemase
BUT...practically speaking, a transfer of resistance from a patient/environment to another patient can occur regardless of the mechanism!

• Whether you are in the presence of a billion of resistant bacteria or just one, the odds of transmission are different but, once transmission occurs, the rest is history!
• Outbreaks reported as a result of BOTH mechanisms!!!
Isolation Practices are Changing!

Pt. with UTI due to ESBL E. coli that is resistant to penicillins, monobactams and cephalosporins but susceptible to piperacillin-tazobactam, ertapenem, Ciprofloxacin, TMP-SMX, nitrofurantoin and gentamycin → currently ISOLATE

vs.

Pt. with UTI due to non-ESBL E. coli that is resistant to, penicillin, cephalosporins, piperacillin-tazobactam, Ciprofloxacin, TMP-SMX, nitrofurantoin and gentamycin and only susceptible to meropenem → currently DO NOT ISOLATE

• Prevent the spread of Multi-drug resistant (MDR) and Extensively drug resistant (XDR) organisms REGARDLESS OF THE MECHANISM OF RESISTANCE!
Labs now have a universal way of calling something resistant

Volume 44-1, January 4, 2018: Emergency planning

Advisory committee statement

Canadian recommendations for laboratory interpretation of multiple or extensive drug resistance in clinical isolates of Enterobacteriaceae, Acinetobacter species and Pseudomonas aeruginosa

GJ German¹, M Gilmour², G Tipples³, HJ Adam⁴, H Almohri⁵, J Bullard⁶, T Dingle³, D Farrell⁷, G Girouard⁸, D Haldane⁹, L Hoang¹⁰, PN Levett⁷, R Melano¹¹, J Minion¹², R Needle¹³, SN Patel¹¹, R Rennie³, RC Reyes¹⁴, J Longtin¹⁵, MR Mulvey²*
# MDR and XDR definitions

<table>
<thead>
<tr>
<th>Organisms: Pseudomonas aeruginosa OR Acinetobacter species</th>
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</thead>
<tbody>
<tr>
<td>Not applicable</td>
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<tr>
<td>Not applicable</td>
</tr>
<tr>
<td>Resistance to all five antimicrobial groups</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
</tr>
<tr>
<td>Ceftazidime</td>
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<tr>
<td>Imipenem OR meropenem</td>
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<td>Tobramycin</td>
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Abbreviations: MDR, multidrug resistant organisms; XDR, extensively drug resistant organisms

*Table 2 - Footnote a* The term ‘OR’ should be interpreted as follows: if an isolate is resistant to either antimicrobial agent listed, it should be considered resistant to that criterion for the purposes of these definitions

*Table 2 - Footnote b* Resistance in *Serratia* spp. should only consider gentamicin susceptibility testing results

*Table 2 - Footnote c* Resistance in *Proteus* spp. should only consider meropenem susceptibility testing results

*Table 2 - Footnote d* Resistance in *P. aeruginosa* may include piperacillin-tazobactam OR piperacillin. For all *Acinetobacter* spp. piperacillin-tazobactam must be used.
Focus on Horizontal Infection Control Strategies a.k.a. Back to the Basics

• No universal ARO screening
  – Ex. A known MRSA positive patient on contact precautions while a MRSA positive patient who has not fallen into the risk group for screening is treated as “negative” and placed in a 4 bed room

• Don’t worry about things we can’t control i.e. ARO transmission outside of hospital environment and don’t use it as an excuse to not care about ARO’s in the hospital environment because patient condition (immune status, personal hygiene, type of care provided etc.) is considerably different in those two settings

• These organisms DO NOT FLY from patient to patient, but are most often spread via contaminated HCW hands, equipment, surfaces, patient hands

• EMPHASIS ON UNIVERSAL PRECAUTIONS
  – HAND HYGIENE (performed by HCW and Patient)
  – HAND HYGIENE
  – HAND HYGIENE
  – ..... 
  – HAND HYGIENE
  – Environmental and equipemtn cleaning
THANK YOU!

- Questions???

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