Use of Antibiotics and its stewardship

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Objectives:

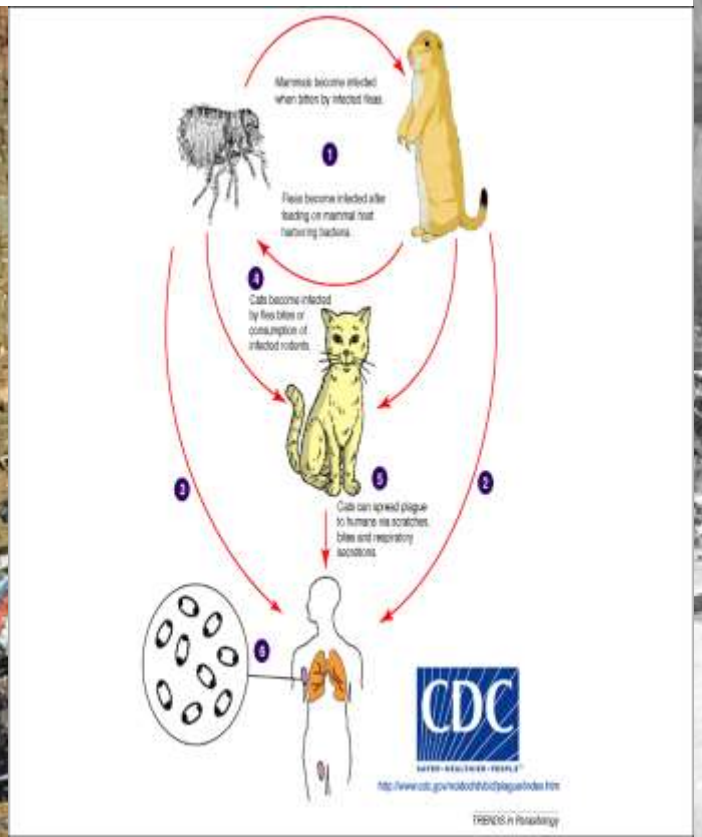
- By the end of the lecture the student should be able to:

1. The different classes of Antibiotics.
2. Learn when to use antibiotics.
3. To monitor antibiotics response and toxicity.
4. To know the impact of antibiotics misuse and the importance of stewardship.

Introduction

- Whey we should know about Antibiotics ?

The first recorded pandemic, the Justinian Plague, was named after the 6th century Byzantine emperor Justinian I. The Justinian Plague began in 541 AD and was followed by frequent outbreaks over the next two hundred years that eventually killed over 25 million people (Rosen, 2007) and affected much of the Mediterranean basin–virtually all of the known world at that time.



WW1

1914-1918

Hx

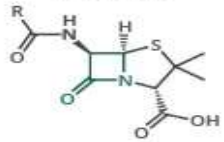
- discovery of the therapeutic value of penicillin by Alexander Fleming from *Penicillium notatum* in 1928.

DIFFERENT CLASSES OF ANTIBIOTICS - AN OVERVIEW

Key: COMMONLY ACT AS BACTERIOSTATIC AGENTS, RESTRICTING GROWTH & REPRODUCTION — COMMONLY ACT AS BACTERICIDAL AGENTS, CAUSING BACTERIAL CELL DEATH

ß-LACTAMS

MOST WIDELY USED ANTIBIOTICS IN THE NHS



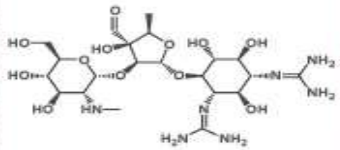
All contain a beta-lactam ring

EXAMPLES
Penicillins (shown) such as amoxicillin and flucloxacillin; *Cephalosporins* such as cefalexin.

MODE OF ACTION
Inhibit bacteria cell wall biosynthesis.

AMINOGLYCOSIDES

FAMILY OF OVER 20 ANTIBIOTICS



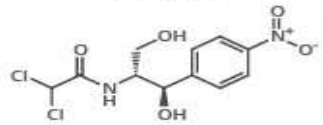
All contain aminosugar substructures

EXAMPLES
Streptomycin (shown), neomycin, kanamycin, paromomycin.

MODE OF ACTION
Inhibit the synthesis of proteins by bacteria, leading to cell death.

CHLORAMPHENICOL

COMMONLY USED IN LOW INCOME COUNTRIES



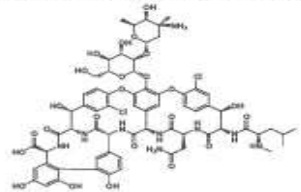
Distinct individual compound

MODE OF ACTION
Inhibits synthesis of proteins, preventing growth.

No longer a first line drug in any developed nation (except for conjunctivitis) due to increased resistance and worries about safety.

GLYCOPEPTIDES

COMMON 'DRUGS OF LAST RESORT'



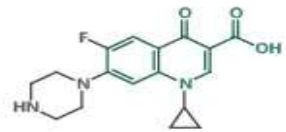
Consist of carbohydrate linked to a peptide formed of amino acids

EXAMPLES
Vancomycin (shown), teicoplanin.

MODE OF ACTION
Inhibit bacteria cell wall biosynthesis.

QUINOLONES

RESISTANCE EVOLVES RAPIDLY



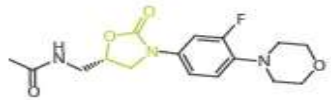
All contain fused aromatic rings with a carboxylic acid group attached

EXAMPLES
Ciprofloxacin (shown), levofloxacin, trovafloxacin.

MODE OF ACTION
Interfere with bacteria DNA replication and transcription.

OXAZOLIDINONES

POTENT ANTIBIOTICS COMMONLY USED AS 'DRUGS OF LAST RESORT'



All contain 2-oxazolidone somewhere in their structure

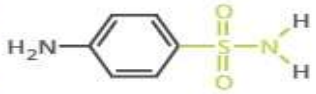
EXAMPLES
Linezolid (shown), posizolid, tedizolid, cycloserine.

MODE OF ACTION
Inhibit synthesis of proteins by bacteria, preventing growth.

DISCOVERY — 1930 — 1940 — 1950 — 1960 — 1970 — 1980

SULFONAMIDES

FIRST COMMERCIAL ANTIBIOTICS WERE SULFONAMIDES



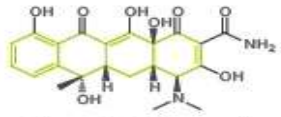
All contain the sulfonamide group

EXAMPLES
Prontosil, sulfanilamide (shown), sulfadiazine, sulfisoxazole.

MODE OF ACTION
Do not kill bacteria but prevent their growth and multiplication. Cause allergic reactions in some patients.

TETRACYCLINES

BECOMING LESS POPULAR DUE TO DEVELOPMENT OF RESISTANCE



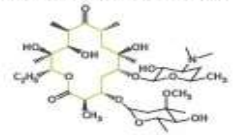
All contain 4 adjacent cyclic hydrocarbon rings

EXAMPLES
Tetracycline (shown), doxycycline, limecycline, oxytetracycline.

MODE OF ACTION
Inhibit synthesis of proteins by bacteria, preventing growth.

MACROLIDES

SECOND MOST PRESCRIBED ANTIBIOTICS IN THE NHS



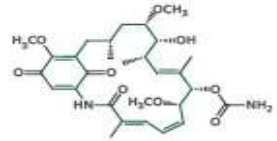
All contain a 14-, 15-, or 16-membered macrolide ring

EXAMPLES
Erythromycin (shown), clarithromycin, azithromycin.

MODE OF ACTION
Inhibit protein synthesis by bacteria, occasionally leading to cell death.

ANSAMYCINS

CAN ALSO DEMONSTRATE ANTIVIRAL ACTIVITY



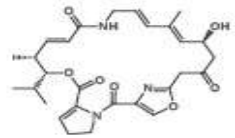
All contain an aromatic ring bridged by an aliphatic chain.

EXAMPLES
Geldanamycin (shown), rifamycin, naphthomycin.

MODE OF ACTION
Inhibit the synthesis of RNA by bacteria, leading to cell death.

STREPTOGRAMINS

TWO GROUPS OF ANTIBIOTICS THAT ACT SYNERGISTICALLY



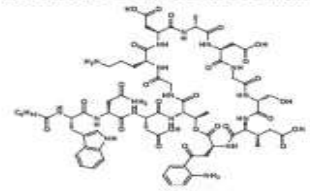
Combination of two structurally differing compounds, from groups denoted A & B

EXAMPLES
Pristinamycin IIA (shown), Pristinamycin IA.

MODE OF ACTION
Inhibit the synthesis of proteins by bacteria, leading to cell death.

LIPOPEPTIDES

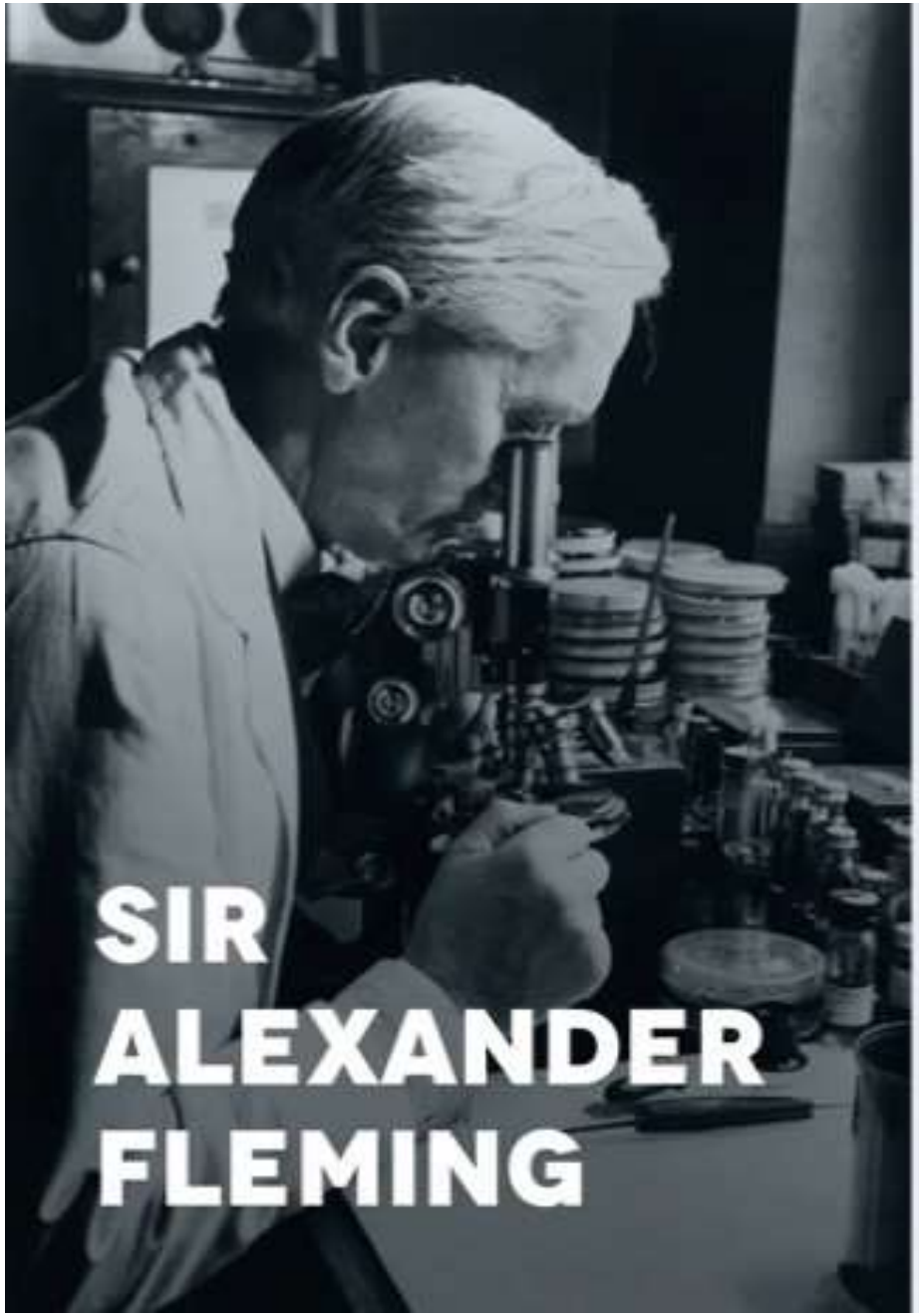
INSTANCES OF RESISTANCE RARE



All contain a lipid bonded to a peptide

EXAMPLES
Daptomycin (shown), surfactin.

MODE OF ACTION
Disrupt multiple cell membrane functions, leading to cell death.



The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism.

Developing Resistance

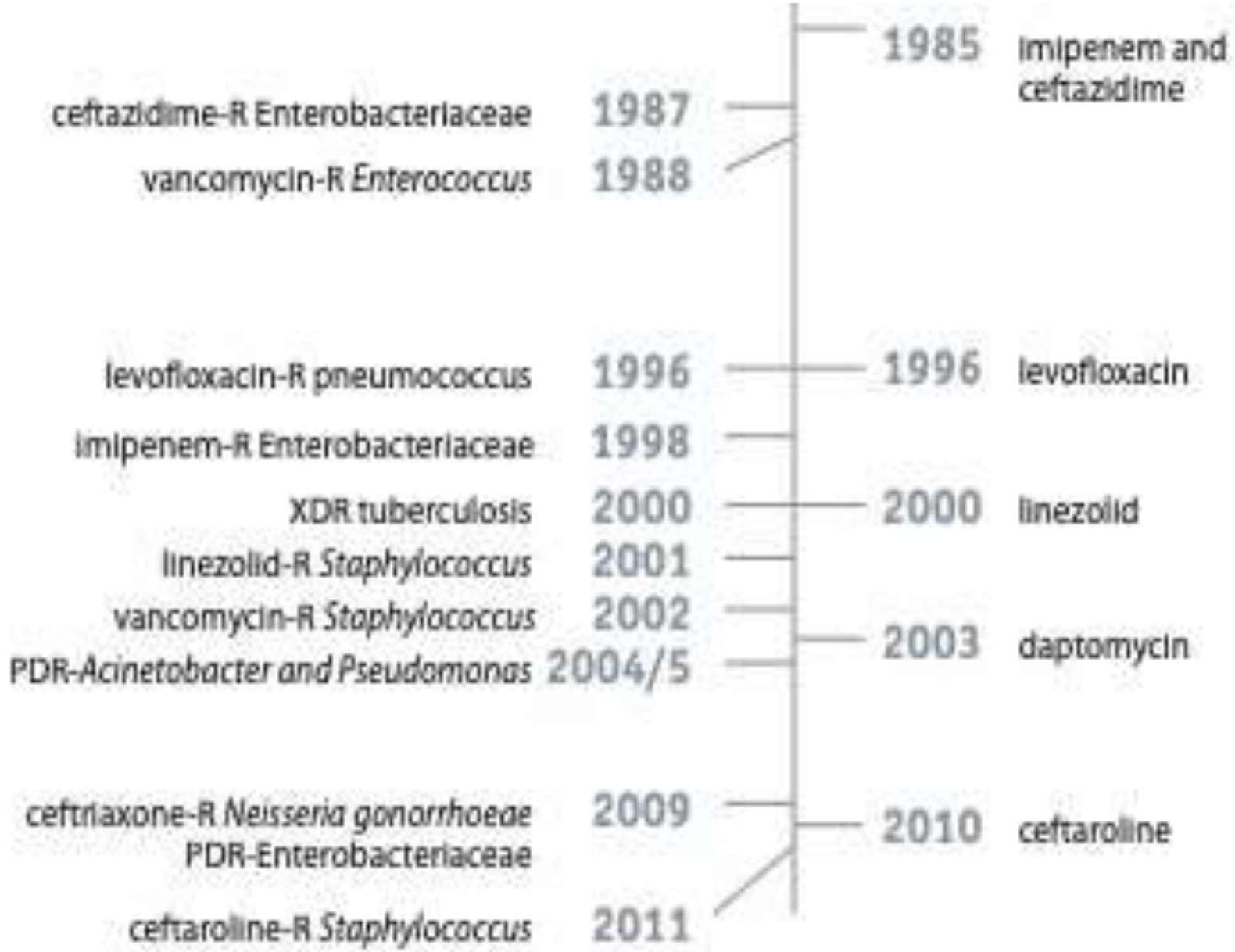
Timeline of Key Antibiotic Resistance Events

Dates are based upon early reports of resistance in the literature. In the case of pan drug-resistant (PDR)-*Acinetobacter* and *Pseudomonas*, the date is based upon reports of healthcare transmission or outbreaks. Note: penicillin was in limited use prior to widespread population usage in 1943.

ANTIBIOTIC RESISTANCE INDENTIFIED		ANTIBIOTIC INTRODUCED	
penicillin-R *Staphylococcus*	1940		
		1943	penicillin
		1950	tetracycline
		1953	erythromycin
tetracycline-R *Shigella*	1959		
		1960	methicillin
methicillin-R *Staphylococcus*	1962		
penicillin-R pneumococcus	1965		
		1967	gentamicin
erythromycin-R *Streptococcus*	1968		
		1972	vancomycin
gentamicin-R *Enterococcus*	1979		

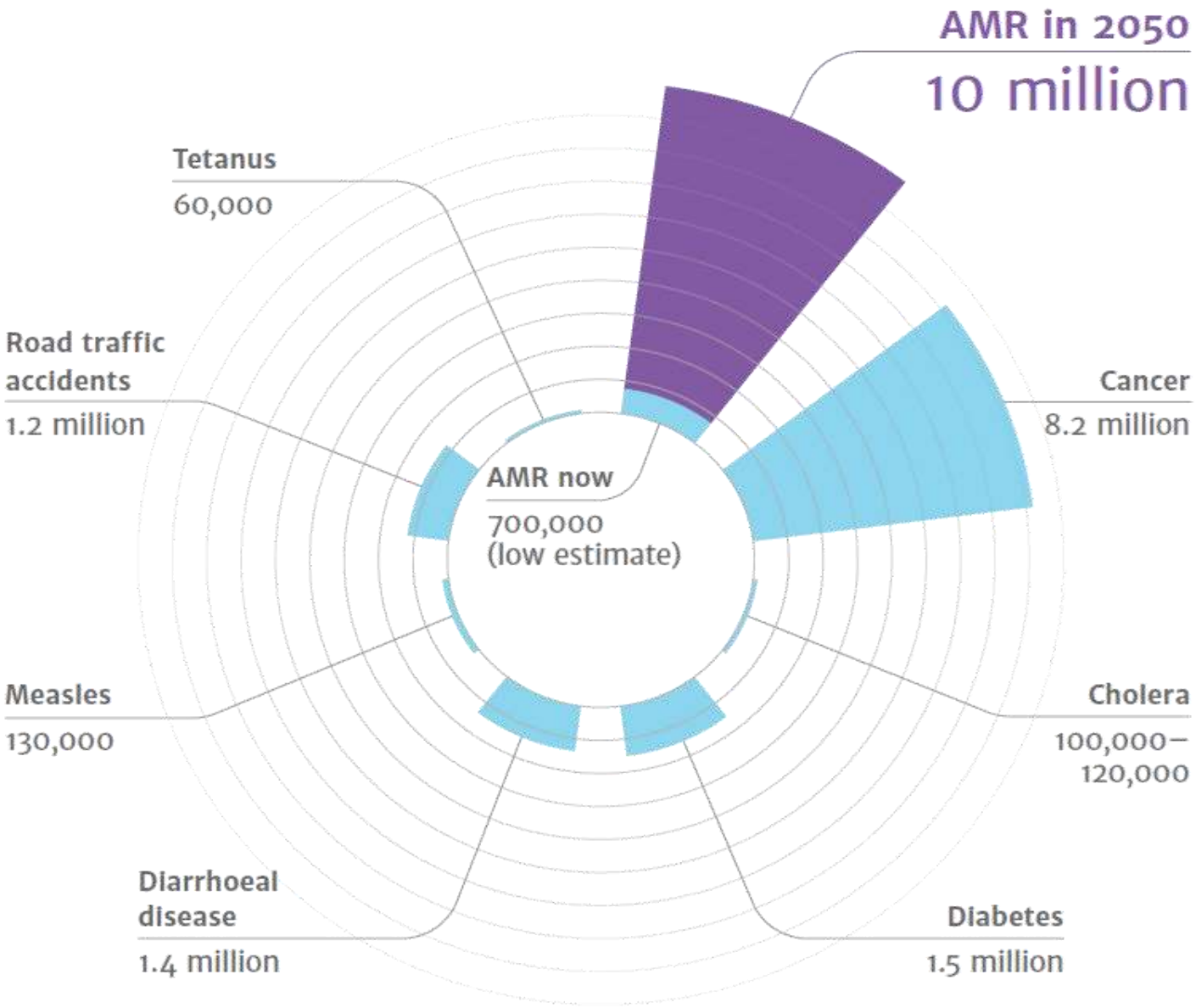
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

ANTIBIOTIC RESISTANCE THREATS in the United States, 2013



CDC U.S. Department of Health and Human Services Centers for Disease Control and Prevention

ANTIBIOTIC RESISTANCE THREATS in the United States, 2013



Source: The Review on Antimicrobial Resistance, Jim O'Neill, 2014

Review on Antimicrobial Resistance
Tackling drug-resistant infections globally

Global Response to AMR

The G7 and G20 have been seized with the issue for several years

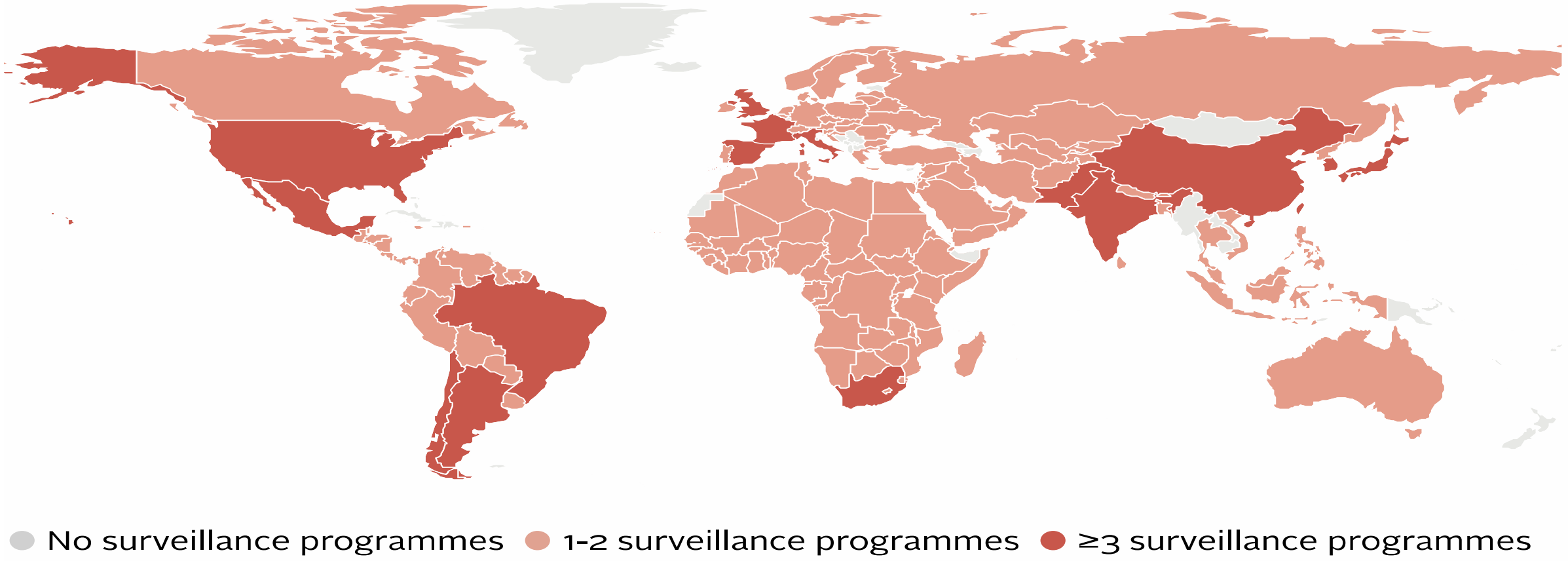
- Global AMR Research and Development Collaboration Hub (June 2017)

UN General Assembly High Level Meeting (September 2016)

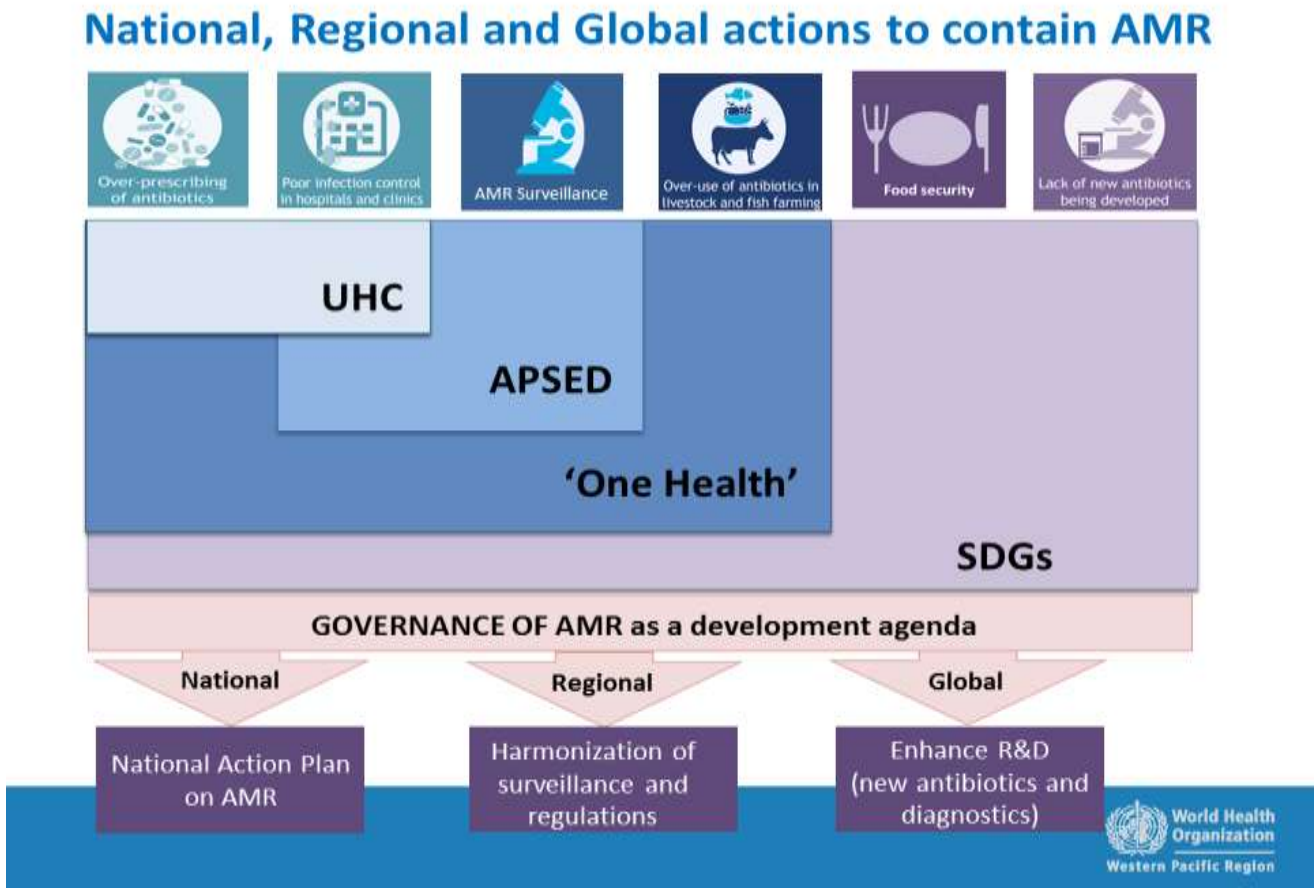
Agreement to develop and implement national action plans

.Only 4th health issue taken up in 72 years

AMR surveillance programs are being conducted in 147 countries worldwide



Global Response to AMR



IDSA Guidelines – Definition of Antimicrobial Stewardship

- Antimicrobial stewardship is an activity that promotes

– The appropriate selection of antimicrobials

– The appropriate dosing of antimicrobials

– The appropriate route and duration of antimicrobial therapy

Choice of the Proper Antimicrobial Agent

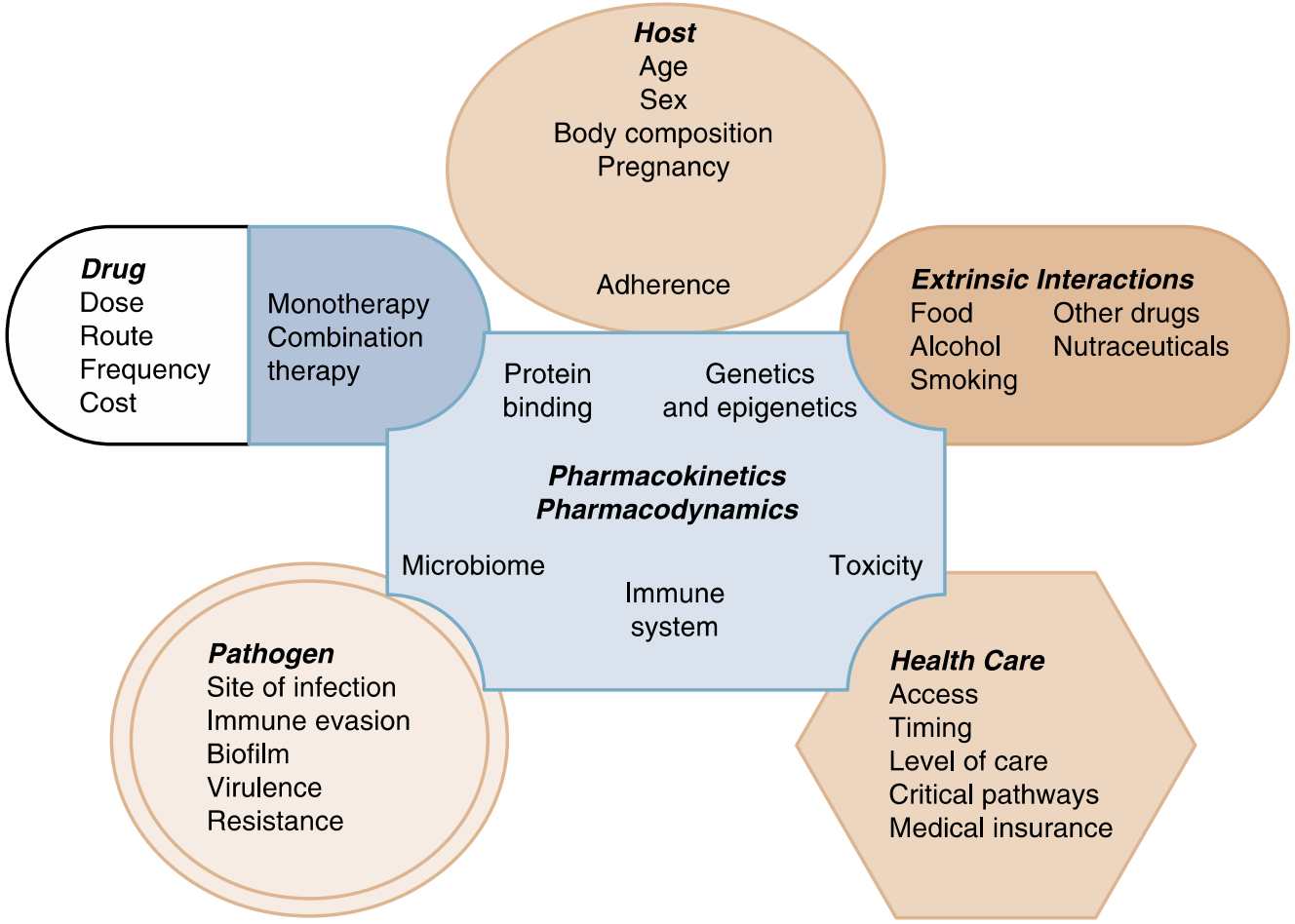


FIGURE 19-1 **Overview of the pharmacologic and nonpharmacologic factors that may influence clinical outcomes in patients.**

Important considerations when prescribing antibiotics:

- 1) Obtain accurate diagnosis of infection.
- 2) Empiric and definitive therapy.
- 3) switch to narrow-spectrum.
- 4) Cost-effective oral agents for the shortest duration necessary.

Important considerations when prescribing antibiotics:

- 5) Understanding drug pharmacodynamics and efficacy at the site of infection..
- 6) Host characteristics that influence antimicrobial activity
- 7) Adverse effects of antimicrobial agents on the host.

1) Obtaining an Accurate Infectious Disease Diagnosis

- Determining the site of infection,
- Defining the host (e.g., immunocompromised)
- Establishing, when possible, a microbiological diagnosis.
- especially for:

Endocarditis, septic arthritis, meningitis..

- Additional investigations to exclude noninfectious diagnoses.

Host Factors to Be Considered in Selection of Antimicrobial Agents

1) Renal and Hepatic Function..

2) Pregnancy and Lactation… Special considerations ..

Teratogenicity or Toxic to the foetus.

:

Sulphonamides : A risk to develop kernicterus, especially preterm infants..

Tetracycline : Staining of the teeth..

Fluoroquinolone: Cartilage damage to the fetus..

3) History of Allergy or Intolerance.

Pencillin and anaphylaxis

Consider Special Host Factors

- Genetic e.g. G6PD
- Renal function
- Liver function
- Pregnancy & Lactation
- Drug interaction

1) Obtaining an Accurate Infectious Disease Diagnosis

- Microbiological diagnosis :

  Bacterial or fungal culture or

  Serologic testing..

- Frequently the "**Most likely**"

  microbiological etiology can be inferred from the clinical presentation:

- Cellulitis (streptococci or staphylococci)…

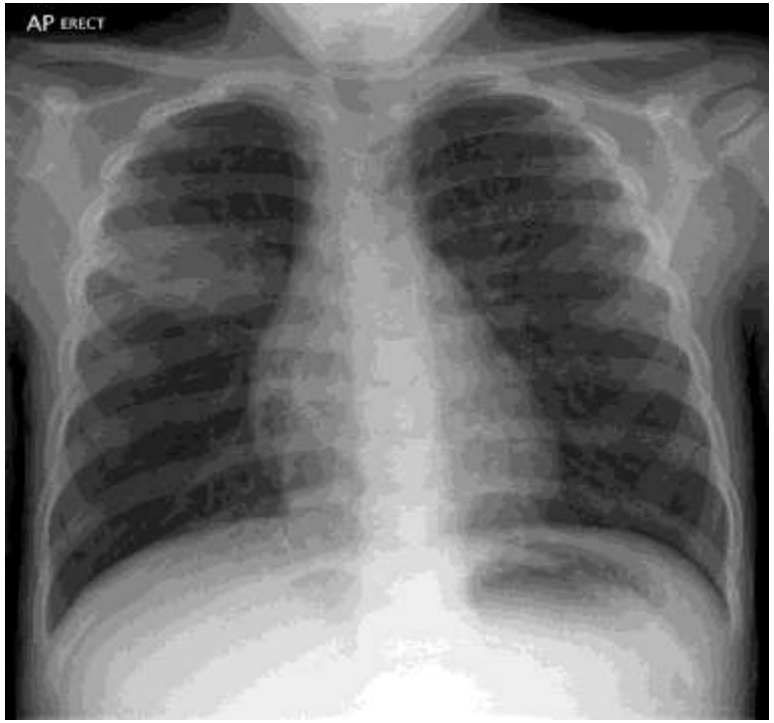
  No need for positive culture.

Cellulitis

1) Obtaining an Accurate Infectious Disease Diagnosis

- **Is An Antibiotic Indicated?**
- **Clinical diagnosis of bacterial infection.**

- **Pneumonia (CAP)**
- can also be treated empirically—
  Macrolide or cephalosporins
  antibiotic—without performing
  specific diagnostic test



Pneumonia

1) Obtaining an Accurate Infectious Disease Diagnosis

- **Timing of Initiation of Antimicrobial Therapy**
- **Urgent situation:**

  1) Acute meningitis

  2) Septic shock

  3) Febrile neutropenia..

- **Empiric therapy should be initiated immediately after or concurrently with collection of diagnostic specimens**.

- **None urgent**:
- 1) febrile and stable patient with fever for several days with no clue to diagnosis..

1) Obtaining an Accurate Infectious Disease Diagnosis

- **In more stable clinical circumstances..**
- **Hold antibiotics until appropriate specimens have been collected and submitted:**
- **Example:**
- **subacute bacterial endocarditis ……. multiple sets of blood cultures**

Urgent vs non urgent: CASE

- 16 year old boy who presented with 3 days H/O high grade fever and severe headache ..examination revealed T: 39 and patient has neck stiffness, otherwise fully conscious and has no neurological deficit :

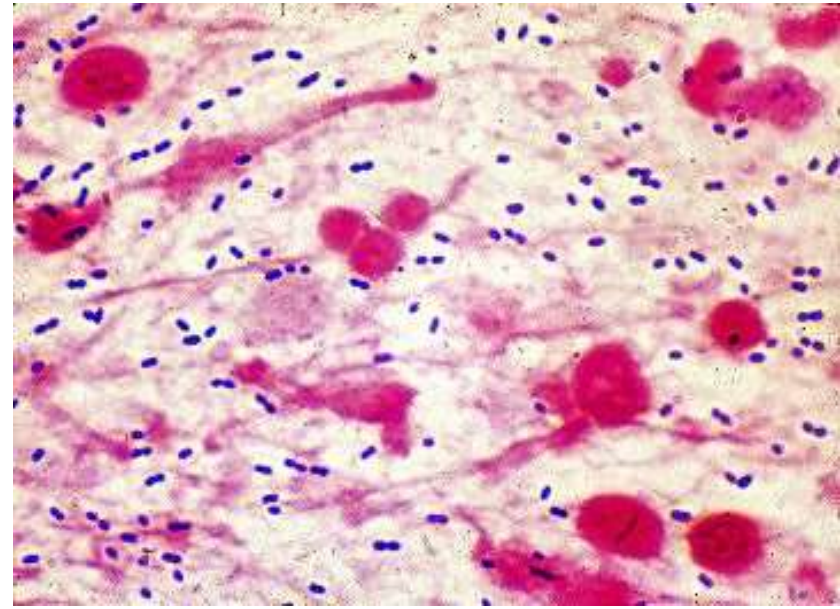
What is the most appropriate steps of approach:

- A) Start combination of antibiotic and arrange for CSF study.
- B) Arrange for urgent CT-scan brain ,
- C) Perform urgent LP and give the first dose of antibiotics.
- D) perform urgent LP and if csf is abnormal ,start RX…

…… ……

- Patient was prescribed a dose of :

  cefetriaxone and vanocmycin and urgent LP is done:
- Result:
- WBC : 1230 cells/mm…90% polymorph..
- RBC : NIL ..
- Gram stain:
- **Gram positive intracellular dipplococci**..



- Premature initiation of antimicrobial therapy…any harm ?

1] Can suppress bacterial growth

2] Preclude the opportunity to establish a microbiological diagnosis,

3] Require several weeks of directed antimicrobial therapy to achieve cure.

2) Empiric vs Definitive Antimicrobial Therapy

- Microbiological results do not become available
- for 24 to 72 hours

- Empiric and guided by the clinical presentation..

- Inadequate therapy for infections in critically ill, hospitalized patients is associated with greater morbidity and mortality

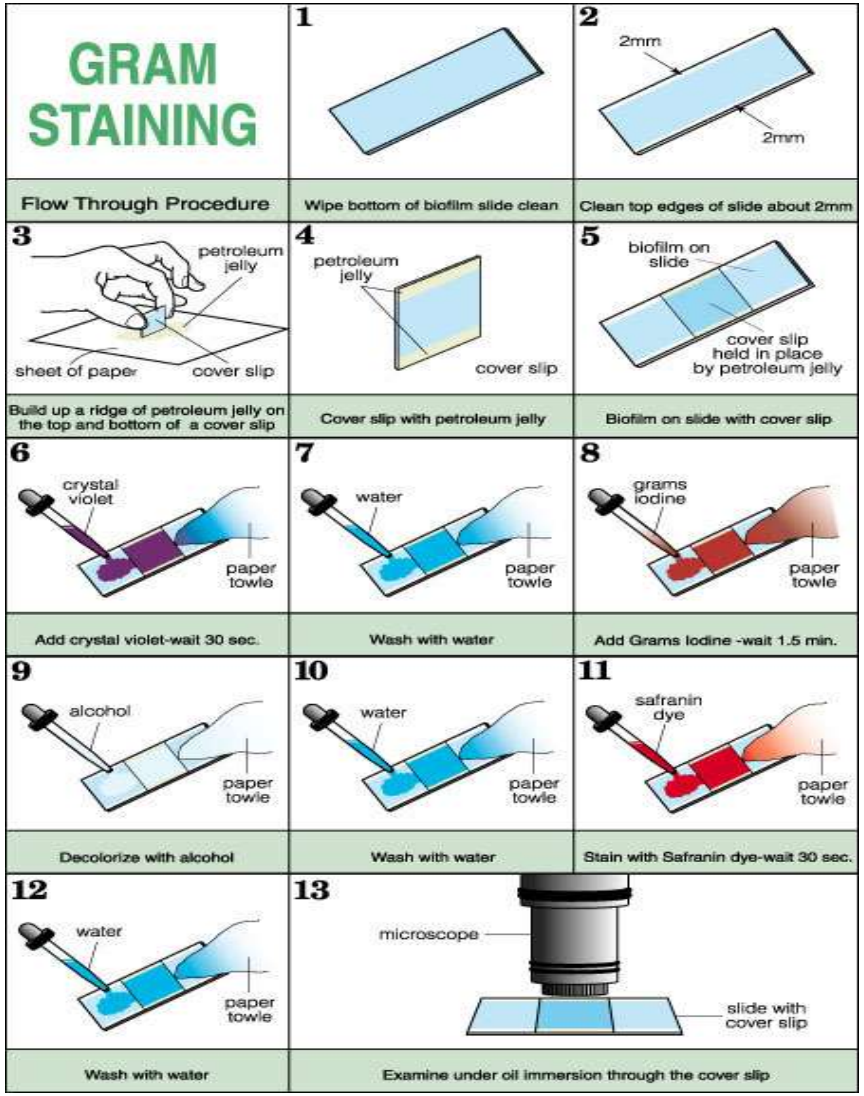
- Use broad-spectrum antimicrobial agents as initial empiric therapy

IDENTIFICATION OF THE INFECTING ORGANISM

IDENTIFICATION OF THE INFECTING ORGANISM

Several methods for the rapid identification of pathogenic bacteria in clinical specimens are available.

A Gram stain preparation is perhaps the simplest, least expensive, and most useful of all the rapid methods of identification of bacterial (and some fungal) pathogens.



Organism	Gram stain features	Clinical importance — some examples
Aerobic/facultative bacteria		
Enterococci		Urinary tract infections, endocarditis
Streptococci A,B,C,D,G		A: pharyngitis, cellulitis B: neonatal sepsis
Viridans streptococci		Endocarditis, abscess, dental caries
Streptococcus pneumoniae		Community pneumonia, septic shock, meningitis
Staphylococcus aureus		Furunculosis, cellulitis, abscess, septic shock, endocarditis
Coagulase-negative staphylococci		Infection of prosthetic devices, bacteraemia
Escherichia coli		Urinary tract infections, septic shock, haemorrhagic colitis
Klebsiella spp.		Urinary tract infections, septic shock, pneumonia
Enterobacter/ citrobacter		Urinary tract infections, pneumonia, septic shock
Pseudomonas aeruginosa		Urinary tract infections, pneumonia, septic shock
Neisseria meningitidis		Septic shock, meningitis
Haemophilus influenzae		Respiratory tract infections
Anaerobes		
Clostridium spp.		Tetanus, botulism, infections of soft tissue, abdominal sepsis, abscess
Peptococcus/ Peptostreptococcus spp.		Infections of soft tissue, abdominal sepsis, abscess
Bacteroides/Porphyromonas/Prevotella spp.		Infections of soft tissue, abdominal sepsis, abscess

(a) MicroScan instrument

(b) MicroScan® panel

Interpretation of Antimicrobial Susceptibility Testing Results

- Antimicrobial susceptibility testing measures the ability of a specific organism to grow in the presence of a particular drug in vitro:

  susceptible, resistant, or intermediate

- Data are reported in the form of minimum inhibitory concentration (MIC):

  The lowest concentration of an antibiotic that inhibits visible growth of a microorganism..

antimicrobial susceptibility testing (AST).

- **Susceptible**:
- indicates that the isolate is likely to be inhibited by the usually achievable concentration of a particular antimicrobial agent when the recommended dosage is used..
- Different antibiotics has different MIC.

A refinement of the disk diffusion technique uses antimicrobial gradient strips (e.g., Etest, by bioMérieux; M.I.C.E. by Oxoid) applied to agar plates seeded with the test organism. With these methods, intersection of the inhibition zone with the graduated strip permits determination of an actual minimal inhibitory concentration endpoint.

2) Empiric vs Definitive Antimicrobial Therapy

:What organisms are likely to be responsible

best Educated Guess? **You need**

- Based on:
  - **Hx & P.E…. You might have a clue to DX.**
  - **Epidemiological data**

    Hospital-acquired vs. community-acquired

2) Empiric vs Definitive Antimicrobial Therapy

- Patient with dyspnoea and cough …..

  Streptococcal pneumonia and atypical organism..

- **Patient with fever and urinary symptomes :**

  E.coli ….

➢ **Patient with erythema over the right leg associated**

➢ **with pain and tenderness …**

Group A Streptococcus and Staphylococcus

2) Empiric vs Definitive Antimicrobial Therapy

- **Hospital-acquired infections**
- Related to the presence of **invasive devices** and **procedures**

- A] **Catherter related bacteremia**:,
  Coagulase negative staph..
  Methicillin-resistant Staphylococcus aureus [MRSA]

- B] **Catheter related UTI**:
  Gram negative (eg, Pseudomonas aeruginosa)

King Saud University Medical City Antibiogram (Percent-Susceptible Isolates) 2018

King Khalid University Hospital

January - June 2017 Cumulative Antibiogram for Gram-Negative Organisms - (Percent Susceptible)

Gram-Negative Organisms	No. of strains	β-lactams							Quinolones		Aminoglycosides		Others	
		AMP	CZ	CXM	CAZ	FEP	MEM	TZP	CIP	MXF	AN	GM	NIT	SXT
Acinetobacter baumannii	143	R	R	R	38	32	22	22	32	---	43	48	---	73
Citrobacter freundii §	28	R	R	R	74	85	93	85	67	54	100	85	---	59
Enterobacter aerogenes §	25	R	R	R	72	84	100	84	92	75	100	80	---	76
Enterobacter cloacae	120	R	R	R	67	80	96	73	93	85	97	96	49	91
Escherichia coli	1119	26	56	58	62	63	100	95	60	52	98	83	98	50
Klebsiella pneumoniae	562	R	61	58	63	65	96	90	76	60	95	82	60	62
Morganella morganii	36	R	R	R	77	80	94	97	60	36	97	69	R	37
Proteus mirabilis	80	48	64	77	84	84	96	93	65	55	87	67	R	52
Pseudomonas aeruginosa	550	R	R	R	75	76	62	77	82	---	94	85	R	R
Salmonella spp.	36	67	---	---	100	100	100	83	46	78	17	---	---	72
Serratia marcescens	52	R	R	R	55	90	96	67	94	88	94	96	R	98
Stenotrophomonas maltophilia	52	R	R	R	24	R	R	R	---	---	---	---	R	87

2) Empiric vs Definitive Antimicrobial Therapy

- Once :
- 1) Microbiology have identified the etiologic pathogen
  and
- 2) Antimicrobial susceptibility data are available..
- Then…

Every attempt should be made to narrow the antibiotic spectrum. :

1) It can reduce cost and toxicity and
2) Prevent the emergence of antimicrobial resistance in the community

- Sign for the narrowest spectrum and shortest duration of therapy, and:
  switching to oral agents as soon as possible.
- In addition,
- Non antimicrobial interventions, such as abscess drainage, are equally or more important in some cases and should be
- pursued diligently in comprehensive infectious disease management.

What is the appropriate dose?

- **The lowest dose that is effective..**
- AVOID SUB-THERAPEUTIC DOSES
- DETERMINED BY:
  - SERIOUS VS NON-SERIOUS INFECTIONS
  - SITE OF INFECTION
  - DRUG PK/PD PROPERTIES
  - OTHER HOST FACTORS (E.G. RENAL FUNCTION … ETC)

Any Modification Needed?

Principles:

- Narrow vs broad spectrum agents.
- Least toxic agent.
- Cheaper.

Criteria for Use of New Agent

- Antimicrobial activity is superior
- Have a therapeutic advantage
- Better pharmacokinetics
  - Site penetration
  - Longer t ½
  - Shorter duration
- Less toxic
- Better tolerance

Bactericidal vs Bacteriostatic Therapy

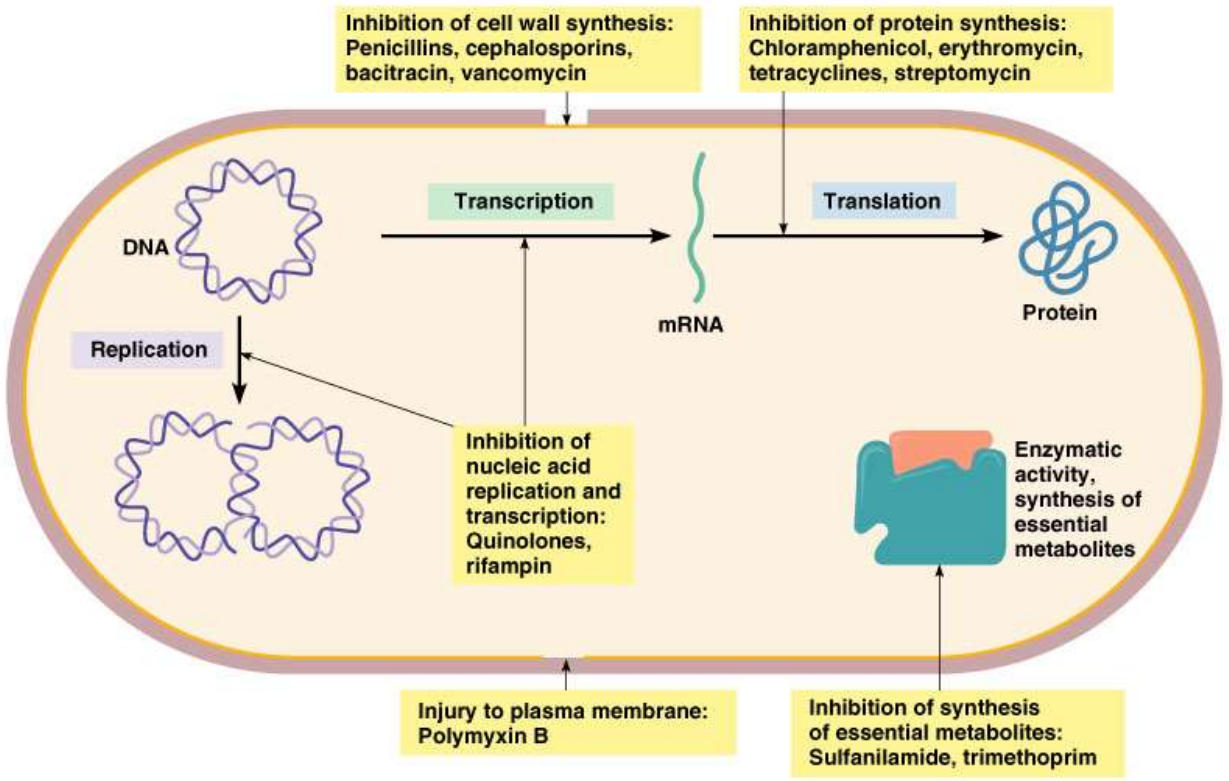
- **Bactericidal**
- Cause death and disruption of the bacterial cell. Drugs act on :

1) The cell wall …….β-lactams
2) **Cell membrane ….. Daptomycin**
3) **Bacterial DNA ……. Fluoroquinolones**

- Preferred in the case of serious infections such as endocarditis & meningitis to achieve rapid cure…

- **Bacteriostatic**
- Inhibit bacterial replication without killing the organism.
- act by inhibiting protein

- Sulfonamides.
- Tetracyclines.
- Macrolides.



Use of Antimicrobial Combinations

Exhibits synergistic activity

is used in the treatment of serious Infections:

A] **Rapid killing is essential**

Endocarditis caused by ***Enterococcus* species** with

a combination of **penicillin and gentamicin**: **bactericidal**,

activity…

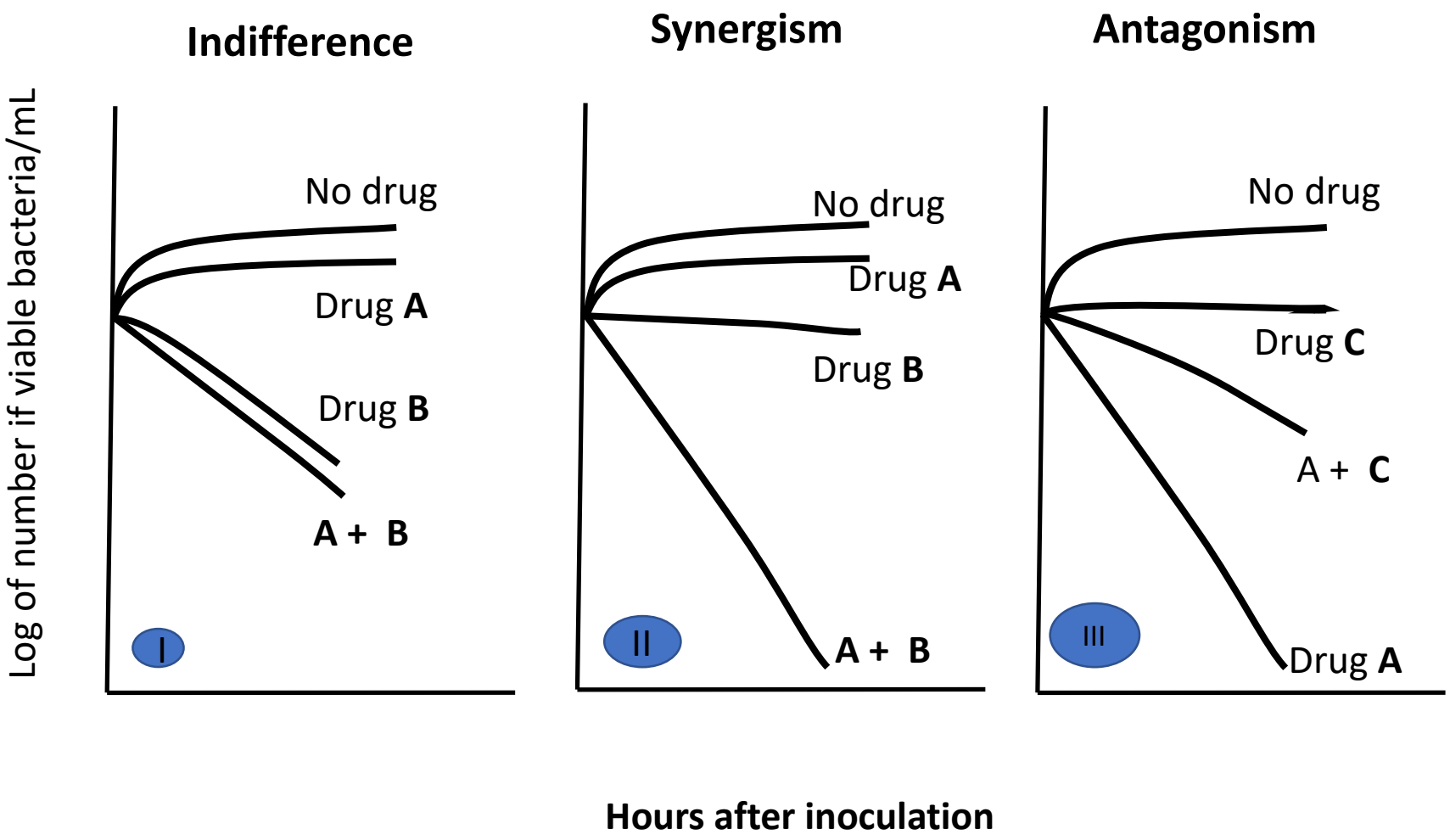
- B] **shorten the course:**
- Endocarditis due to viridans group streptococci,

penicillin or ceftriaxone with

gentamicin for 2 weeks can be as effective as penicillin or

ceftriaxone alone for 4 weeks).

- **D] Polymicrobial Infections:**
- Antimicrobial combinations, such as a third-generation cephalosporin or a fluoroquinolone **plus** metronidazole,


Indifference
Synergism
Antagonism
Log of number if viable bacteria/mL
No drug
Drug A
Drug B
A + B
I
No drug
Drug A
Drug B
II
A + B
No drug
Drug C
A + C
III
Drug A
Hours after inoculation

Oral vs Intravenous Therapy

- Candidates for treatment mild to moderate infections

- well-absorbed oral antimicrobial agents :

A] **Pyelonephritis**

Fluoroquinolones ..

B] Community-acquired pneumonia

Augmentin and macrolides coverage

- **Bioavailability**

The percentage of the oral dose that is available unchanged in the serum).

Examples of antibiotics with excellent bioavailability are:

Trimethoprim-sulfamethoxazole

.

- The efficacy of antimicrobial agents depends on their capacity to achieve :

  Concentration equal to or greater than the MIC at the site of infection..

- Ocular fluid, CSF, abscess cavity, prostate, and bone) are often much lower than serum levels

  For example:

  First- and second- generation cephalosporins do not cross the blood-brain barrier

- **Aminoglycosides: are less active** in the :
  low-oxygen, low-pH, **of Abscesses**

- **Fluoroquinolones** achieve high concentrations in the prostate
  preferred oral agents for the treatment of **Prostatitis..**

- **Moxifloxacin** does not achieve significant urinary concentrations
  therefore **not suitable** for treatment of **UTIs.**

Assessment of Response to Treatment

- Response to treatment of an infection:

  Clinical parameters
- improvement of symptoms and signs (eg,

  fever, tachycardia, or confusion

- laboratory values
- decreasing leukocyte count
- radiologic decrease in the size of an abscess).,

Antimicrobial Agents as Prophylactic

- **1) Presurgical Antimicrobial Prophylaxis**
- is used to reduce the incidence of postoperative surgical site infections..

- A single dose of a cephalosporin (such as cefazolin) administered
- within 1 hour before the initial incision is appropriate for
- most surgical procedures..

Antimicrobial Agents as Prophylactic

2) Prevent Transmission

of Communicable Pathogens to Susceptible Contacts

- **ciprofloxacin** for close contacts of a patient with N.meningitis

3) Antimicrobial Prophylaxis Before Dental Procedures**:**

- Prosthetic valves
- Rheumatic heart..
- to prevents Endocaridits

Treatment of a Positive Clinical Culture in the Absence of Disease:

- **Colonization** without any associated manifestation
- of disease occurs frequently in certain populations:

Colonization of :

- Old women with indwelling urinary catheter:

  Active infection are absent

  (asymptomatic bacteriuria)

- Endotracheal tubes in mechanically ventilated patients,
- chronic wounds..

MRSA

- R mechanism: PBP2a
- Antibiotics:
  - Vanocomycin
  - Teicoplanin
  - Linezolid
  - Tedizolid
  - Daptomycin
  - Telavancin
  - Dalbavancin
  - Oritavancin
  - Tigecycline
  - Delafloxacin
  - Ceftaroline
  - **Ceftobiprole**

VRE

- Antibiotics:
  - Teicoplanin
  - Linezolid
  - Tedizolid
  - Daptomycin
  - Oritavancin
  - Tigecycline
  - Eravacycline

ESBL

- Antibiotics:
  - Carbapenems
  - Piperacillin/tazobactam, nitrofutantoin, fosfomycin (UTI)
  - Tigecycline
  - Eravacycline
  - Colistin
  - Plazomicin

CRE

- Antibiotics:
  - Nitrofutantoin, fosfomycin (UTI)
  - Tigecycline
  - Eravacycline
  - Colistin
  - Ceftazidime/avibactam
  - Meropenem/vaborbactam
  - Plazomicin

Acinetobacter

- Antibiotics:
  - Carbapenems
  - Tigecycline
  - Eravacycline
  - Aminoglycosides
  - Colistin

Pseudomonas aeruginosa

- Antibiotics:
  - Piperacillin/tazobactam
  - Ceftazidime, cefepime **Ceftobiprole**
  - Meropenem, imipenem
  - Aztreonam
  - Some fluoroquinolones
  - Aminoglycosides
  - Colistin
  - Ceftolozane/tazobactam
  - Ceftazidime/avibactam

Building the Stewardship team

Thank you