ANTIBIOTIC RESISTANCE
A CME Presentation
Pohnpei State Hospital
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Disclosures

Financial Obligations/Affiliations: None
Gratuity: FSM Health Services

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- Australia & New Zealand Governments

CME No of Credit?
- Per your respective Medical Association’s Regulations & Bylaws
Objectives (By the end of this presentation, the participants should have):

1. Refreshed their understanding of Infectious Diseases & Antibiotics
2. Grasp the basics of Antibiotic Resistance
3. Developed awareness of the immensity of the problem of Antibiotic Resistance
4. Been able to apply the proper principles of antibiotic use to help lessen the factors perpetuating resistance
5. Acquired some understanding which can help in the formulation of measures that can help mitigate the problem
6. Acquired enough understanding re Antibiotic Resistance to pass the CME QUIZ 😊
ANTIBIOTICS RESISTANCE

Dedicated to
Brief Outline

• Brief History of Infectious Disease
• Brief History of Antibiotics
• How antibiotics work (Mechanisms of action)

• Antibiotic Resistance

A. What is Antibiotic Resistance?

B. How does Antibiotic Resistance occur (Mechanisms)?

C. What are some of the Contributing Factors?

D. What are the currently known resistant bacteria

E. How serious is Antibiotic Resistance?

F. What can be done about it?

G. Can Antibiotic Resistance be prevented?

H. Is there any Hope?
(Antibiotic Resistance)

**Infectious Diseases (IDs)**

Or

Communicable Diseases (CDs)

“Diseases caused by pathogenic microorganisms”

(1/4 for today’s presentation)

Brief History:

**Early days:**

- Hippocrates to 16th century: “Miasma” (Greek for pollution)
- Dr. Fracastoro, mid-1500s: “Germ” Theory
- Dr. Semmelweis, mid-1800: “Puerperium” (1)
- Late 1800s: Pasteur & Koch: confirmed microbes (Germs) using “lenses-in-series”:

**The Microscope!**

(1) History of Biology, 1960
With the discovery of microbes (germs) causing Infectious Diseases (ID), the search for cure started;

The “birth of Anti-microbials”!

Anti: (against), bios (life)
(Selman Waksman, Jewish microbiologist), 1942
(Antibiotic Resistance)  
(Mortality due to Infectious Diseases)
ANTIBIOTIC RESISTANCE

ANTIBIOTICS

- chemotherapeutic agents (either bactericidal or bacteriostatic)
- several classes
- among the most prescribed medication in the world
- most are made by bacteria and fungi
- some later ones are synthetic (esp. in the last 2-4 decades)
- used for both human and animals (Animal Husbandry)

(2) Ehsan ul haq; Director Medical Education, University Medical & Dental College, Faisalabad: “Antibiotics Resistance; Contributing Factors”; JUMDC, Vol. 1, No. 2, Jul-Dec 2010
History of Antibiotics

Early History (Ancient times to early 1600s):

*Cause of Infectious Diseases: “Miasma” (Greek for pollution)

Rx: -molds, plants
    -warm soil
    -beer soup mixed with turtle shells and snake skins.
    -mixture of frog bile and sour milk
    -oil cake
    -“magic”
    -et cetera

I am sure our ancestors had their own cures (including “magic”?)
Modern history:

*mid 1640s – late 1890s: mold species (*Penicillium glaucium*) with some antibacterial activities, no definite chemical identified.

*1928: Penicillin & Lysozyme (*Penicillium notatum*)

Sir Alexander Fleming, Scottish Biologist

*1932: Protonsil (1st Sulfonamide)

Gerhard Domagk, German chemist

*1940s – 50s: Streptomyacin

Chloramphenicol

Tetracycline

Note: Four decades, 5 Antibiotics!
(Antibiotic Resistance)
(con’t. History)

1950s to present:

Beta-lactams:

-PCNs (PCN, Amox, Clox, Dicar, Piper, Pen G/K; Diclox, Mezlo, Naf, Oxacil, Carpen, etc.)

-Cephalosporins: (1st Gen: x15; 2nd Gen: x9; 3rd Gen: x19; 4th Gen: x7; 5th Gen: 2 not classified Ceph: x16; Combination: x1)

**69 CEPHALOSPORINS!!!!!!!!!!

Monobactams: x1
Carbapenems: x4
Macrolides: x4
Ketolide x1
Lincosamides: Clinda & Linco (x2)
Streptogramins: x2
Aminoglycocides: x8
Quinolones: 1st Gen: x6; 2nd Gen: x8; 3rd Gen: x9; 4th Gen: x4 (27)
Sulfonamides x4
Tetracyclines: x5
Glycyclines: x1
Unclassified: x19 (Metro, Rifam, Vanco, Bacit, Neo-B, INZ)

**Three decades >150 new antibiotics!
***Last Antibiotic class in late 1980s
No new ones to date!!!!!!!!!! (except)
Big deal?
(Antibiotic Resistance) (Mortality due to Infectious Diseases)
# Antibiotic Resistance

## Classes of Antibiotics

<table>
<thead>
<tr>
<th>Class</th>
<th>e.g.</th>
</tr>
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<tbody>
<tr>
<td>Beta lactams:</td>
<td>PCNs (Pen V, K, Amox, Clox, etc)</td>
</tr>
<tr>
<td></td>
<td>Cephalosporins (Cepha, Ceclor, Triamcin)</td>
</tr>
<tr>
<td>Monobactams:</td>
<td>Aztreonam (only one)</td>
</tr>
<tr>
<td>Carbapenems:</td>
<td>Imienem, Ertapenem</td>
</tr>
<tr>
<td>Macrolides:</td>
<td>Clarithromycin, Azithromycin, etc.</td>
</tr>
<tr>
<td>Ketolide:</td>
<td>Telithromycin--modified macrolides</td>
</tr>
<tr>
<td>Lincosamides:</td>
<td>Clindamycin &amp; Lincomycin</td>
</tr>
<tr>
<td>Streptogramins:</td>
<td>Streptogramin A, B</td>
</tr>
<tr>
<td>Aminoglycocides:</td>
<td>Gentamycin, Tobramycin, Neomycin, Kanamycin</td>
</tr>
<tr>
<td>Quinolones:</td>
<td>Ciprofloxacin, Norfloxacin, etc.</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Azulfidine, Sulfazine, etc.</td>
</tr>
<tr>
<td>Tetracyclines:</td>
<td>Tetracycline, Docycycline, Minocycline, etc.</td>
</tr>
<tr>
<td>Glycyclines:</td>
<td>Tigecycline</td>
</tr>
<tr>
<td>Unclassified:</td>
<td>Metro, Rifam, Vancomycin, Bacit, Neo-B, INZ, SMX/TMP, etc.</td>
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</table>
How do antibiotics work?
(Mechanisms of Action)

1. Prevent cell wall synthesis & Integrity
2. Interfere with DNA functions
3. Interfere with Protein synthesis

Bacterial Anatomy
Antibiotic Resistance
Mechanisms of Action
(Which antibiotic work where on bacteria?)

Cell Wall Synthesis
- Beta Lactams
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - Monobactams
- Vancomycin
- Bacitracin

Folate synthesis
- Sulfonamides
- Trimethoprim

Nucleic Acid Synthesis
- DNA Gyrase
  - Quinolones
- RNA Polymerase
  - Rifampin

50S subunit
- Macrolides
- Clindamycin
- Linezolid
- Chloramphenicol
- Streptogramins

30S subunit
- Tetracyclines
- Aminoglycosides

Cell Membrane
- Polymyxins

Protein Synthesis
Antibiotic Resistance!!!

“Superpill”  “Superbug”
Antibiotic Resistance!

A. What is Antibiotic Resistance? (Definition)

The process by which bacteria have become “immune” to antibiotics.

or

Antibiotics lost their bactericidal or bacteriostatic properties

or simply:

Bacteria are no longer affected by antibiotics

Trivia Q: Who first mentioned antibiotic resistance; When?
Antibiotic Resistance

“Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug, make them resistant.”

Any guess who said this?

(Sir Alexander Fleming; accepting speech; Nobel Prize, 1945)

Note: Bacterial resistance is not new BUT, resistance to antibiotic is.

(Bacteria survive by adapting and adjusting to their hostile environment, just like any living organisms:

“Survival of the fittest”
Antibiotic Resistance

B. How does Antibiotic Resistance occur? (Mechanisms)

* Make their **cell wall impermeable** to antibiotics (glycocalyx) and modify their surface proteins so antibiotics can’t attach

* Improve their **Efflux pump** (decrease antibiotic concentration in their cytoplasm)

* Develop **enzymes** to deactivate parts of antibiotic structure (beta lactamase)

* **Share genetic information by** conjugation & transformation

* Genetic changes
MECHANISMS OF ANTIMICROBIAL RESISTANCE

Inactivation (add a phosphate group on the antibiotic, which will reduce its ability to bind to the bacterial ribosomes)
Pumping out (increasing active efflux of the drugs)
Modification (modified drug target)
Impermeability (modified cell wall protein)
Plasmid
Resistance related to Gene their genes:

1. **Intrinsic Resistance:**

2. **Genetic Change:**

3. **Genetic Transfer:**

4. **Acquired Resistance:**
   - get resistance from other bacteria, bacteriophages

Univ. of Utah, Genetic Science Learning Center;
Retrieved November 19, 2016, from http://learn.genetics.utah.edu/content/microbiome/resistance/
“Selective Pressure” (survival of the fittest):

-one way resistance spread
**Antibiotic Resistance**

*Contributing Factors to Resistance*

**Overuse**

The longer the use, the more likely for resistance to occur

e.g.: the old ones (Sulfa meds, PCNs, Cephalosporins)

The more the use, also induces resistance:

e.g.: Quinolones esp. **Fluoroquinolones**
>50% resistance in some parts of the world (E. coli causing UTIs)

**Inadvertent exposure**

- antibx use in animal husbandry
  - from animals fed antibiotics & use to treat infections
    (cattles, pigs, chicken)

- **80% of use in USA is on livestocks!!**
  - resistant strain picked up by human consuming affected meats
PITY THE POOR HUMANS WHO HAVE TO EAT US!

DRUG RESISTANT

E. COLI

SALMONELLA

(Antibiotic Resistance)
Antibiotic use in animal husbandry 2010 and projected in 2030 (top 10 Countries)
State of the World Antibiotics (SWA); CDC Dynamics, Economy & Policy 2015
(Antibiotic Resistance)

*Misuse & Irrational use by Health Professionals*

- systemic use for localized infections

- Inappropriate dose, esp. under dosing
  - need to consider Volume of Distribution, MIC, MBC & Half Life

- lack of follow-up to ensure compliance and progress (3-5 days)

- Irrational & Inappropriate use
  - use of ineffective antibiotics
    - need to be aware of local situation (presence of resistance)
    - check with Lab for available data
  - use for viral infections (cold, flu, bronchitis, bronchiolitis, GE, acute sinusitis, etc)*
    - please pts; parents**

- Ulterior motives (profiting)?
  - Prescribing antibx without definite diagnoses***
  - prescribing expired meds****

- lack of Antibiotic Stewardship (responsibility, efficaciousness, ownership, etc.)

*3 y/o seen 11/21/16: “flu”; given Amoxicillin!
**three weeks ago: toddler given antibx for “fall off walker hitting nose”; no signs nor symptoms of infection!
*** 1 week ago: Pt. c/o: crampy abd pain with vomiting and fever; CBC (among other labs) shows leukocytosis; given antibx for “infection in the blood“! Did not look ill; stool c/w Viral Gastroenteritis; resolved with hydration and supportive measures.
****Med prescribed to toddler Sept. 2016 for “lung infection” with Azithromycin; expiration: Sept. 2015!
What is Antibiotic Stewardship?

• Working guidelines and strategies which can be formulated to guide antibiotic use at the community level (health centers) and other health institutions (hospitals) regarding Responsible, Rational and Thoughtful use by prescribers’ to prevent adverse effects and loss of efficacy

• Help to ensure patients are given the optimal and proper use of antibiotics

• Contributes immensely to prevention of antibiotic abuse, over/underuse
Antibiotic Resistance

(Con’t. Contributing Factors)

*Dispensation by illegal providers (quacks)
  - even in USA (Southeastern states, esp. Florida)
  - many developing countries
  (hopefully we are not among them)

*Illegal sales by
  - pharmacies
  - drug stores
  - non-pharmaceutical businesses
    (without Rx)
    - happen locally!

*Misuse by patients
  - feels better; stop meds (not completing course)
    * pt. stop med @ 5 days (felt good); gave ½ of course to
      friend who did not feel better so sought another antibx!
  - “lost meds”
  - not follow-up as advised to ensure cure or improvement
  - sharing with family, friends
  - irrational use (HA, fever, pain, etc.)
  - lack of understanding and communication
    - doctor-patient; pharmacist-patient, doctor-pharmacy-patient, etc.
Antibiotic Resistance

(Con’t. Contributing Factors)

*Use of Counterfeit Medications* (a biggie)!

*medications with inactive, insufficient & wrong ingredients but labeled and packaged the same as real ones*

*a multibillion industry annually worldwide*

*exploded since the availability of online ordering (Internet)*

*estimated: 1 million deaths per year due to their use*

*(67% considered dangerous)*

*2015: 97% confiscated in USA from China, Honk Kong, India & Singapore *(lucky for them: FDA):*

**What about us????**

**Who protect our people against such fraud?**

* Dec. 18, 2015: Sanofi Study (6 SE Asian countries): 67% meds from China, Philippines, Thailand, Indonesia, Malaysia, & Vietnam


**(FFT) 2Qs:** *Where do we get ours and how do we know they are not among these 97% and 67% that are not real medications?*

*Is it o.k. to sacrifice the health of our fellow citizens on account of cost?*

**Note:** These countries do make real medications BUT, they also have makers that are counterfeiters
Antibiotic Resistance

What are the Resistant Bacteria now known?

(Was 17 + 1; now 17 + 3)

Three Categories of Threats Levels (CDC)

*Urgent Threats

*Serious Threats

*Concerning Threats

As of last month: 20!!!! (17 + 3)**

**U.S. Centers for Disease Control and Prevention News Release, Nov. 4, 2016
American Medical Association News: Nov. 7, 2016
Antibiotic Resistance

(17 + 3)

**Urgent Threats:**
- Clostridium difficile (CDIFF)
- Carbapenem-Resistant Enterobacteriaceae (CRE)
- Neisseria gonorrhea

**Serious Threats:**
- MDR Acinetobacter
- DR Campylobacter
- Aspergillus *
- Extended Spectrum Enterobacteriaceae (ESBL)
- Vancomycin-Resistant Enterococcus (VRE)
- MDR Pseudomonas Aeruginosa
- DR Non-Typhoidal Salmonella
- DR Salmonella Serotype Typhi
- DR Shigella
- Staphylococcus Aureus (MRSA)
- DR Streptococcus Pneumoniae
- MDR Tuberculosis
- Two Candida Species*

**Concerning Threats:**
- Vancomycin-Resistant Staphylococcus Aureus (VRSA)
- Erythromycin-Resistant Group A Streptococcus (ERGA)
- Clindamycin-Resistant Group B Streptococcus (CRGB)

*Fungi (Candida Auris: 13 cases in October 2016; 4 deaths); CDC, AMA & AAFP News Nov. 4, 2016*
ESTABLISHED (KNOWN) RESISTANT BACTERIA NOW (CDC)

KLEBSIELLA PNEUMONIAE
METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)*
CLOSTRIDIUM DEFICELE
EXTREMELY RESISTANT MYCOBACTERIM TUBERCULOSIS (XDR TB)*
DRUG RESISTANT NEISEIRIA GONORRHOEAE*
SHIGA TOXIN PRODUCING ESCHERICHIA COLI (STEC)
PENICILLIN RESISTANT STREP PNEUMONIAE (PRSP)
RESISTANT SYPHILLIS*
MULTIRESISTANT ACINETOBACTER
FLUCONAZOLE RESISTANT CANDIDA
BETA LACTAMASE RESISTANT ENTEROBACTERIAEAE
VANCOMYCIN RESISTANT ENTEROBACTERIAEAE
MULTIDRUG RESISTANT PSEUDOMONAS
DRUG RESISTANT SALMONELLA TYPHI & SHIGELLA
EES RESISTANT STREPTOCCUS GRP A
CLINDAMYCIN RESISTANT STREPTOCCUS GRP B
Carbapenem resistant Enterobactericea
DR Cambylobacter

MORE ON THE WAY!!!!!!!!!!!!!!!!!!!
Percentage of Staphylococcus aureus isolates that are methicillin resistant (MRSA), by country (most recent year, 2011–14)  

CDDEP 2015, WHO 2014 and PAHO
Antibiotic Resistance

Percentage of extended-spectrum beta-lactamase producing Escherichia coli*, by country (most recent year, 2011–2014) CDDEP 2015, WHO 2014 and PAHO
Antibiotic Resistance

K. pneumoniae carbapenem-resistant Klebsiella pneumoniae by country, 2015
Antibiotics for resistant bacteria

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<td>Vancomycin</td>
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Antibiotic Resistance

How serious is it?

*CDC Aug. 2016:

-Each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections.

*WHO/Medscape Nov. 4, 2016:

-All regions of the world are experiencing resistance to carbapenem antibiotics for treatment of Klebsiella pneumoniae.

-Resistance to fluoroquinolones, one of the most commonly used antibiotics for the treatment of Escherichia coli (caused urinary tract infections), is very widespread. Fluoroquinolones are now ineffective in more than half of patients in some countries.

-Third-generation cephalosporins, the last-resort treatment for gonorrhea, have been found to be ineffective in Austria, Australia, Canada, France, Japan, Norway, South Africa, Slovenia, Sweden, and the United Kingdom. At least 1 million people are infected with gonorrhea around the world every day.

WHO, Sept. 21, 2016

-Without urgent action, it is conceivable that simple infections could soon become entirely untreatable with existing drugs.

James Gallagher; Health, BBC Web Site Nov. 19, 2015

“A terrible future could be on the horizon, a future which rips one of the greatest tools of medicine out of the hands of doctors.”

*Keith Scott-Mumby MD, MB ChB, PhD:

The "Golden Age" Of Antibiotics Is Over! Deadly new organisms, resistant to all known antibiotics, are emerging all over the planet and gaining ground FAST...
“Without harmonized and immediate action on a global scale, the world is heading towards a post-antibiotic era in which common infections could once again kill”.

Dr. Margaret Chan, MD
Director-General, WHO; 2015
Antibiotic Resistance

What can be, need be, should be done?

(mua) Need to address the **contributing factors** and establish
Strategies to counter them.

*Overuse
*Misused & Irrational use by both physicians & patients
*Antibiotic Stewardship
*Dispensation by non-qualified individuals (quacks)
  *Illegal sales
  *Misuse by patients
*Use of unacceptable products (counterfeits & expired)
  *ulterior motives
Antibiotic Resistance

Some suggestions on how to improve or reverse contributing factors which in the long run might help:

• Education (basic health issues should be incorporated into curriculum, even at the Primary level)

• Community based health information can be done (news, community meetings, posters, patients’ handouts, etc.) on appropriate health issues)

• Laws and Regulations can be formulated to safeguard our citizens from fraud, illegal practices, and practices regarding proper medications procurement use and dispensation.

• Health Care Systems need to ensure prescribers are qualified to prescribe medications (e.g: Licensing Boards; Quality Assurance Committee, etc.)

• Ensure our laboratories are able to do tests for resistant microbes and maintain accessible records for prescribers use; inform prescribers on known resistant bacteria locally, regionally and internationally, etc.
(Antibiotic Resistance)
Suggestions for Prescribers

• Prescribe correctly
• Avoid treating viral syndromes with antibiotics, even when patients ask for them.
• Pay attention to dose and duration:
  – The right antibiotic needs to be prescribed at the right dose for the right duration.
• Be aware of antibiotic-resistance patterns in your area.
• Reassess (pt. follow-up) to ensure compliance & response
• Adjust the prescription, if necessary.
• Try to stay UP TO DATE on the latest clinical practice guidelines for infectious diseases.
• Talk to your patients about appropriate use of antibiotics.
• Include microbiology cultures, when possible, when ordering antibiotics.
• Work with pharmacists to ensure appropriate antibiotic use
• Make sure you are not prescribing counterfeit medications
• Embrace Antibiotic Stewardship
Some advises to patients

• Ask your healthcare professional if there are steps you can take to feel better and get symptomatic relief without using antibiotics.

• Take the prescribed antibiotic exactly as your healthcare professional tells you.

• Discard any leftovers.

• Never skip doses or stop taking an antibiotic early unless your healthcare professional tells you to do so.

• Never take an antibiotic for a viral infection (cold, flu, acute sinusitis, acute bronchitis, non-perulent conjunctivitis)

• Never pressure your healthcare professional to prescribe an antibiotic.

• Never save antibiotics for the next time you get sick.

• Never take antibiotics prescribed for someone else (don’t share)!
Antibiotic Resistance

Can a Post antibiotic Era be prevented?

Any Hope?

*There has been no new antibiotics and Classes since late 1980s! (until this year)

The number of resistant microbes are increasing!

Any Hope?
October 2016: Sydney University Study: Some antibiotic resistant “super bugs” including MRSA are killed by their milk! (work in progress)
Antibiotic Resistance
Help on the way?

**Lugdunin**

*Staphylococcus Lugdunensis:*

Kills MRSA

October 2016, *Health Radar*; Vol.6 Issue 10 (German Study)
Antibiotic Resistance

**Mursamacin**

A new antibiotic released by bacteria from a round worm
Kills MRSA

Presented during the “Falling Walls Scientific Conference”;
Munich, Germany; November 9, 2016

Dr. Ryan Musamba Awori, et al; Kenya
Summary

Antibiotic Resistance

1. History of Antibiotics and how they affect bacteria; Infectious Disease
2. Mechanisms of development & Contributing Factors to Resistance
3. Learn of the currently known Antibiotic Resistant Bacteria & Fungi
4. Consider the Seriousness and have a feel for the international situations
5. Mentioned possible strategies that can help and need to be done
6. Ponder the future with regards to Infectious Diseases, Treatment and the possibility of running out of antibiotics to manage bacterial infection: HEADING INTO A POST-ANTBIOTIC ERA:
   (déjà vu: Back to the pre-antibiotic era)?
7. Learn of possible upcoming help on the horizon (Cathelicidin, Lugdunin & Mursamucin)
“Antimicrobial resistance threatens the very core of modern medicine and the sustainability of an effective, global public health response to the enduring threat from infectious diseases. Effective antimicrobial drugs are prerequisites for both preventive and curative measures, protecting patients from potentially fatal diseases;.... Yet systematic misuse and overuse of these drugs in human medicine and food production have put every nation at risk.

Director-General, WHO; 2015

"We need to inform in different ways, all over the world, why it's crucial we stop treating our antibiotics like “sweets” or candies!

Lord Jim O'Neill (WHO Economist, Dec. 2015)
ANTIBIOTICS RESISTANCE

THANK YOU!

any questions?