Disclosure

- No reportable conflicts of interest
- This activity was not supported by any commercial or granting sources
Learning Objectives

- Understand the global threats of antimicrobial drug resistance (AMDR), including epidemiology and multi-drug resistance
- Explore the mechanisms responsible for the spread of AMDR
- Recognize and apply the principles of antibiotic drug stewardship, encompassing medical policies and practices to control the spread of AMDR
Outline

- Introduction and Historical Perspectives
- Etiology and Epidemiology
  - Incidence and Prevalence
  - Major Micro-organisms Resistant to Antibiotic Drugs
- Control and Prevention
  - Global Impacts of AMDR
  - Infections and Chronic Disorders
  - Infection Control
  - Environmental Contamination Management
  - Antibiotic drug pipeline
  - Policies and Standards
- Conclusions
  - Anti-Microbial Drug Stewardship
  - Guidelines and policy resources
Section 1

INTRODUCTION AND HISTORICAL PERSPECTIVES
WHO MR Day April 7, 2011

Statement by the Director General

“Antimicrobial resistance: no action today, no cure tomorrow.”

WMA Statement 2008

- The global increase in resistance to antimicrobial drugs, including the emergence of bacterial strains resistant to all available antibacterial agents, has created a multi-faceted public health problem of crisis proportions.
- AMDR carries significant economic and human implications.
- The development of resistant microorganisms is a problem whenever antimicrobial agents are used.
- The increase in high-risk populations who frequently require antimicrobial therapy has amplified the problem.
- Certain infectious diseases have been linked to the development of chronic disease and cancer adds another dimension to the problem.
4.3 billion years ago Archæobacteria appear

13,000 years ago

- First settlements and
domestication

1928

- Penicillin discovered by A. Fleming
- Mass production by Howard Florey, Norman Heathley and Ernst Chain

1944

- Penicillin mass manufactured by Pfizer

1950

- Emergence of microbial resistance to penicillin

1950 - 2001

- New epidemics and pandemics
- New classes of antibiotic drugs and new resistant strains

2001

- WHO expressing concerns
- US Concern: CDC begins the “Get Smart” educational campaign

2006

- ISMR, AMA and WMA fall summit sponsored by the GMU to update the AMDR policy

April 7, 2011 World Health Day is designated by WHO as the AMDR Day

“… the microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed on to other individuals and perhaps from there to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save. In such cases the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted.”

~ Sir Alexander Fleming, New York Times, June 26, 1945
Section 2

ETIOLOGY, EPIDEMIOLOGY, INCIDENCE AND MAJOR AMDR PATHOGENS
Statement of the Problem

- Prescribing Antibiotic Drugs
  - Misuse (inappropriate use)
  - Overuse (exceeding the standards of practice)
  - Over-the-counter availability (nonprescription dispensing)
  - Low-potency preparations (counterfeit or adulterated generic drugs)
  - Excessive and unregulated agricultural use
  - Patient expectations and attitudes

- Counterfeit drugs
  - Market value will reach USD 75 billion in 2010
  - Will account for 78% of the total consumption in developing countries
  - Will constitute half of all the antimalarial drugs sold in Southeast Asia
  - Antiparasite and antibiotic drugs are 2 to 10 times more frequently adulterated than other drugs
Etiology and Epidemiology

Etiology

- The 2000 EU hospital estimates of AMDR transmission:
  - Microorganisms naturally produce substances as defense against other pathogens and antibiotic drugs
  - Thirty percent to 40% of cases are linked to cross-infection by the hands of healthcare workers (HCW)
  - Twenty percent to 25% of cases are due to selective antimicrobial pressure
  - Twenty percent to 25% of patients suffer from new pathogen introduction
  - The remaining 20% of nosocomial infections are caused by the lack of proper control and oversight of antibiotic prescriptions
  - According to Who in 2010 only 26% of all countries adopted policies/guidelines to combat AMDR

Epidemiology

- AMDR carries more severe consequences in developing countries, and is promoted by the:
  - Careless use of antibiotics globally
  - Lack of adherence to the prescribed treatment regimen
  - Poor environmental hygiene and antibiotic use in agriculture or contamination of the food supply chain by antibiotics
  - Farmed and domesticated animals receiving preventive

Antibiotic Drugs and AMDR

AB Resistant Gene (s) Transfer

Bacteria + Antibiotics + Time = Resistance (MRSA)
Major AMDR Pathogens

- HA & CA-MRSA
- Pseudomonas aeruginosa
- Vancomycin-Resistant Enterococcus faecium
- Escherichia Coli
- Acinetobacter Baumannii

Source: CDC Public Health Image Library (PHIL)
Major AMDR Pathogens

- *Streptococcus pneumonia*
- Russian Influenza-A H1N1
- *Mycobacterium tuberculosis*
- HIV-1
- *Clostridium difficile*

*Source: CDC Public Health Image Library (PHIL)*
Factors Contributing to AMDR Development

1. Age of the individual
2. Nutritional deficiencies
3. Increased gastric pH
4. Compromised immune system
5. Broncho-pulmonary disorders interfering with sputum clearance
6. Invasive procedures or devices (such as orthopedic prostheses, indwelling catheters, or heart valves)
7. Intensive interventions such as hemodialysis, surgery, or catheterization
8. Drugs administered for chronic and/or debilitating diseases
## Summary of HA- and CA-MRSA Properties

<table>
<thead>
<tr>
<th>Epidemiology/Pathology</th>
<th>HA-MRSA (USA)</th>
<th>CA-MRSA (USA)</th>
<th>European Union HA-MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Age</strong></td>
<td>Adult and Seniors</td>
<td>Children and Youth</td>
<td>Adults and Seniors</td>
</tr>
<tr>
<td><strong>Infection Type</strong></td>
<td>SST 35%, causes sepsis &amp; toxic shock syndrome due to <em>Enterotoxin A</em></td>
<td>75% presenting as soft tissue infections (SST). Necrotizing fasciitis, pneumonitis, endocarditis, sepsis &amp; osteomyelitis are complications</td>
<td>Same as USA (in Japan a different strain with 13 specific virulence-associated genes)</td>
</tr>
<tr>
<td><strong>Colonization</strong></td>
<td>Infrequent</td>
<td>Frequent (20% of the population)</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Transmission mode</strong></td>
<td>Nosocomial, HCW</td>
<td>Close contact, poor hygiene practices, topical antibiotics</td>
<td>Similar to U.S.</td>
</tr>
<tr>
<td><strong>Strain Type</strong></td>
<td>USA 100 &amp; ST 36: USA 200</td>
<td>ST 8: USA 300 &amp; ST 1: 400</td>
<td>Similar to ST36: USA 200 (MRSA252)</td>
</tr>
<tr>
<td><strong>PLV toxin gene</strong></td>
<td>5%</td>
<td>100%</td>
<td>Variable (&gt;5%)</td>
</tr>
<tr>
<td><strong>Antibiotic resistance</strong></td>
<td>Primarily β-lactams &amp; cephalosporins</td>
<td><em>Erythromycin, clindamycin, others?</em></td>
<td>Primarily β-lactams &amp; cephalosporins</td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td>Estimated at &gt;4.5 cases/100 admissions</td>
<td>&gt; 25% of all soft tissue and skin infections, 20% nasal colonization</td>
<td>Countries with high antibiotic usage rates 25-50% (e.g. UK, Spain, Italy, Greece, Turkey, etc.)</td>
</tr>
</tbody>
</table>

*Note: version 2*
AMDR Surveillance Networks
(18 Global Epidemiology Data Sources on WWW)

Private Networks: The Alexander Project

- The Alexander Project was initiated by SmithKline Beecham Pharmaceuticals in 1992 and continued by Glaxo Smith Kline is the first international multi-center surveillance effort of community-acquired respiratory infections..
- The project defined standardized methods for the collection of isolates and determination of susceptibility
- Temporal trends in antimicrobial susceptibility of *H. influenza*, *Haemophilus parainfluenzae*, *S. pneumoniae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*.
- The project also includes comparisons of antimicrobial usage patterns and resistance prevalence over time (including measurements of MIC)

Examples of Government or WHO Sponsored Networks

- U.S. Centers for Disease Control and Prevention
- EU surveillance network ([www.rivm.nl/earss/](http://www.rivm.nl/earss/))
- Canada ([microbiology.mtsinai.on.ca](http://microbiology.mtsinai.on.ca))
- RedMiva
- UK
- Australia
- WHO
Example: Prevalence of *C. difficile* in the Environment

<table>
<thead>
<tr>
<th>Environment</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivers</td>
<td>80</td>
</tr>
<tr>
<td>Community Swimming Pools</td>
<td>50</td>
</tr>
<tr>
<td>Lakes</td>
<td>47</td>
</tr>
<tr>
<td>Sea water</td>
<td>44</td>
</tr>
<tr>
<td>Soil</td>
<td>21</td>
</tr>
<tr>
<td>Hospitals</td>
<td>20</td>
</tr>
<tr>
<td>Dogs</td>
<td>10</td>
</tr>
<tr>
<td>Raw Vegetables</td>
<td>2</td>
</tr>
<tr>
<td>Main Tap (potable water faucets)</td>
<td>2</td>
</tr>
<tr>
<td>Private Residences (individual homes)</td>
<td>2</td>
</tr>
<tr>
<td>Cats</td>
<td>2</td>
</tr>
</tbody>
</table>

Source: ISMR file version 2 17
Section 3

CONTROL AND PREVENTION
Antibiotic resistance is a major European and global public health problem and is, for a large part, driven by misuse of antibiotics,

Resistance in bacteria commonly responsible for infections such as *Escherichia coli* and *Klebsiella pneumoniae* has been increasing Europe-wide for all antimicrobial classes under surveillance,

Combined resistance to several antibiotics (multi-drug resistance) continues to increase in bacteria such as *Escherichia coli* and *Klebsiella pneumoniae*,

*Klebsiella pneumoniae*, resistance to last-line antibiotics, is now established in Greece, and is emerging in all other European countries.

The occurrence of methicillin-resistant *Staphylococcus aureus* (MRSA) – a multidrug-resistant bacteria – shows a decrease in some European countries, and

One third of EU countries are reporting that MRSA accounts for more than 25% of all *Staphylococcus aureus* invasive infections.

Many infections are now linked to the development of chronic disorders. It is suspected that microbial resistance will lead to an increase of such disorders in the aging world population, thus contributing to the rise of global health care costs.
Antibiotic Drugs Approval & Prescription Practices in US

Source: public.health.oregon.gov and U.S. Food and Drugs Administration version 2
Infection Control

Antibiotic Drug Availability

- Limited number of antibiotic drugs are in the development pipeline.
- The average cost for each new drug is in the range of USD 70 to 2 billion.
- Most of the antibiotic drugs entering the market are a modification of the already existing compounds.
- There is an early resistance development for each new antibiotic entering the market.

Control

- Personal and environmental hygiene
- Administer antibiotics only when indicated (includes the use of topical antibiotics)
- Pathogen culture and sensitivity testing should guide therapy (MIC levels)
- Prescreening all patients on admission for carrier status is controversial
- Adherence to treatment protocols and guidelines
Hospital “High Touch” Areas
(Environmental Control/Hygiene)

- Light switches
- Bed
- Bed rails
- Bedside table
- Over bed Table
- IV Pole
- IV Pump
- Television knobs remote controller
- Nurses call button
- Shower chair
- Commode Chair
- Carpeted areas
- Patient gowns
- Personal effects (razors, combs, toothbrushes and paste, make-up kits, etc.)
- Food containers and trays
- Medical equipment such as blood pressure cuffs, pulse oximeters
- Disposable cannisters with contaminated or soiled materials
- Commode buckets containing body fluids
Practices to Reduce AMDR Spread in Health Care Institutions

- Hand washing or alcohol-based rinses by staff between patients and before undertaking invasive procedures such as injections
- Use of barrier precautions, e.g., wearing gloves and gowns for procedures that might result in transmission of pathogens
- Adequate sterilization and disinfection of all supplies and equipment
- Use of sterile techniques, together with protocols, for medical and nursing procedures capable of bridging skin or mucosal membrane integrity such as: bladder catheterization, administration of injections, insertion of intravenous cannulas, use of respirators, sterilization of equipment, and other surgical interventions
- Maintenance of appropriate disinfection and sanitary control of the hospital environment, including:
- Adequate ventilation
- Cleaning of wards, operating theater, laundry, and other objects used by patients
- Provision of adequate water supply and sanitation
- Safe food handling
- Safe disposal of infectious equipment, e.g., dirty needles, body fluids, and other suspected contaminated materials
- Isolation of infected patients from non-infected patients, e.g., separation of suspected and proven sputum-positive TB cases (particularly from HIV-positive patients)
- Visiting policies, such as preventing visitors with infections from visiting patients who may be immunocompromised (for example, patients with AIDS or leukemia or premature babies)
- Training of healthcare staff in appropriate sterile techniques and infection control procedures
Patient Education

- Patients need knowledge to make informed decisions about how to prevent infection and reduce transmission of infectious diseases through simple, cheap and effective measures. Such measures include prevention of:
  - Diarrheal disease through hand washing, using safe water sources and containers, boiling unsafe water and using latrines
  - Malaria through the use of bed nets impregnated with insecticide
  - Sexually transmitted infections through the use of condoms
  - HIV/AIDS and hepatitis B and C through the avoidance of injections (unless oral medicines cannot be used, in which case a sterile needle and syringe must be used)
  - Benefits of vaccines to reduce morbidity and mortality

- Many organizations such as WHO, US CDC and Ministries of Health have developed resources for health care providers to distribute to their patients and communities they serve.
Section 4

CONCLUSIONS

AMDR GUIDELINES
WEB BASED RESOURCES
Conclusions

- About 70% of bacteria that cause infections in hospitals are resistant to at least one of the common antibiotics.
- Some organisms are resistant to all approved antibiotics and must be treated with experimental and potentially toxic drugs.
- Antibiotics are given to patients more often than called for in set guidelines.
- Premature discontinuation or early interruption of antibiotic therapy help the spread of resistant strains (example: MDR-TB).
- Combination therapy with 2 antibiotics prevents the emergence of resistant strains in contrast to sequential antibiotic therapy.
- Early initiation of antibiotics is among the most important factors for preventing the emergence of resistant strains.
The ABCD of Antibiotic Stewardship

1. **Antibiotic** formularies and restrictions

2. **Basic** environmental and physical hygiene

3. **Consistent** administrative policies and practices

4. **Dose optimization** and proper de-escalation therapy

version 2
Sources for Policies and Standards


