Workshop #7
Drug Resistant Infectious Agents

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Review Workshop #6
- Varicella
- Hep A
- Hep B
- Mononucleosis
- Legionella
- Norwalk Virus
- West Nile Virus

Workshop #7 Objectives
- The learner will be able to:
  - Describe multiple-drug resistant (MDR) infectious agents (IA).
  - Discuss prevention of MDR IA.
  - Differentiate modes of transmission of MDR IA.
  - List incubation period of MDR IA.
  - Describe laboratory testing for MDR IA.
  - Describe management of consumer/staff with MDR IA.
What is drug resistance?

Ability of bacteria, viruses, parasites or fungi to grow in the presence of a drug that would normally kill it or limit its growth.
History of Antibiotics

- Prior to 1928 antibiotics did not exist
- Scottish scientist Alexander Fleming coined name “antibiotic”
- Literally means “kills living organisms”
- Antibiotic came into wide-spread use during WWII
- saved countless lives
- blunted serious complications of many feared diseases and infections

Development of drug resistance

- Microbes evolve and adapt to their environment
- Evolve rapidly and adapt quickly
- Change genetic structure to deal with adversities
- Ensures off spring are also resistant

Gene transfer

Microbes can also get genes from each other, including genes that make them drug resistant
In 2009, research showed that many antibiotic-resistant genes and toxins are bundled and transferred together from one bacteria to another. Process thought to speed the development of toxic and resistant strains.

Causes of drug resistance:
- Selective pressure
- Societal pressures
- Inappropriate use of antibiotics
- Inadequate diagnostics
- Hospital use of antibiotics
- Agricultural use of antibiotics
Selective Pressure

- any phenomena which alters the behavior and fitness of living organisms within a given environment.
- driving force of evolution and natural selection,
- two types of pressure:
  - Biotic pressure: living organisms within the same ecosystem that interact with the affected organism.
  - Abiotic pressure: non-living factors within the organism's environment, such as light, wind, and soil.
- All of these factors interact with the organism to provide opposition to its continued survival.
- lead over time to selection of favorable characteristics which give the organisms that possess those favorable features an advantage
- “survival of the fittest”

Societal Pressure

- Patients and/or caregivers pressuring health care providers to prescribe antibiotics even if they are not indicated.
- Advertising the need to use “antibacterial” products for routine cleaning tasks
Inappropriate use of Antibiotics

- The most direct contributor to resistance is the overuse of antibiotics
- Unnecessary use of antibiotics by humans
- Use in animal feeds in low doses
- Availability over-the-counter in many countries
- Patient failure to follow prescribed course of treatment
- Antibiotic application in agriculture, aquaria and family pets

Inadequate diagnostics

- Most of the commonly used diagnostic methods, such as cultivation of the agent ex vivo or detection of specific antibodies, are slow or insensitive or lack sufficient specificity.
- In about 55% of cases do doctors know what strain of bacteria is causing a person’s meningitis, septicemia or pneumonia.
- MDs cannot afford to wait for pathological laboratory results.
- Need to use their clinical judgment and experience.
- Prescribe one or more broad-spectrum antimicrobial until they are sure
- Contribute to selective pressure and accelerate antimicrobial resistance.

Hospital Use of Antibiotics

- Critically ill patients are more susceptible to infections
- The heavier use of antimicrobials in these patients can worsen resistance by selecting for antimicrobial-resistant microorganisms.
- Use of antimicrobials and close contact among sick patients creates a fertile environment for the spread of antimicrobial-resistant germs.
MDR Infectious Agents

- MDR Infectious Agents to be covered:
  - Methicillin resistant Staph aureus (MRSA)
  - Vancomycin resistant Staph epidermidis (VRSE)
  - Vancomycin resistant enterococcus (VRE)
  - Clostridium difficile (C. diff)
  - MDR/XDR Mycobacterium Tuberculosis

Methicillin resistant Staphylococcus aureus

Methicillin resistant Staph aureus (MRSA)

- Identification: Methicillin-resistant Staph aureus; and other common antibiotics: amoxicillin, oxacillin and pencillin.
- Laboratory Testing: culture & sensitivity
- Reservoir: Humans. Persons at risk include patients in non-hospital settings, nursing homes and long term care facilities. Persons with MRSA are protected by ADA.
MRSA

- MRSA was first noted in 1961
- One of the most common MDRO in non-hospital settings
- resistance to methicillin due to a penicillin-binding protein coded for by a mobile genetic element termed the methicillin-resistant gene (mecA)

MRSA – A “superbug?”

- Currently resistant to several different antibiotics
  - penicillin,
  - Oxacillin
  - Amoxicillin (Amoxil, Dispermox, Trimox).
- Hospital acquired MRSA (HA-MRSA) often also resistant to
  - tetracycline (Sumycin),
  - erythromycin (E-Mycin, Eryc, Ery-Tab, PCE, Pedialyte, Ilosone),
  - clindamycin (Cleocin).
- Sometimes termed a "superbug" because of its ability to become resistant to several antibiotics.
Transmission

- Direct skin-to-skin contact with:
  - Person with MRSA or is a carrier
  - Fomites (door handles, floors, sinks, or towels, wrestling mats other exercise/sports equipment
- Requires break in skin integrity:
  - cuts,
  - abrasions,
  - Skin conditions that cause break in skin integrity such as psoriasis
- Airborne droplets from persons with pneumonia due to MRSA

Person at Risk

- Those with obvious skin breaks
  - surgical or traumatic wounds
  - intravenous lines
  - burns
  - skin ulcers
- People with depressed immune systems
  - infants
  - the elderly
  - Persons on corticosteroid medications
  - HIV-infected individuals
- Persons with chronic diseases (diabetes or cancer).

S/S OF MRSA

- Most are skin infections
  - Impetigo a skin infection mainly on the face, legs and arms
Cellulitis
a skin infection caused mainly by the bacteria staphylococcus and streptococcus.

Carbunkle infections are a cluster of boils.

Boil: bacterial infection of the skin (usually staphylococcus aureus) due to a hair follicle becoming infected. They are generally red, painful, pus-filled bumps on the face, neck, back, legs, and buttocks.

Carbuncles is the name given to a cluster of boils and carbuncles are due to a hair follicle becoming infected with bacteria, usually staphylococcus aureus.

Abscess: localized collection of pus in any part of the body that is surrounded by swelling (inflammation).
**Sty**

An acute infection of the secretory glands of the eye

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**Systemic MRSA**

- Occasionally the skin infection can spread to almost any other organ in the body.
- More severe s/s of systemic MRSA:
  - Fever,
  - chills,
  - low blood pressure,
  - joint pains,
  - severe headaches,
  - shortness of breath, and
  - "rash over most of the body"
- Require immediate medical attention, especially when associated with skin infections.

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**Complications of MRSA**

- Complications of severe CA-MRSA and HA-MRSA infections:
  - endocarditis
  - necrotizing fasciitis
  - osteomyelitis
  - sepsis
  - death may occur.
Prevention of Transmission

- Avoid direct contact with skin, clothing, and any items that come in contact with either MRSA patients or MRSA carriers
- Cover any skin breaks
- Use meticulous hygiene practices, especially hand washing

Colonization vs. Infection:

- Colonization = organism is present in or on the body but is not causing illness.
- Infection = organism is present and is causing illness.
MRSA

- Treatment: Standard precautions should be used for all consumer care.
- In addition, contact precautions may be adapted if needed.
- Consumer placement-private room. If not available; place with another consumer who is colonized or infected with the same organism (cohorting).

MRSA

- Treatment: Group activities-colonized or infected person can participate in group meals and activities if wounds are covered, body fluids are contained. Consumers need to observe good hygienic practices.
- Caregivers should wash hands w/ soap and H2O after physical contact with colonized or infected persons.
- Towels only used only once.
- PPE worn for contact w/ body fluids.
- Linens changed or washed.

Vancomycin Resistant Staph epidermidis (VRSE)

Staph epidermidis
VRSE

- normal resident of the skin, the gut and upper respiratory tract
- opportunistic pathogen, requires a major breach in the host's defenses to establish infection
- Usually hospital-acquired
- major importance in the development of foley catheter related urinary tract infections in women in hospitals

Contributing factor to resistance may be that some antibiotics can be secreted in sweat, so the normal flora is routinely exposed to them.

- Major virulence factor: ability to form biofilms (viscous slime) on plastic devices
- One probable cause: surface proteins that bind blood and extracellular matrix proteins.
- S. epidermidis capsule, known as polysaccharide intercellular adhesion (PIA), sulfated polysaccharide allows other bacteria to bind to the already existing biofilm.
- Creates a multilayer biofilm.
- Such biofilms impair diffusion of antibiotics inhibiting them from effectively clearing infection.

Vancomycin resistant Staph epidermidis (VRSE)

- Identification: public health concern r/t Van A gene. It can be transferred in vitro from enterococci to a variety of Gram + organisms including
  - Staph aureous
  - Staph epidermidis
  - Staph heamolyticus
- Lab testing: culture & sensitivity
- Reservoir: Humans
modes of transmission: contact with a person who either has a purulent lesion or discharge or is an asymptomatic carrier, (usually nasal).
- 20% to 30% of the general population are nasal carriers of S. aureus and S. epidermidis
- airborne spread is rare
- transmission via contaminated surfaces has been documented

Incubation Period 4-10 days
- In localized skin infections: systemic antibiotics are not indicated
- Local skin cleaning followed by the application of an appropriate topical antimicrobial agent is adequate.
- Avoid hot wet compresses which may spread infection
- hot dry compresses may help localize infections.
- Abscesses should be incised to permit drainage of pus

Prevention:
- Use gloves when having contact with infected area or dressings.
- Place all contaminated articles in a plastic or leak proof bag prior to
- Wash hands with an antimicrobial lotion soap.
- If soap and water are not available, the use of an alcohol gel or foam may be used followed by hand washing as soon thereafter as possible.
- Clean and disinfect person’s immediate surroundings as well as commonly touched surfaces.
- Dedicated equipment
Vancomycin-resistant enterococci

Identification: Enterococci found in intestines and female genital tract. Enterococci become resistant to antibiotics with inappropriate use.

Lab testing: culture & sensitivity

Reservoir: Humans
VRE

- First identified in the 1984
- First case in the US in 1989
- Most common type of infection acquired by hospitalized persons
- According to the CDC in 2004, VRE caused about one of every three infections in hospital intensive-care units
- In 2007 scientists confirmed the transfer of a key antibiotic resistance gene from Enterococcus to Staphylococcus.

Enterococci

- can survive for months
- primarily resides in the human digestive system and the female genital tract;
- make up a significant part of the normal bacterial population of these sites in healthy people
- Of more than a dozen forms of enterococci bacteria, two are the primary concern for human disease: E. faecium and E. faecalis.
- E. faecium is the most frequent species of VRE found in hospitals.

Transmission

- Person to person most commonly by healthcare workers whose hands have inadvertently become contaminated from
  - feces
  - Urine
  - Blood
- Indirectly via hand contact with open wounds or by touching contaminated environmental surfaces,
- Bacterium can survive for weeks on fomites
- Rarely if ever transmitted through the air
Persons at Risk

- Risk factors for progression for colonization to infection:
  - Previous treatment with vancomycin and/or combinations of other antibiotics, such as penicillin and gentamicin
  - Chronic diseases, including diabetes
  - Hospitalization, particularly if antibiotic treatment for long periods of time
  - Weakened immune system, such as person with cancer
  - Stays in intensive-care units or transplant wards
  - Surgical procedures, such as abdominal or chest surgery
  - Medical devices that stay in for some time, such as urinary catheters or central intravenous catheters
  - Residence in long-term care facilities and skilled nursing homes

VRE

- Modes of Transmission: Spread by hands person-to-person and by touching contaminated surfaces.
- 2007- 1/8 hospital infection-enterococci-30% VRE.
- Prevention: Hand washing!
- Treatment: colonized persons—but no s/s—no treatment. Std precautions
- S/S illness treatment with antibiotics other than vancomycin.

S/S OF VRE

- Depends on site of infection
- Skin: red, warm, tender
- Urinary tract: back pain, burning on urination, frequency
- Blood: Weakness, fever, chills
Prevention of transmission

- Meticulous handwashing
- Frequently clean areas such as the bathroom that may become contaminated with VRE
- Wear gloves when in contact with body fluids that may contain VRE, such as stool or bandages from infected wounds.
- Persons colonized or infected with VRE should wash his/her hands after any personal hygiene activities and prior to leaving his/her room for group activities

Clostridium difficile

Identification: spore-forming, Gram + anaerobic bacteria which makes 2 exotoxins; toxin A and toxin B. Common cause of antibiotic associated diarrhea (15-25%).
S/S watery diarrhea, fever, anorexia N/V. Characteristic smell.
Complications: pseudomembranous colitis, toxic megacolon, colon perforation, sepsis, shock, death.
Clostridium difficile

- Also called *C. difficile* or *C. Diff* for short
- First linked to disease in 1978
- Gram positive motile bacteria of the *clostridium* genus
- Anaerobic (in the absence of oxygen)
- Spore-forming rods (bacillus)
- Ubiquitous in nature and are especially prevalent in soil
- Naturally reside in the body

*C difficile* toxins found in the stool of 15% to 25% of patients with antibiotic-associated diarrhea

- Found in more than 95% of persons with pseudomembranous colitis

How it causes disease

- Normal flora of intestine must be disrupted
- *C. diff* ingested
- Toxins essential for development of disease Toxins A and B
- New strain- NAP-1- produces 16 times more A and 23 times more B
- NAP-1 also produces third toxin-binary toxin
*Clostridium difficile* is spread via the fecal-oral route. The organism is ingested either as the vegetative form or as hardy spores, which can survive for long periods in the environment and can tolerate the acidic stomach.

In the small intestine, spores germinate into the vegetative form. Toxin A attracts neutrophils and monocytes, and toxin B degrades the colonic epithelial cells, both leading to colitis, pseudomembrane formation, and watery diarrhea.

*C difficile* reproduces in the intestinal crypts, releasing toxins A and B, causing severe inflammation. Mucous and cellular debris are expelled, leading to the formation of pseudomembrane.

In the large intestine, *C difficile*-associated disease can arise if the normal flora has been disrupted by antibiotic therapy.

Toxin A attracts neutrophils and monocytes, and toxin B degrades the colonic epithelial cells, both leading to colitis, pseudomembrane formation, and watery diarrhea.

### Persons at risk
- People on antibiotic therapy
  - >90% of *C.Diff* infections occur after or during antimicrobial therapy
  - All antimicrobials except aminoglycosides (generic ends in –cin)
  - Broad spectrum antimicrobials and fluoroquinolones (generic ends in –floxacin) more likely to cause CDAD
  - Increased risk if on multiple antimicrobials and longer duration of treatment

### Other risk factors
- Age great than 65
- Severe underlying disease
- Nasogastric intubation
- Antiulcer medications
- Longer hospital stays
- Most common cause of acute diarrheal illness in LTC facilities
C. difficile

Transmission: Fecal-oral direct contact via hands or surfaces contaminated with C. diff.

- Lab tests: Stool culture & sensitivity.
  - Antigen detection via immunochromatographs assays.
  - Toxin testing enzyme immunoassay detects Toxin A and B.
  - Tissue culture for Toxin B.

S/S of C. Diff

- Continuum from asymptomatic up to fulminant colitis
- Mild disease:
  - Non-bloody diarrhea
  - Sometimes low abdominal cramping
  - Mild abdominal tenderness
  - Systemic symptoms absent

S/S of C. Diff

- Mild disease can progress to severe disease quickly
- Moderate disease:
  - Fever
  - Profuse diarrhea
  - Abdominal pain
  - Leukocytosis
- Severe disease
  - Sepsis
  - Volume depletion electrolyte imbalance
  - Hypotension
  - Peritonitis
  - WBC over 20 x 10^9/L
  - Elevated creatinine
Complications

- Severe diarrhea
- Pseudomembranous colitis
- Toxic megacolon
- Colonic perforation
- Sepsis
- Death

Pseudomembranous colitis

[Images of pseudomembranous colitis]

[Images of pseudomembranous colitis]

[Images of pseudomembranous colitis]
Toxic megacolon

Mark W. Hull, MD; Paul L. Beck, MD, PhD, FRCP(C), Gastroenterology and Hepatology

• Bowel wall thickening
• Loss of haustral markings (thin arrow)
• Dilation of the ascending and transverse colon (thick arrow);

Recurrence

- 12-24% will have second episode within 2 months
  - Relapse: recurrence within 2 months
  - Reinfection: recurrence after 2 months
  - However: 48-5% within 2 months have a different strain of C. Diff
  - Two or more episodes increases risk for recurrences to 50-65%

Accessed June 15th, 2009
Treatment

- Stop inciting antibiotic
  - 25% recover without further treatment
- Oral metronidazole for mild disease
  - 10 day regime
  - 97% effective
- Vancomycin for severe disease
- Avoid antiperistaltic agents
- Do NOT treat asymptomatic colonization.

Prevention

- Contact precautions
  - Vigilant handwashing with soap and water
  - Alcohol NOT effective in killing *C. Diff* spores
- Bleach for environmental disinfection
  - Spores highly resistant to routine disinfectants
  - Spores survive many weeks or months on dry surfaces
  - Particular attention to high touch areas, especially in bathrooms
  - dedication of single-use items when possible

Multidrug Resistant TB
MDR/XDR M. Tuberculosis
- Identification: Multidrug resistant (MDR) M. TB bacteria that become resistant to first line of anti-TB medications: isoniazid and rifampin.
- Extensively drug resistant (XDR) M. TB bacteria that become resistant to first line meds and any fluoroquinoline and at least 1/3 injectable second line medications.

MDR/XDR Mycobacterium TB
First line medications:
- Isoniazid
- Rifapentine
- Rifampin
- Ethambutol
- Rifabutin
- Pyrazinamide

MDR/XDR M. TB
- Second line Medications:
  - Aminoglycosides (IV)
    - Amikacin* # second line = XDR
    - Kanamycin* #
    - capreomycin
  - Fluoroquinolones (oral/IV)
    - Moxifloxacin*#
    - Gatifloxacin*# * not FDA approved
    - Levofoxacin*# for TB treatment
MDR/XDR M. TB

- Second line medications:
  - Capreomycin (IV) #
  - Ethionamide (oral)
  - Cycloserine (oral)
  - Para-aminosalicylic acid (oral)
  - Linezolid (oral/IV)

Multidrug Resistant TB

- During the early 1990s, nosocomial outbreaks (characterized by delayed diagnosis and inadequate treatment regimens) contributed to rising rates of MDRTB in New York City (NYC) and elsewhere in the United States.
- emerged from the mismanagement of multidrug-resistant TB (MDR-TB).

Transmission

- XDR-TB is spread through the air
- The spread of TB bacteria depends on factors such as:
  - the number and concentration of infectious people in any one place
  - the presence of people with a higher risk of being infected (such as those with HIV/AIDS)
  - the length of time that a previously uninfected person spends in the same room as the infectious case
  - closed environments like overcrowded houses, hospitals or prisons
  - the risk will be further increased if ventilation is poor.
Diagnosis

- cultures cannot distinguish between drug-susceptible and drug-resistant TB
- To evaluate drug susceptibility, the bacteria need to be cultivated and tested in a suitable laboratory. Final diagnosis in this way for TB, and especially for XDR-TB, may take from 6 to 16 weeks.[6] To reduce the time needed for diagnosis, new tools for rapid TB diagnosis are urgently needed.

Treatment

- requires extensive chemotherapy for up to two years.
- People are often hospitalized for long periods in isolation.
- XDR-TB is associated with a much higher mortality rate than MDR-TB, because of a reduced number of effective treatment options.
- Mortality rate of up to 80%
- Successful outcomes depend on a number of factors including
  - the extent of the drug resistance,
  - the severity of the disease
  - how many drugs the patient is given (patients treated with five or more drugs do better),
  - Whether an injectable drug is given or not (it should be given for the first three months at least),
  - The expertise and experience of the physician responsible,
  - How co-operative the patient is with treatment (treatment is arduous and long, and requires persistence and determination on the part of the patient),
  - Whether the patient is HIV positive or not (HIV coinfection is associated with an increased mortality).

MDR/XDR M. TB

- MDR treatment more expensive and less tolerated or not available.
- CDC 2006- 2% M. TB = MDR.
- XDR M. TB more worldwide
Questions?