Use of Antibiotics and its stewardship

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Objectives:

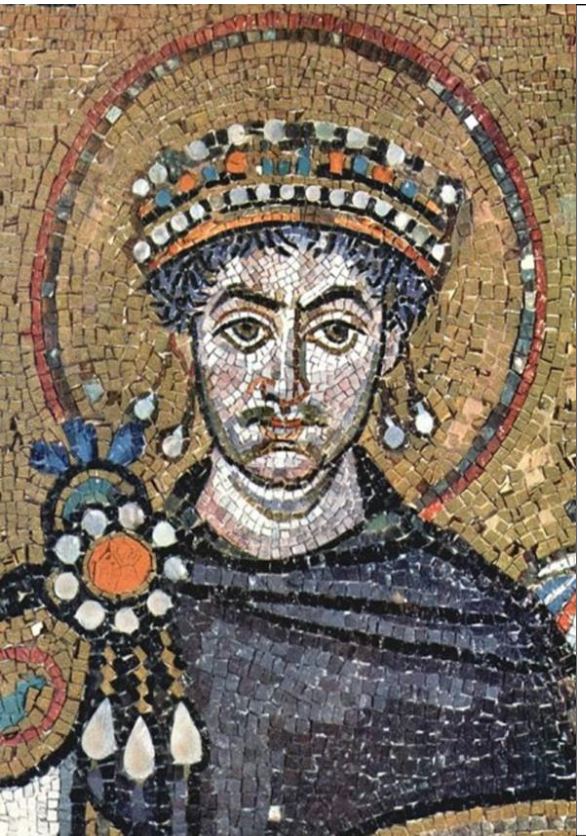
- By the end of the lecture the student should be able to:

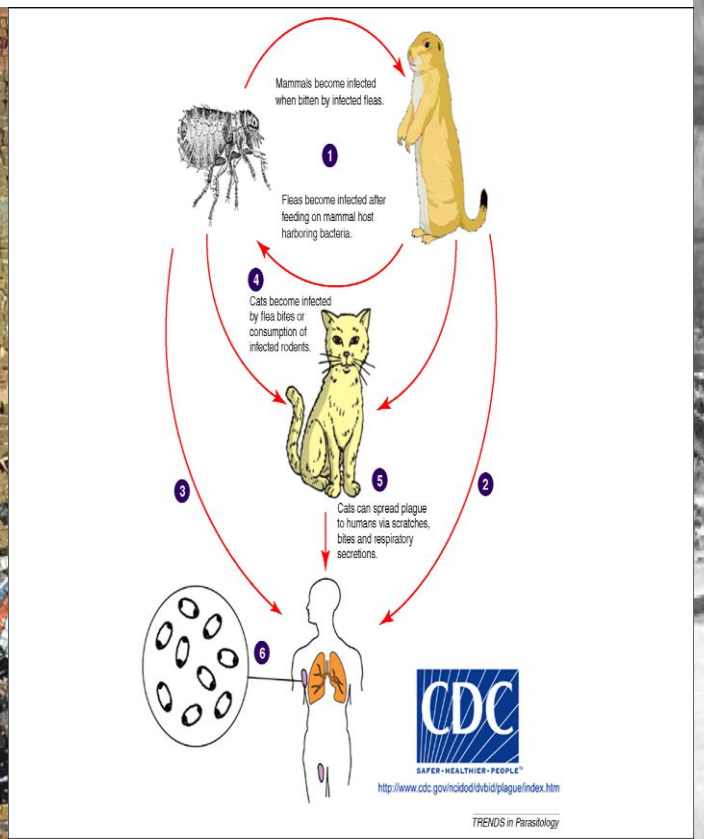
1. The different classes of Antibiotics.
2. Learn when to use antibiotics.
3. To monitor antibiotics response and toxicity.
4. To know the impact of antibiotics misuse and the importance of stewardship.

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

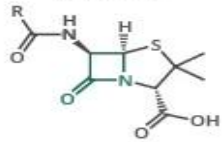
- discovery of the therapeutic value of penicillin by Alexander Fleming from *Penicillium notatum* in 1928.

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



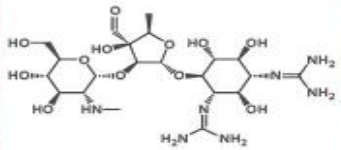
All contain a beta-lactam ring

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



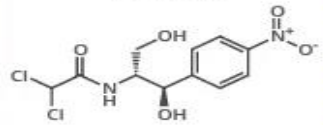
All contain aminosugar substructures

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



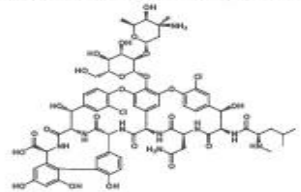
Distinct individual compound

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'



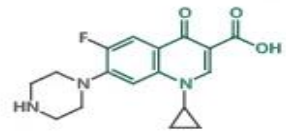
Consist of carbohydrate linked to a peptide formed of amino acids

EXAMPLES
Vancomycin (shown), teicoplanin.

MODE OF ACTION
Inhibit bacteria cell wall biosynthesis.

QUINOLONES

RESISTANCE EVOLVES RAPIDLY



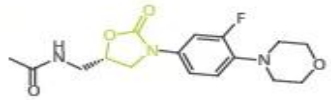
All contain fused aromatic rings with a carboxylic acid group attached

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

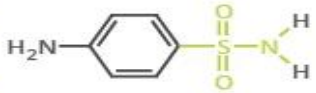
EXAMPLES
Linezolid (shown), posizolid, tedizolid, cycloserine.

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

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

SULFONAMIDES

FIRST COMMERCIAL ANTIBIOTICS WERE SULFONAMIDES



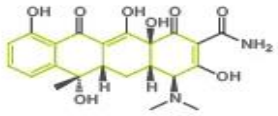
All contain the sulfonamide group

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



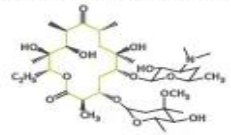
All contain 4 adjacent cyclic hydrocarbon rings

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



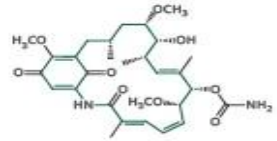
All contain a 14-, 15-, or 16-membered macrolide ring

EXAMPLES
Erythromycin (shown), clarithromycin, azithromycin.

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

ANSAMYCINS

CAN ALSO DEMONSTRATE ANTIVIRAL ACTIVITY



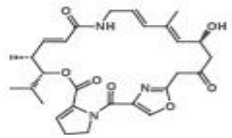
All contain an aromatic ring bridged by an aliphatic chain.

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



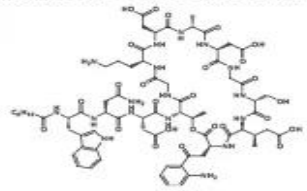
Combination of two structurally differing compounds, from groups denoted A & B

EXAMPLES
Pristinamycin IIA (shown), Pristinamycin IA.

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

LIPOPEPTIDES

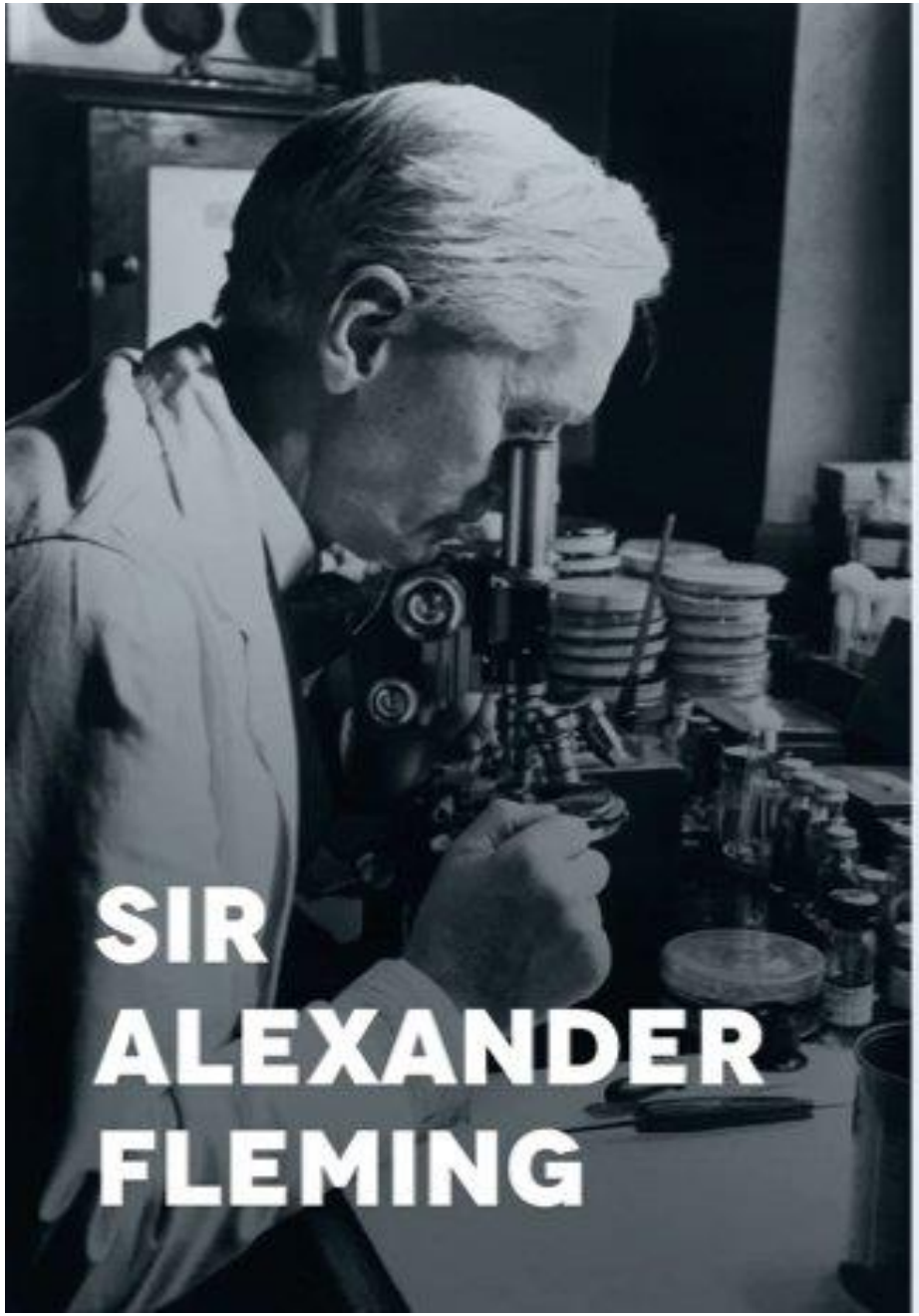
INSTANCES OF RESISTANCE RARE



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

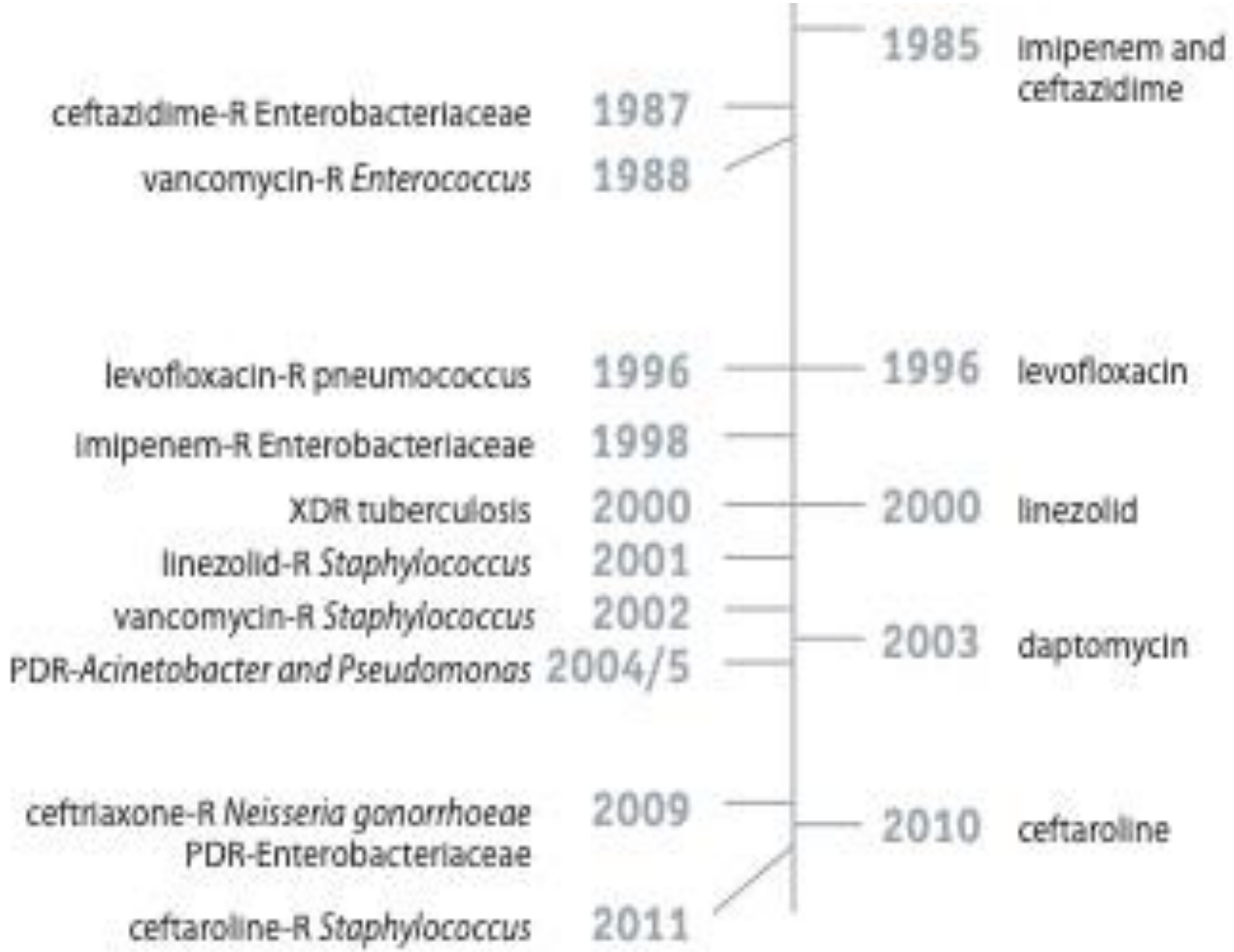
Timeline of Key Antibiotic Resistance Events

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		
erythromycin-R *Streptococcus*	1968		
		1967	gentamicin
		1972	vancomycin
gentamicin-R *Enterococcus*	1979		

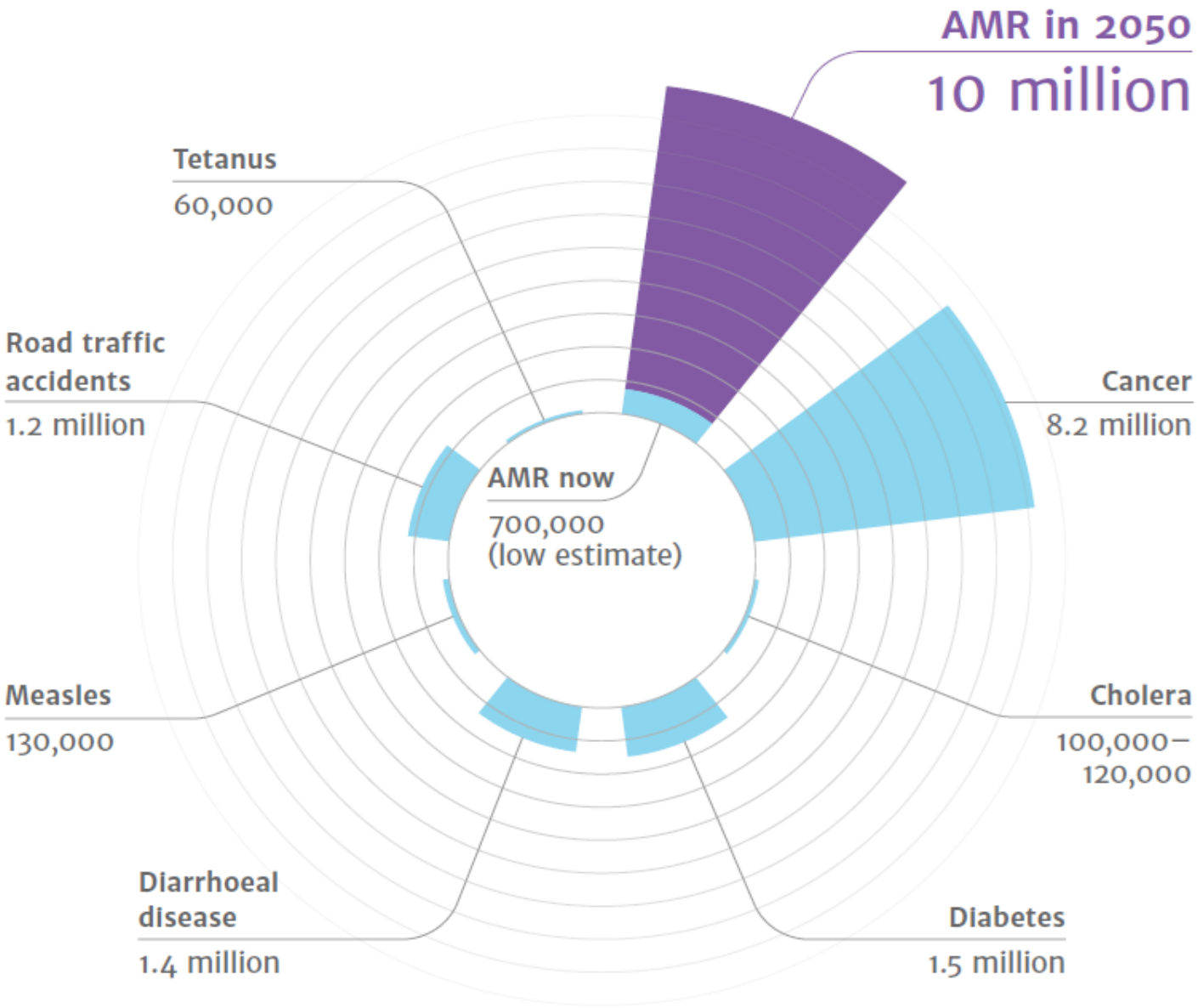
CDC U.S. Department of Health and Human Services Centers for Disease Control and Prevention

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

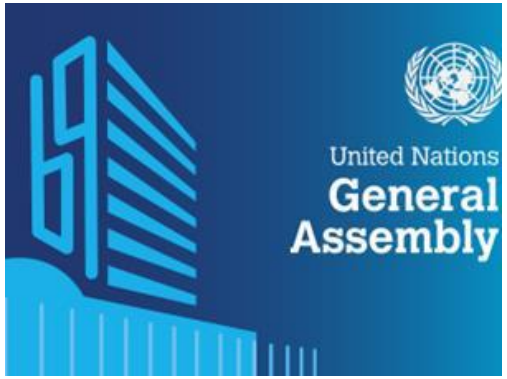
The G7 and G20 have been seized with the issue for several years

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

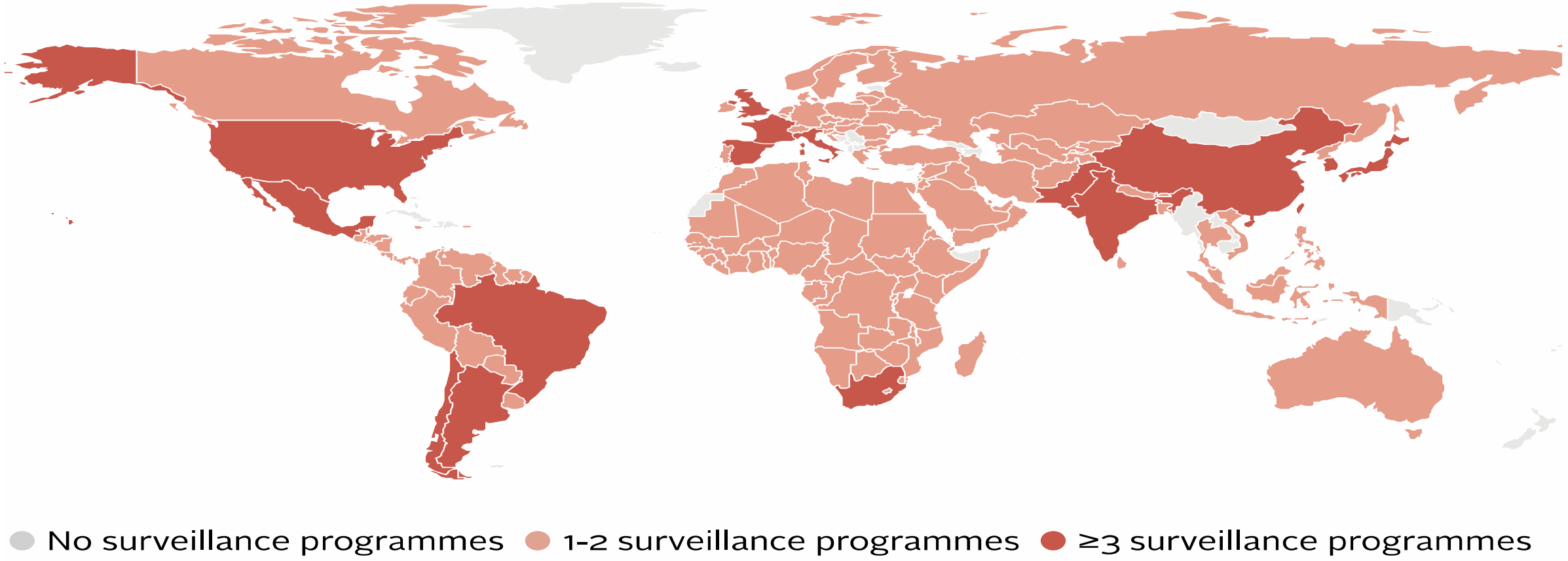
UN General Assembly High Level Meeting (September 2016)

Agreement to develop and implement national action plans

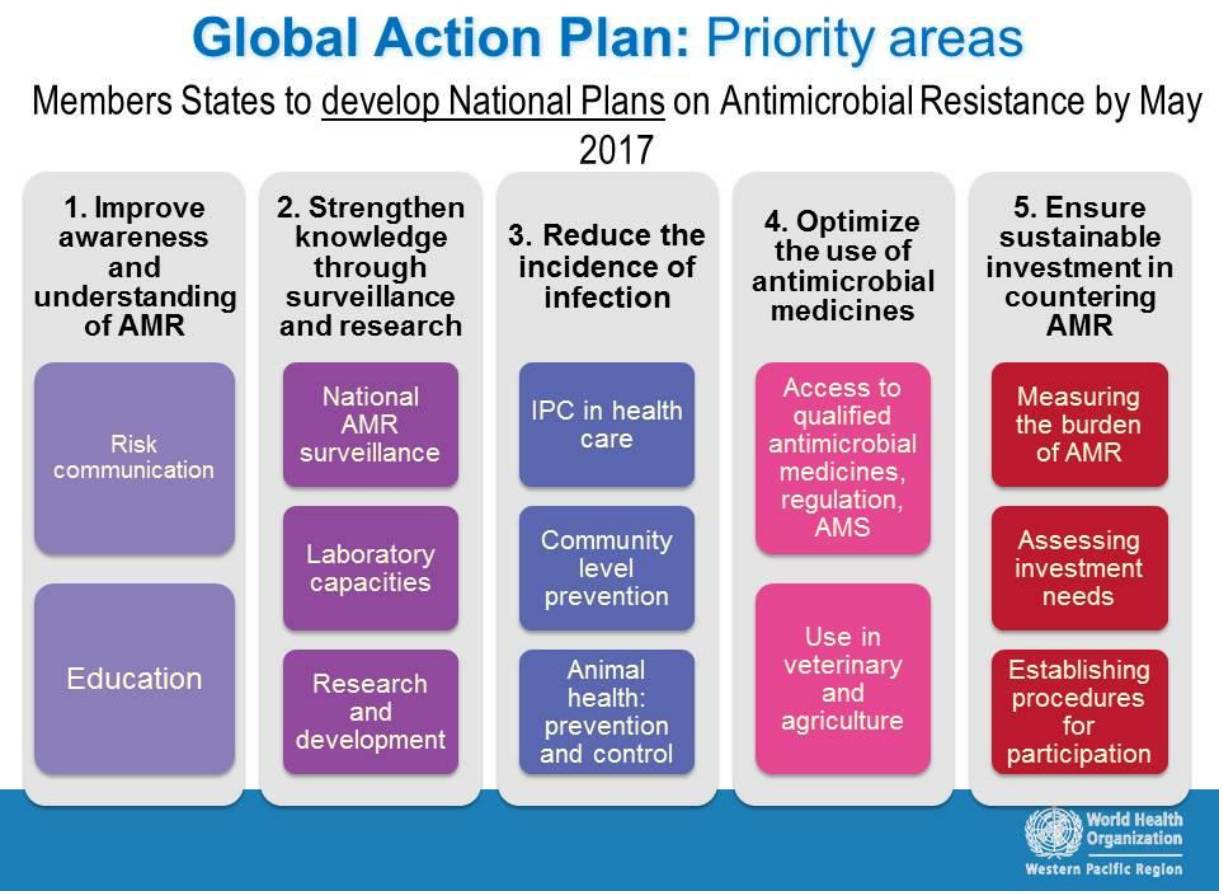
.Only 4th health issue taken up in 72 years

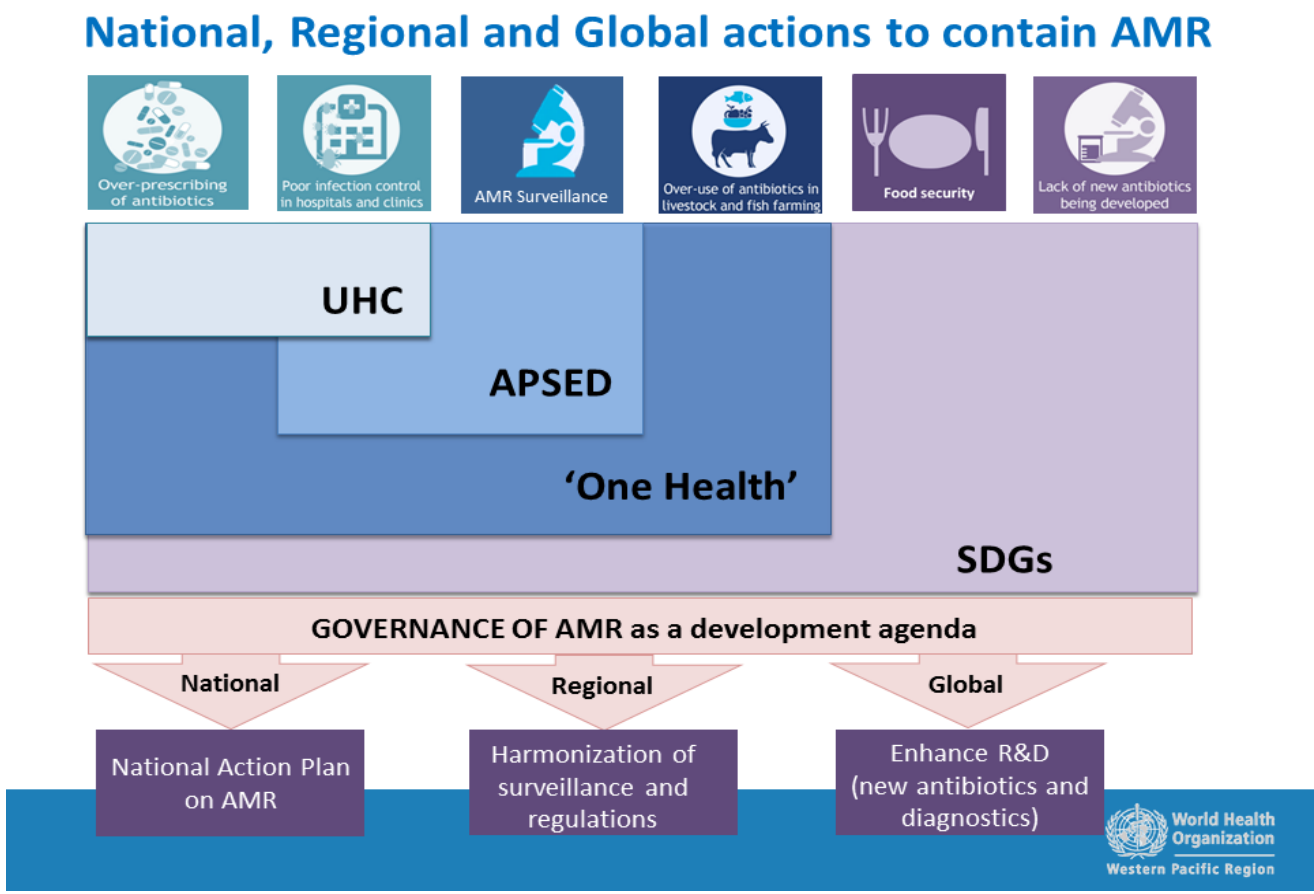


AMR surveillance programs are being conducted in 147 countries worldwide



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

Which AB is appropriate for this patient?

Approach

- 1- Patient factors
- 2- microbiological factors
- 3- Pharmacological factors

1- Patient factors
Obtaining an accurate infectious Disease Diagnosis

- 1- History :
- Include detailed history and examination of his current presentation
- History of chronic diseases(Renal, Liver , Immune status, etc…)
- History of allergy
- History of travel
- History of contact
- History of animal contact
- Drug history
- History of antibiotic use or other risk factors of HCAI
- History of previous Microbiological cultures
- Pregnancy and lactation

1- Patient factors

Age.

- Patients at both extremes of age handle drugs differently, primarily due to differences in body size and kidney function.
- Most pediatric drug dosing is guided by weight.
- In geriatric patients, the serum creatinine level alone is not completely reflective of kidney function, and the creatinine clearance should be estimated by factoring in age and weight for these patients.

1- Patient factors
Renal and Hepatic Function.

- Because the kidney and the liver are the primary organs responsible for elimination of drugs from the body, it is important to determine how well they are functioning during antimicrobial administration.
- In most cases, one is concerned with dose reduction to prevent accumulation and toxicity in patients with reduced renal or hepatic function.
- However, sometimes doses might need to be increased to avoid under dosing young healthy patients with rapid renal elimination or those with rapid hepatic metabolism due to enzyme induction by concomitant use of drugs such as rifampin or phenytoin.

1- Patient factors
Genetic Variation.

- Genetic susceptibility to the adverse effects of antimicrobial agents, which has been demonstrated for several antimicrobial agents, is occasionally significant enough to warrant testing for such variability before administration of certain drugs.
- For example, the antiretroviral drug abacavir, which has become part of the standard combination treatment for HIV infection, is associated with a well-described and potentially fatal hypersensitivity reaction that can manifest with any combination of fever, rash, abdominal pain, and respiratory distress.
- The risk of experiencing this reaction has been shown to be significantly higher in patients with the human leukocyte antigen allele HLA-B*5701 and current HIV treatment guidelines recommend routine screening for the presence of this genetic susceptibility in patients before prescribing this drug.
- Another example is that of glucose-6-phosphate dehydrogenase (G6PD) deficiency, which can result in hemolysis in individuals when exposed to certain antimicrobial agents, such as dapsone, primaquine, and nitrofurantoin.

1- Patient factors
Pregnancy and Lactation.

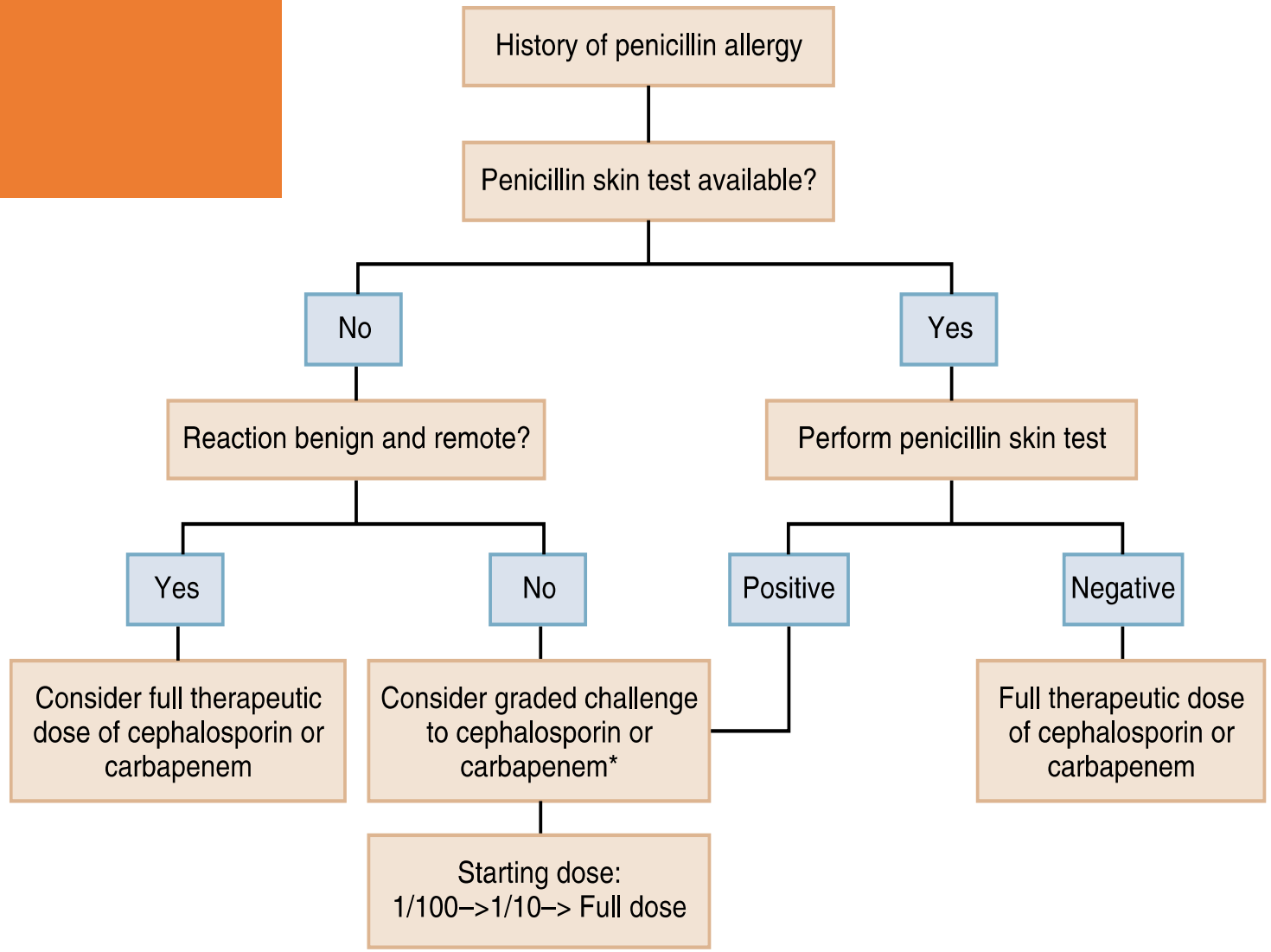
- Special considerations for the use of antimicrobial agents in pregnancy relate to both the mother and the fetus.
- In the case of the mother, increases in plasma volume and renal blood flow, especially by the third trimester, can result in more rapid clearance and lower serum levels of pharmaceutical agents, including antimicrobial agents.
- However, data to support the clinical relevance of this change are sparse, and higher antimicrobial doses are not routinely recommended in the third trimester of pregnancy.

Antibiotic	FDA Pregnancy Category Rating[b]	Notes
Aminoglycosides	D	Streptomycin linked to hearing loss in newborns and should be avoided, unless specific benefit established. Short-term use of others in class acceptable with monitoring, if benefits outweigh the risks
Beta-lactams and mono-bactams		
Penicillins		
Including amino-penicillins; extended-spectrum penicillins; and beta-lactam/beta-lactamase inhibitor combinations	B	Generally safe to use
Cephalosporins (all generations) and cephamycins[a]	B	Generally safe to use; use ceftriaxone with caution at term due to risk of kernicterus
Carbapenems		
Doripenem, ertapenem, and meropenem	B	Use with caution only when penicillins or cephalosporins not an option
Imipenem-cilastatin	C	
Aztreonam	B	Use only if severe allergy to beta-lactams
Fluoroquinolones	C	Avoid in pregnancy unless benefits outweigh risks
Glycopeptides and lipoglycopeptides		
Vancomycin	B	Appears to be safe and effective
Lipoglycopeptides		
Telavancin, dalbavancin, oritavancin	C	Avoid in pregnancy unless benefits outweigh risks
Macrolides and ketolides		
Macrolides		
Azithromycin, erythromycin	B	Generally safe to use azithromycin; use erythromycin and clarithromycin with caution and only if benefits outweigh risks
Clarithromycin	C	
Telithromycin	C	May use if benefits outweigh risks
Oxazolidinones		
Linezolid, tedizolid	C	May use if benefits outweigh risks
Tetracyclines		
Tetracycline, minocycline, doxycycline	D	Should be avoided
Miscellaneous Antibiotics		
Clindamycin	B	Appears to be safe and effective; review STI guidelines regarding oral vs vaginal routes
Daptomycin	B	May use if benefits outweigh risks
Fidaxomicin	B	Limited use, however limited systemic exposure decreases potential risk to fetus
Fosfomycin	B	Appears to be safe and effective
Metronidazole	B	Topical metronidazole should be avoided
Nitrofurantoin	B	Appears to be safe and effective
Polymyxins		
Polymyxin B, polymyxin E	C	Should be used with caution. Careful monitoring of adverse events
Folate antagonists		
Sulfamethoxazole, trimethoprim	C	Avoid trimethoprim and sulfamethoxazole in first trimester due to major congenital malformations. Sulfamethoxazole should be avoided after 32 wks' gestation due to risk of kernicterus
Tigecycline	D	Avoid in pregnancy unless benefits outweigh risks
Antimycobacterial agents		
Isoniazid (INH)	C	Hepatic enzymes should be monitored closely during pregnancy while on tuberculosis therapy. Pyridoxine (B6) should be given with INH during pregnancy
Ethambutol	B	
Pyrazinamide	C	
Rifampin, rifabutin, rifapentine	C	
Bedaquiline	B	

[a]Ceftolozane-tazobactam and ceftazidime-avibactam were recently approved at the time of this manuscript, but also carry a Pregnancy Category B rating.

1- Patient factors
History of Allergy or Intolerance.

- A history of antimicrobial allergy or intolerance should be routinely obtained in the evaluation and management of infection



*All patients with prior drug reaction histories are at increased risk for future drug reactions. Drug challenges should therefore be performed with equipment and personnel available to treat anaphylaxis.

1- Patient factors
timing Of initiation Of antimicrobial therapy

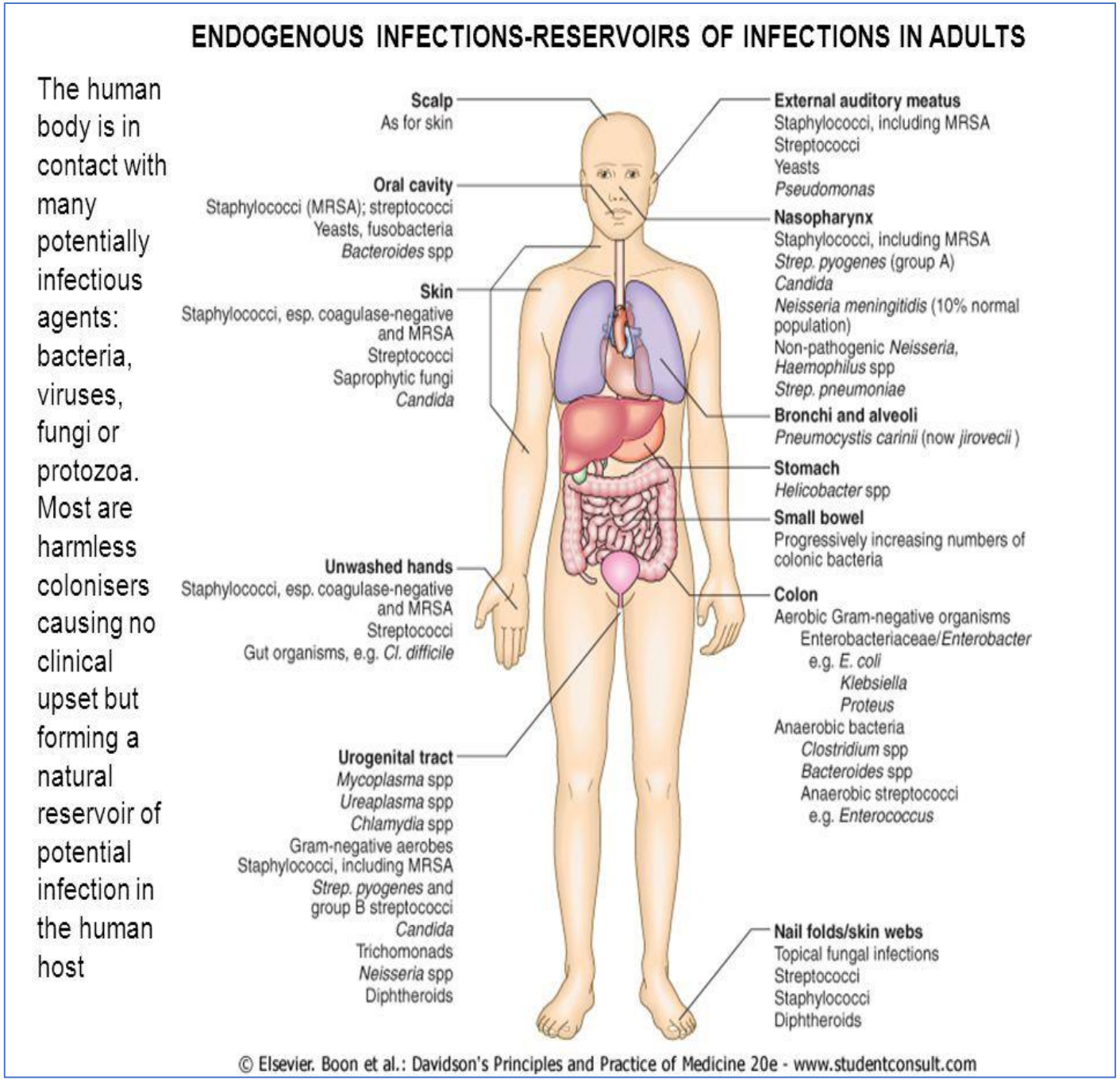
- The timing of initial therapy should be guided by the urgency of the situation.
- In critically ill patients, such as those in septic shock, febrile neutropenic patients, and patients with bacterial meningitis, empiric therapy should be initiated immediately after or concurrently with collection of diagnostic specimens.
- In more stable clinical circumstances, antimicrobial therapy should be deliberately withheld until appropriate specimens have been collected and submitted to the microbiology laboratory.

1- Patient factors
timing Of initiation Of antimicrobial therapy

- Important examples of this principle are subacute bacterial endocarditis and vertebral osteomyelitis/diskitis.
- Patients with these infections are frequently ill for a period of several days to weeks before presentation, and administration of antibiotic therapy should be delayed until multiple sets of blood cultures (in the case of endocarditis) or disk space aspirate and/or bone biopsy specimens (for osteomyelitis/diskitis) have been obtained.
- Premature initiation of antimicrobial therapy in these circumstances can suppress bacterial growth and preclude the opportunity to establish a microbiological diagnosis, which is critical in the management of these patients, who require several weeks to months of directed antimicrobial therapy to achieve cure.

1- Patient factors site of infection

The human body is in contact with many potentially infectious agents: bacteria, viruses, fungi or protozoa. Most are harmless colonisers causing no clinical upset but forming a natural reservoir of potential infection in the human host



Approach

- 1- Patient factors
- 2- microbiological factors
- 3- Pharmacological factors

2- microbiological factors

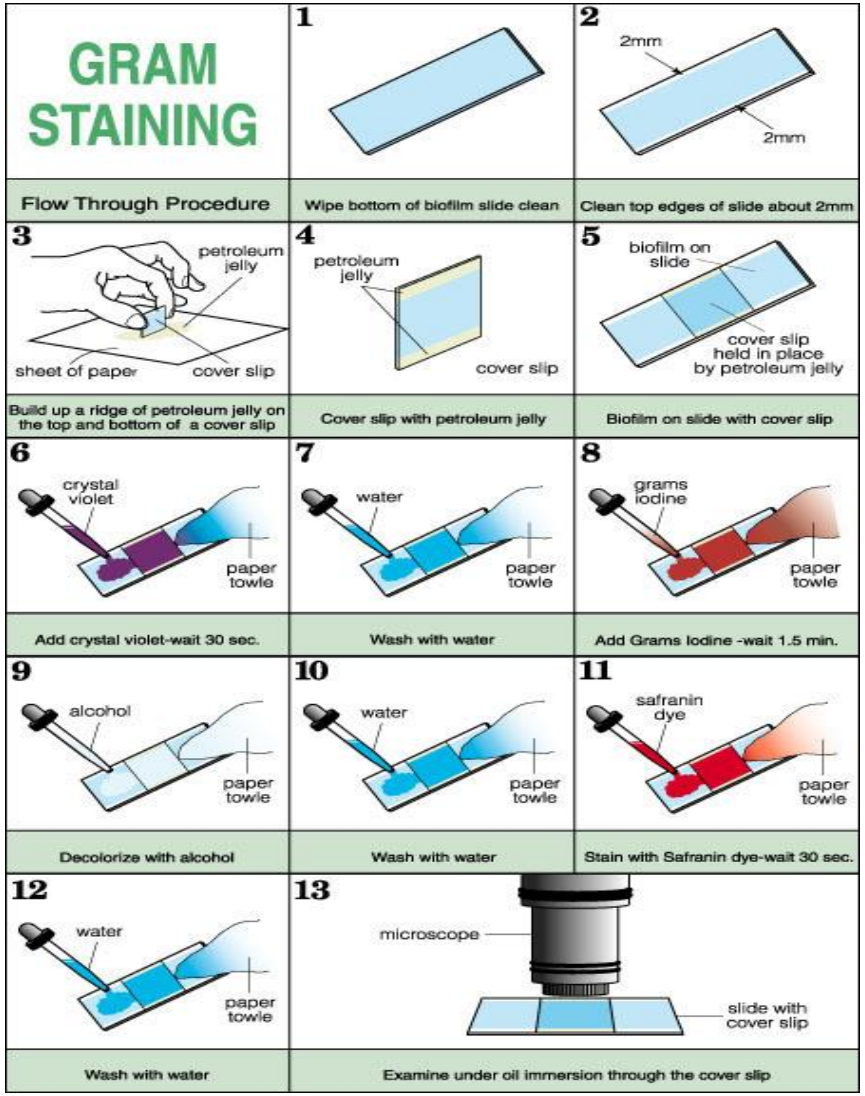
2- microbiological factors

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.



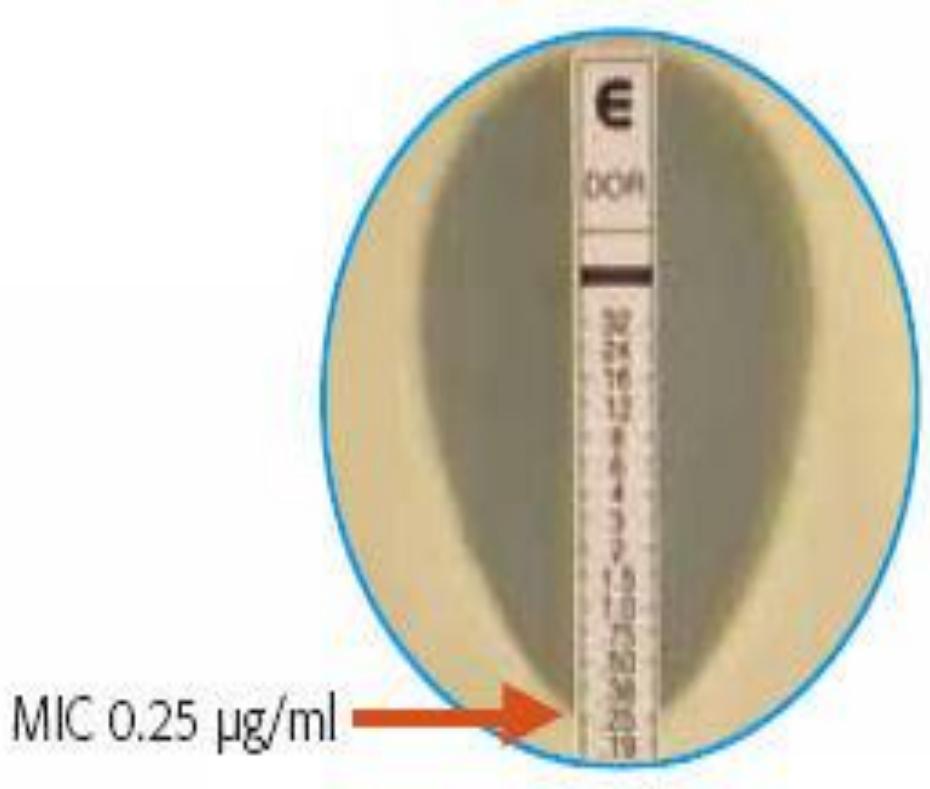
2- microbiological factors

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

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- microbiological factors

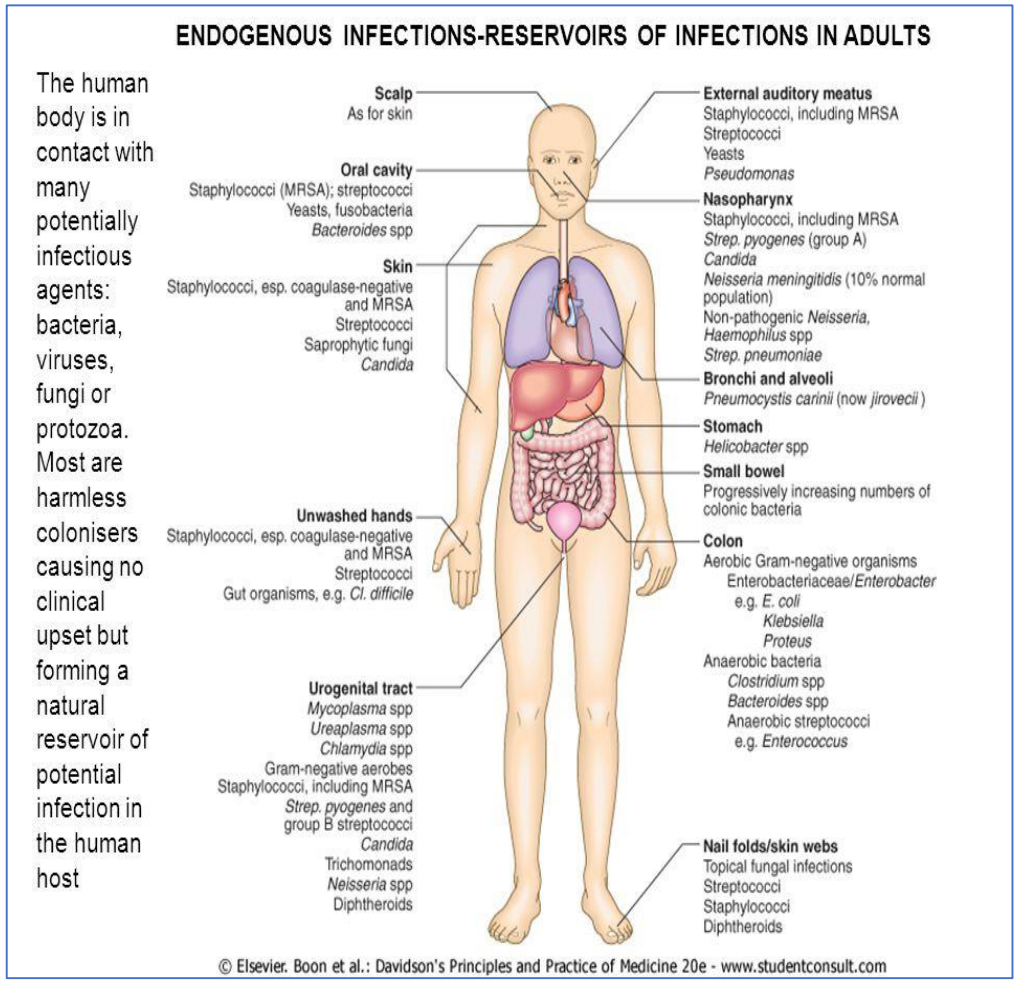
Empiric vs Definitive antimicrobial therapy

- Because microbiological results do not become available for 24 to 72 hours, initial therapy for infection is often empiric and guided by the clinical presentation.
- It has been shown that inadequate therapy for infections in critically ill, hospitalized patients is associated with poor outcomes, including greater morbidity and mortality as well as increased length of stay.
- Therefore, a common approach is to use broad-spectrum antimicrobial agents as initial empiric therapy (sometimes with a combination of antimicrobial agents with the intent to cover multiple possible pathogens commonly associated with the specific clinical syndrome).
- This is true for both community and hospital-acquired infections

2- microbiological factors Community vs HCAI

Table 1: Risk Factors for Multidrug-resistant Pathogens Causing Hospital-acquired Pneumonia, Healthcare-associated Pneumonia, and Ventilator-associated Pneumonia

- Antimicrobial therapy in the previous 90 days
- Current hospitalization of at least 5 days
- Presence of risk factors for HCAP
- Hospitalization for 2 days or more in the preceding 90 days
- Home wound care
- Residence in a nursing care facility
- High frequency of antibiotic resistance in the community or in the hospital where admitted
- Immunosuppressive disease and/or therapy
- Home infusion drug therapy
- Chronic dialysis within the previous 1 month
- Family member with multidrug-resistant pathogen



- **History of Recent Antimicrobial Use.**
- Eliciting a history of exposure to antimicrobial agents in the recent past (approximately 3 months) can also help in selection of antimicrobial therapy.
- Because the causative microorganism for a current episode of infection emerged under the selective pressure of a recently used antimicrobial agent, it is likely to be resistant to that drug and/or drug class, and an alternative agent should be used.

2- microbiological factors Antibiogram

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

Approach

- 1- Patient factors
- 2- microbiological factors
- 3- Pharmacological factors

3- Pharmacological factors

Patterns of antibiotic action

	Pattern of activity	PK/PD parameter	Goal of therapy	Examples
Type I	Concentration dependent prolonged PAE	AUC/MIC C_{max}/MIC	Maximize concentration	Aminoglycoside Fluroquinolones Daptomycin Ketolides
Type II	Time dependent minimal PAE	T>MIC	Maximize duration of exposure	Penicillins Carbapenems Cephalosporins Linezolids E.mycin
Type III	Time dependent prolonged PAE	AUC/MIC	Maximize amount of drug	Azithromycin Clindamycin Tetracycline Vancomycin

3- Pharmacological factors

Site of action	Antibacterial	Bacteriostatic or bactericidal
Cell wall	Beta-lactams • penicillins • cephalosporins • carbapenems	Bactericidal
	Vancomycin	Bactericidal
	Teicoplanin	Bactericidal
	Daptomycin	Bactericidal
Protein synthesis inhibitors	Tetracyclines	Bacteriostatic
	Aminoglycosides	Bactericidal
	Macrolides Clindamycin Fusidic acid	Low concentrations: bacteriostatic High concentrations: bactericidal
	Chloramphenicol	Bacteriostatic
	Quinupristin with dalfopristin	Bactericidal
	Linezolid	Bacteriostatic
	Tigecycline	Bacteriostatic
Nucleic acid synthesis inhibitors	Nitroimidazoles	Bactericidal
	Quinolones	Bactericidal
	Trimethoprim	Bacteriostatic
	Sulfonamides	Bacteriostatic

Source: Shanson (1999).[2]

3- Pharmacological factors

Principles:

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

3- Pharmacological factors
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

3- Pharmacological factors
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)

3- Pharmacological factors

- **Bioavailability**

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

Examples of antibiotics with excellent bioavailability are:

Trimethoprim-sulfamethoxazole

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3- Pharmacological factors

- 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

3- Pharmacological factors

- **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.**

3- Pharmacological factors
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

3- Pharmacological factors

- 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.

use Of antimicrobial combinations

- Although single-agent antimicrobial therapy is generally preferred, a combination of 2 or more antimicrobial agents is recommended in a few scenarios.

When Agents Exhibit Synergistic Activity Against a Microorganism.

- Synergy between antimicrobial agents means that, when studied in vitro, the combined effect of the agents is greater than the sum of their independent activities when measured separately.
- For example, the combination of certain b-lactams and aminoglycosides exhibits synergistic activity against a variety of gram-positive and gram-negative bacteria and is used in the treatment of serious infections, for which rapid killing is essential (eg, treatment of endocarditis caused by *Enterococcus* species with a combination of penicillin and gentamicin).
- In this setting, the addition of gentamicin to penicillin has been shown to be bactericidal, whereas penicillin alone is only bacteriostatic and gentamicin alone has no significant activity.
- For certain streptococci, similar synergistic combinations that result in more rapid clearance of the infecting microorganism can also be used to shorten the course of antimicrobial therapy (eg, for endocarditis due to viridans group streptococci, a combination of penicillin or ceftriaxone with gentamicin for 2 weeks can be as effective as penicillin or ceftriaxone alone for 4 weeks).

When Critically Ill Patients Require Empiric Therapy Before Microbiological Etiology and/or Antimicrobial Susceptibility Can Be Determined.

- antibiotic combinations are used in empiric therapy for health care–associated infections that are frequently caused by bacteria resistant to multiple antibiotics.
- Combination therapy is used in this setting to ensure that at least 1 of the administered antimicrobial agents will be active against the suspected organism(s).
- For example, when a patient who has been hospitalized for several weeks develops septic shock and blood cultures are reported to be growing gram-negative bacilli, it would be appropriate to provide initial therapy with 2 agents that have activity against gram-negative bacilli, particularly *P aeruginosa*, which is both a common nosocomial pathogen and frequently resistant to multiple agents in this case, a combination of an antipseudomonal b-lactam with a fluoroquinolone or aminoglycoside could be used.

To Extend the Antimicrobial Spectrum Beyond That Achieved by Use of a Single Agent for Treatment of Poly microbial Infections.

- When infections are thought to be caused by more than one organism, a combination regimen may be preferred because it would extend the antimicrobial spectrum beyond that achieved by a single agent.
- For example, most intra-abdominal infections are usually caused by multiple organisms with a variety of gram-positive cocci, gram-negative bacilli, and anaerobes +- candida.

To Prevent Emergence of Resistance.

- The emergence of resistant mutants in a bacterial population is generally the result of selective pressure from antimicrobial therapy.
- Provided that the mechanisms of resistance to 2 antimicrobial agents are different, the chance of a mutant strain being resistant to both antimicrobial agents is much lower than the chance of it being resistant to either one.
- In other words, use of combination therapy would provide a better chance that at least one drug will be effective, thereby preventing the resistant mutant population from emerging as the dominant strain and causing therapeutic failure.
- This is why combination drug therapy is used as the standard for treatment of infections such as tuberculosis and the human immunodeficiency virus (HIV) when treatment duration is likely to be prolonged, resistance can emerge relatively easily, and therapeutic agents are limited.

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
  - Cefidricol

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


THANKS