Anti-Microbial Drug Resistance
Center for the Study of International Medical Policies and Practices
Teaching Resource
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Disclosure

- No competing conflicts of interested
- Resources provided by CSIMPP/SPP
Learning Objectives

- Understand the global threats presented by the antimicrobial drug resistance (AMDR),
- Explore the mechanisms responsible for the global spread of AMDR, and
- Recognize and apply the principles of antibiotic drug stewardship and infection control.
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
Introduction

WHO AMDR 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.
Historical Perspectives

- **4.3 billion years ago** Archæbacteria appear on Earth

- **13,000 years ago**
  - First human settlements and domestications

- **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
  - Novel classes of antibiotic drugs discovered and followed by new resistant strains

- **2001**
  - WHO expressing concerns
  - CDC initiates 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
Antibiotic Drugs and AMDR

Antibiotic Resistant Gene (s) Transfer/Molecular Response and neutralizing indoles (persister cells)

Bacteria + Antibiotics + Time = Resistance

Acquired
Selected
From persisters

Update 2
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

Factors Contributing to AMDR Development

1. Age of the individual;
2. Poor or deficient nutritional status;
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 (invasive) such as hemodialysis, repeated catheterizations or surgical procedures; and
8. Drugs administered for chronic and/or debilitating diseases.
Contributing to the AMDR Problem(s)

Prescribing Practices

- 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 or Adulterated Drugs

- Market value reached USD 75 billion in 2010
- Primarily in developing countries
- Estimated at 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
- Distributed to large volume purchasing retail pharmacies and offered through internet outlets.
Examples

SELECT AMDR MICROORGANISMS
Major AMDR Pathogens

HA & CA-MRSA

Pseudomonas aeruginosa

Vancomycin-Resistant Enterococcus fecalium

Escherichia Coli

Acinetobacter Baumannii

Source: CDC Public Health Image Library (PHIL)

Update 2
Major AMDR Pathogens

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

Source: CDC Public Health Image Library (PHIL)
# 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 skin &amp;soft tissue infections (SST). Life-threatening necrotizing fasciitis, pneumonitis, endocarditis, sepsis &amp; osteomyelitis</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>Erythromycin, clindamycin, others?</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 (<a href="https://www.cdc.gov/mrsa/">global spread of USA300-1114</a>)</td>
<td>Countries with high antibiotic usage rates show 25-50% incidence (e.g. UK, Spain, Italy, Greece, Turkey, etc.)</td>
</tr>
</tbody>
</table>
Mobile drug-resistance genes with identical nucleic acid sequences carried by community-acquired multidrug-resistant *Escherichia coli* infections are increasingly dispersed worldwide.

The following bacteria were identified isolates:

- *E. coli* 44% (25% dfrA17-aadA5 integron gene cassette)
- *Klebsiella pneumoniae* 13%,
- *Pseudomonas aeruginosa*, 7%,
- *Enterobacter cloacae* 5%, and
- The remainder 24% comprised 26 different *GNB* species.

Extended-spectrum β-lactamase (ESBL) genes were found in 10% of *E. coli* isolates, and in nearly 40% of blood stream *E. coli* isolates in the study hospital.

A substantial proportion of BSI among hospitalized patients was caused by *E. coli* strains carrying drug-resistance genes that are dispersed globally.

*Gram-negative bacteria   **Blood Stream Infections*
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 Update 2
XDR-TB/TDR Tuberculosis
(Treatment/Control Failures)

<table>
<thead>
<tr>
<th>Country</th>
<th>First Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global emergence of MDR TB (1/2 million cases worldwide)</td>
<td>2006</td>
</tr>
<tr>
<td>China and India</td>
<td>2006 (1/4 million MDR TB)</td>
</tr>
<tr>
<td>Iran</td>
<td>2009</td>
</tr>
<tr>
<td>Poland</td>
<td>XMDR/TDR TB 2011</td>
</tr>
<tr>
<td>India</td>
<td>2011</td>
</tr>
<tr>
<td>Mumbai</td>
<td>2012</td>
</tr>
</tbody>
</table>
Section 3
CONTROL AND PREVENTION
Global Impacts of AMDR
(WHO/EU report April 7, 2011)

- 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.
Travel, Migrations, Mass Gatherings & Extreme Tourisms (2011)

Problem
- WTO reports > 900 million tourists crossing international borders
- > 10 million refugees
- > 300 million at religious and other events
- > 10 million extreme sports
- In 13% US foreign adoptions (>900)
- > 1.2 million medical tourists

Risks
- Spread of infections and AMDR too
- Bioterrorism
- Food poisoning
- Disasters and trauma

Control
- Surveillance
- Implement IHR guidelines
Antibiotic Drugs Approval by Federal Drugs Administration Prescription per Capita for US

Source: public.health.oregon.gov and U.S. Food and Drugs Administration

Update 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
- Screening for travelers returning from suspected areas of high prevalence of AMDR
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
EU Steps to Ban the Antibiotic Growth Promoters (AGP)

**Events**
- 1963-1965 epidemic of resistant *Salmonella typhimurium* in UK
- 1993 VRE reported in food of animal origin in UK
- 1997 WHO Berlin Meeting on the use of antibiotics in farming
- 1998 the Copenhagen
- 1999 EU Scientific Advisory Commission recommends phasing AGPs uses

**Bans and legislations**
- 1969 Swann Committee recommends differentiation between feed additives and therapeutic uses (UK)
- 1972-74 European ban on use of penicillin, tetracycline and streptomycin
- 1988 Sweden stops all uses of AGP
- 1994 Denmark institutes bans and limits profits from antibiotic sales by veterinarians
- 1995 Sweden and Finland lobby EU for adopting a universal ban
- 1990 US Congress passes Organic Food Act (Title XXI Farm Bill)
- 1999 EARS established
- 2000 WHO passes a resolution on health and international food trade
- 2006 EU ban all AGPs
- 2008 EU establishes ESVAC
- (2011 US Government Accounting Office Report and recommendations issued to the US Congress)
- 2012 FDA announces a directive for voluntary restricting of AGP uses
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
AMDR Surveillance and Resource Networks
(Falagas ME: World Wide Web Resources on Antimicrobial Resistance)

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 Major Surveillance Networks

- U.S. Centers for Disease Control and Prevention (www.cdc.gov/drugresistance/surveillance.html)
- EU surveillance network (www.rivm.nl/earss/)
- Canada (microbiology.mtsinai.on.ca)
- RedMiva of Spain (www.csisp.gva.es/web/si/redmiva)
- WHO (http://rhone.b3e.jussieu.fr/arinfobank/)
Sources for Policies and Standards


