Lecture 43

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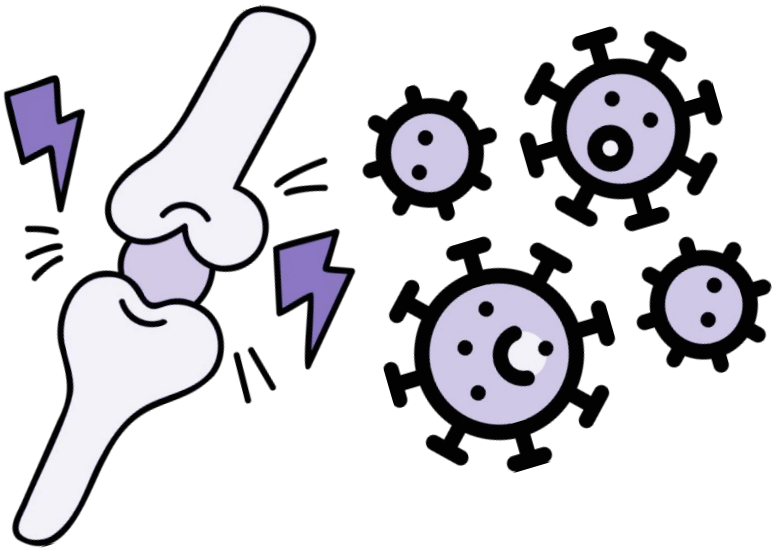

Reviewed By
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Use of Antibiotics

Objectives:

- ★ Know the different classes of Antibiotics.
- ★ Learn when to use antibiotics.
- ★ Learn to monitor antibiotics response and toxicity.
- ★ Learn to know the impact of antibiotics misuse and the importance of stewardship.

Color index:

Original text Females slides Males slides
Doctor's notes Textbook Important Golden notes Extra

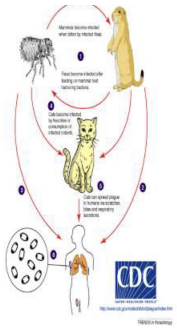
Introduction To Antibiotics

- **Why should we know about antibiotics?**

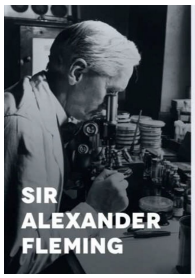
Because they are weapons in the hands of all physicians regardless of the specialty they work in.

◄ History of 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.
- In contrast, world one 1 resulted in **1 million casualties.** Infectious diseases are the most aggressive enemy to humans until the discovery of antibiotics.



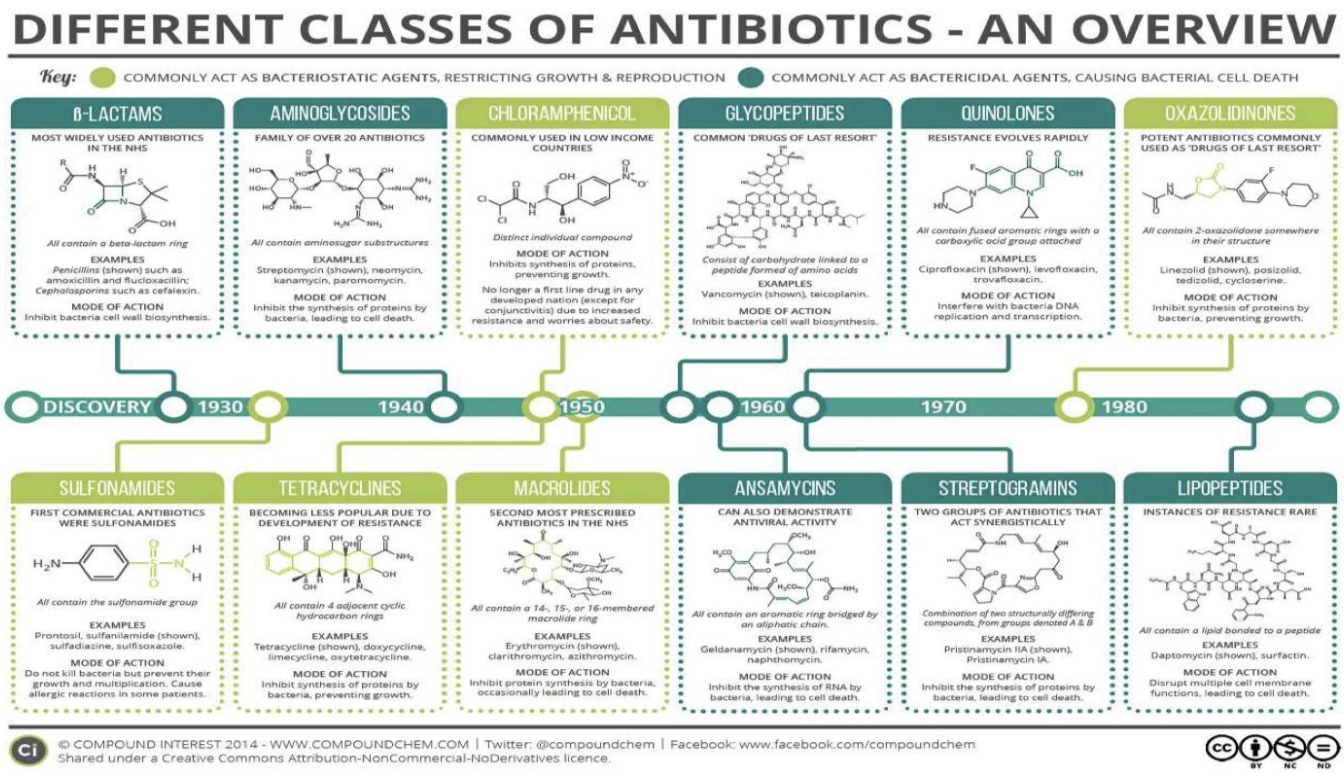
- Discovery of the therapeutic value of penicillin by Alexander Fleming from Penicillium notatum in 1928. A life saving discovery. Its discovery was by incidence, while he was eating a sandwich, a breadcrumb fell on the agar of staph.aureus, after 2 days the crumbs got moldy and he noticed an inhibition of growth zone in the agar, and that was the beginning of abx era



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.

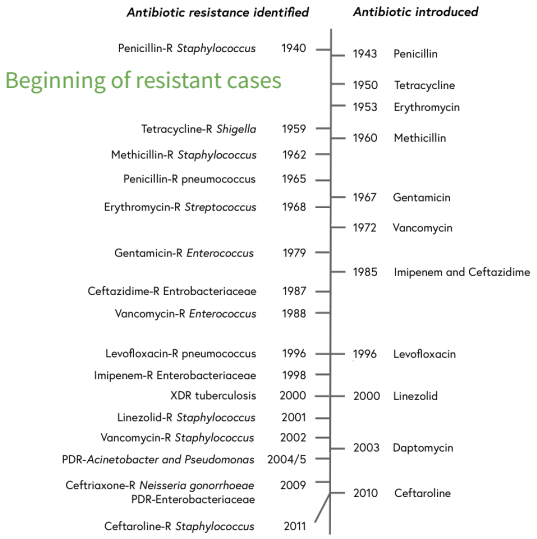
The resistance to penicillin was expected from the beginning

◄ Classes of antibiotics



Introduction To Antibiotics

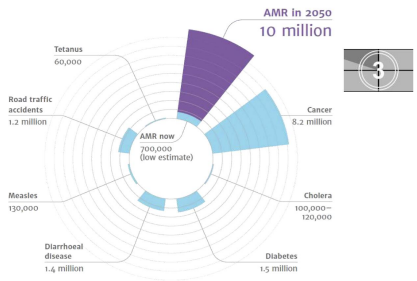
◀ Developing resistance, a timeline



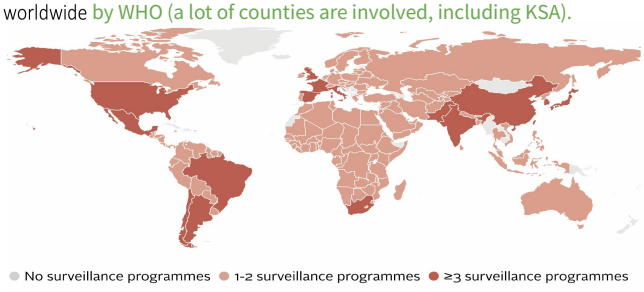
Resistance increased at a rapid rate & is still continuing

◀ Deaths & global response to AMR

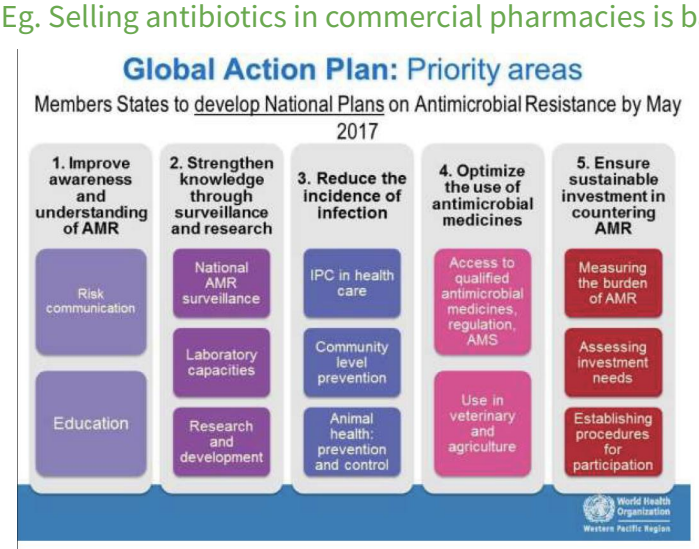
- Currently, 700,000 deaths are estimated yearly secondary to antimicrobial resistance.
- In 2050, an increase of 10 million deaths per year is expected (i.e every 3 seconds, a death will occur secondary to antimicrobial resistance yearly).
- The G7 and G20 have been seized with the issue for several 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

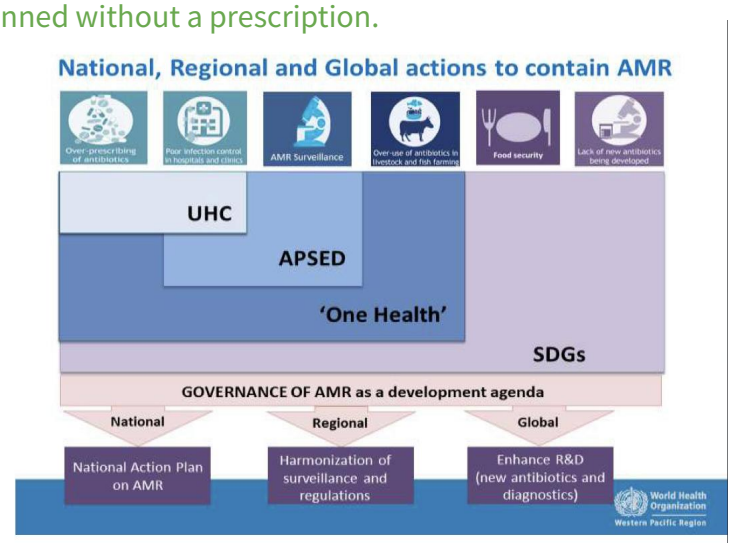


AMR surveillance programs are being conducted in 147 countries worldwide by WHO (a lot of counties are involved, including KSA).



Eg. Selling antibiotics in commercial pharmacies is banned without a prescription.





Antibiotics

Antibiotics

Chemical produced by:

1) **A microorganism:**
   - Antibiotics are secondary metabolites produced by microorganism such as bacteria, fungi, and actinomycetes as their natural defense system against other microbes living in their vicinity.
2) **Synthetics:**
   - That kills or inhibits the growth of another microorganism.
   - Isolation of antibiotics from microorganism is much easier than chemical synthesis of these compounds.

◀ Important considerations when prescribing antibiotics

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

Now, we will discuss each of these separately

An area for your notes

Antibiotics *(cont.)*

1 Obtain accurate diagnosis of infection.

Determining the **site** of infection from detailed history.

Defining the **host** (e.g., immunocompromised)

Additional investigations to exclude noninfectious diagnoses especially in cases where a non-clear assessment that the patient has an infection is present.

Establishing (when possible) a microbiological diagnosis.
Especially for:

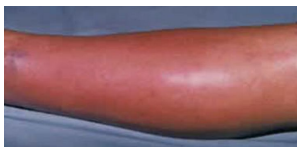
- **Endocarditis** (3 blood samples for culture, 30 mins apart)
- **Septic arthritis** (take patient to the OR to drain abscess then send for culture before giving antibiotics to narrow down the spectrum, but use broad-spectrum antibiotics before that because we cannot wait)
- **Meningitis**

Microbiological diagnosis:
important to guide your therapy

- Bacterial or fungal culture or Serologic testing
- Swab is not as effective as pus, body fluid or tissue culture

Frequently the most likely microbiological etiology can be inferred from the clinical presentation:

- **Cellulitis** (streptococci or staphylococci) No need for positive culture → Empirical therapy can be used in certain types of infections e.g. Cellulitis WITHOUT wound*, it's difficult to obtain cultures so we treat based on the most common organisms that cause this infection which are streptococci (20%) and staph (80%). Cellulitis without wound is more common in those with LL edema, either acute (Lymphedema in those with obstructed lymphatic chains after pelvic surgery) or chronic (HF)
- **cellulitis with wound** and the patient has diabetic foot then probably it's **secondary cellulitis** from the wound itself, so organism will be the one in the wound not the usual ones



◀ Case study 1 (is an antibiotic indicated):

A 30-year-old male presented to an urgent care clinic with a 4-day history of dry cough, progressing to rusty colored sputum, sudden onset of chills the previous evening, subjective fever, and malaise. Originally, the man thought he had a cold, but the symptoms had worsened and he "barely slept last night with all this coughing."

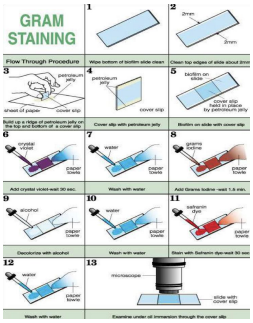
- **What is your diagnosis?**
- Pneumonia (CAP) No risk factor for healthcare facility associated pneumonia like admission in the last 30 days, use of antibiotics in the last 90 days, frequent visitor of a healthcare facility, admission to the ICU, etc… We know the most likely organism will be strep. pneumoniae, staph. aureus, and CA MRSA.
  - Can be treated empirically:
    - (macrolide or cephalosporins antibiotic) without performing specific diagnosis test.

Antibiotics *(cont.)*

1 Obtain accurate diagnosis of infection *(cont.)*

◀ Identification of the infecting organism

1 Gram stain



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. Gives the initial guidance.

- Gram +ve cocci in clusters → staph. (coagulase -ve or coagulase +ve)
- Gram +ve cocci in chains → enterococcus or streptococcus
- Gram +ve diplococci → pneumococcal
- Gram -ve diplococci → neisseria
- Gram -ve rods → many
- Gram -ve coccobacilli → brucella

2 Direct detection of organisms or organism component

- **Microscopy:**
  - bright microscopy: uses stains to enhance visual contrast between the organism and its background. Examples include Gram staining of bacteria and Ziehl–Neelsen or auramine staining of acid- and alcohol-fast bacilli (AAFB) in tuberculosis.
  - dark field microscopy: used to examine genital chancre fluid in suspected syphilis.
  - electron microscopy: used to examine stool and vesicle fluid to detect enteric and herpesviruses, respectively
  - flow cytometry: used to analyse liquid samples
- **Detection of organism components:** include nucleic acids, cell wall molecules, toxins and other antigens.
- **Nucleic acid amplification:** The most commonly used amplification method is the polymerase chain reaction (PCR).

3 Tests of the host's specific immune response (indirect)

- Antibody detection
- Interferon-gamma release assays (IGRA)

Antibiotics *(cont.)*

1 Obtain accurate diagnosis of infection *(cont.)*

◀ Identification of the infecting organism *(cont.)*

4 Culture of organisms

Bactec machine:

- An incubator, each hole has a fluorescent detector, whenever there's growth in the bottle (Blood culture bottle) there will be consumption of O2 and production of CO2, the increasing levels of CO2 will be detected by the fluorescent detector and will notify you when there's growth.
- After growth is seen, they will pull bottle out and start **gram staining** (First window in which we can see the microorganisms) and will help in determining the empiric therapy
- Next is **inoculation of the blood bottles** in 3 different agars (Blood, Macconkey and Chocolate) and leave it for 24hrs, after growing they will take 1 or 2 colonies and dilute it and put it in kits, kits will perform certain biochemical tests that will help differentiate the organisms and this will also take another 24hrs
- **Results: The organism and its susceptibility**, after knowing this you can change the empiric therapy and use abx specific for the organism found.

note: In certain cases the results of microbiology may take longer e.g. If the automated machine reports resistance to meropenem or carbapenem, you will have to confirm it manually or by PCR before releasing the final report (may take another 24hrs)

- **limitations of cultures:**
  - results are not immediate, even for organisms that are easy to grow
  - negative cultures rarely exclude infection.
  - Organisms such as *Mycobacterium tuberculosis* are slow-growing
  - organisms, such as *Mycobacterium leprae* and *Tropheryma whipplei*, cannot be cultivated on artificial media
  - *Chlamydia* spp. and viruses grow only in culture systems, which are slow and labour-intensive.

An area for your notes

Antibiotics *(cont.)*

2 Empiric and definitive therapy.

◀ What organisms are likely to be responsible?

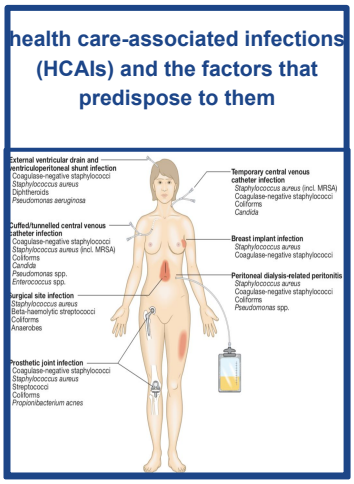
➔ The aims of investigating a patient with suspected infection are to confirm the presence of infection, identify the specific pathogen(s) and identify its susceptibility to specific antimicrobial agents in order to optimise therapy.

Best Educated Guess? You should know exactly what you're treating.

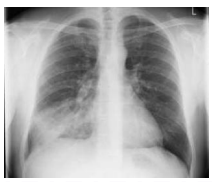
- How urgent?
- What are your patient's risk factors? immune status, age, pregnancy, lactation, hepatic and renal profile, allergies, comorbidities, usage of other drugs…
- Hospital acquired or community acquired infection?

Based on:

- History & physical examination —> You might have a clue to diagnosis. eg. long hospitalization → multiple organisms, MRSA...
- Epidemiological data
- Community-acquired
- Hospital-acquired: some patients have a lot of risk factors that makes them more susceptible to extensive drug resistance so it's important to identify these risk factors
    - Hospital-acquired is related to the presence of invasive devices and procedures. eg. ventilator → pneumonia (we should remove foreign body causing the infection, and have a hint about the most common causing organism).
    - Catheter related bacteremia:
        - Coagulase negative staph.
        - Methicillin-resistant Staphylococcus aureus [MRSA]
    - Catheter related UTI:
        - Gram negative (eg, Pseudomonas aeruginosa, Klebsiella)

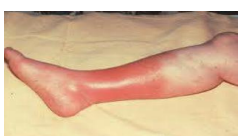


Patient with dyspnoea and cough:
Streptococcal pneumonia and atypical organism (e.g. Legionella and mycoplasma)
Treatment for this case: Cephalosporins and macrolides.



Patient with fever and urinary symptoms: E.coli
Note:
The increase in ESBL-producing E coli (ESBL-EC) among community-onset UTI is an important public health concern as these organisms are resistant to multiple antimicrobial agents. There are few abx that can be used to cover ESBL-EC: bactrim/fluoroquinolones or just nitrofurantoin if patient has cystitis only

Patient with erythema over the right leg associated with pain and tenderness:
Group A Streptococcus and Staphylococcus
This condition is called Erysipelas. How is it different from cellulitis? Here it has demarcated margins unlike cellulitis pic (Page 5) in which it's diffuse. Erysipelas is a superficial infection, affecting the upper layers of the skin, while cellulitis affects the deeper tissues.
Erysipelas → Most common Strep
Cellulitis → Most common Staph



Antibiotics *(cont.)*

2 Empiric and definitive therapy (cont.)

◀ 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: One of those:

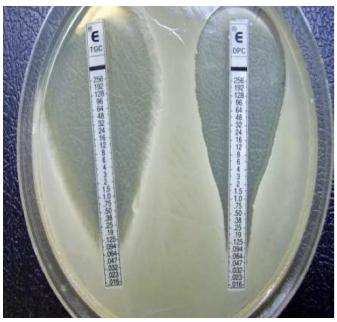
- susceptible:
  - indicates that the isolate is likely to be inhibited by the usually achievable concentration of a particular antimicrobial agent when the recommended dosage is used.
- resistant
- intermediate

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

- The lowest concentration of an antibiotic that inhibits visible growth of a microorganism. MIC that is necessary to be used by antibiotics to stop its growth.
- If the MIC is less than or equal to a predetermined breakpoint threshold, the organism is considered susceptible, and if the MIC is greater than the breakpoint, it is resistant.
- Different antibiotics have different MIC. i.e certain antibiotics have an MIC of 4 and other of 2
  - breakpoints depend on each organism. Breakpoints are determined for each antimicrobial agent from a combination of **pharmacokinetic** and **clinical data.**

1 Susceptibility test

1. disc diffusion test: using antimicrobial-impregnated disc,
2. diffusion strip test: using strip that is impregnated with antimicrobial at concentration gradient that decreases steadily → asses 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. Confirmation of resistance with a manual test.

- The relationship between in vitro antimicrobial susceptibility and clinical response is complex, as response also depends on **immune status, pharmacokinetic variability, comorbidities** that may influence pharmacokinetics or pharmacodynamics, and **antibiotic dosing,** as well as **MIC/MBC**. Thus, although treating a patient according to the results of susceptibility testing increases the likelihood of recovery, it does not guarantee therapeutic success.

Antibiotics *(cont.)*

2 Empiric and definitive therapy *(cont.)*

◀ KSUMC angiobiogram: percent-susceptible isolates 2018

- It is a collection of all samples that were collected from a certain hospital in the past 6 months or year, it shows the sensitivity percentage of each organism to a specific antibiotic.
- It helps a lot in hospital acquired infections (if patient came in from another hospital, we should obtain its antibiogram to know how to manage, especially if there's an outbreak in that hospital).

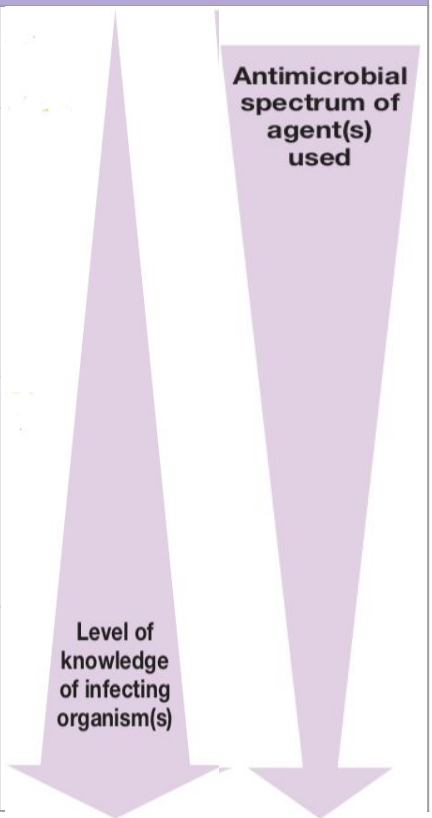
King Khalid University Hospital
January - June 2017 Cumulative Antibiogram for Gram-Negative Organisms - (Percent Susceptible)

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

Only 22% is sensitive to TZP → it should not be used in a patient who is suspected to have acinetobacter.

Stages in the selection and refinement of antimicrobial therapy: 'Start Smart – Then Focus'

stage	information available	treatment
Clinical diagnosis	• organ system involved • exogenous or endogenous infection • Likely pathogens	**empiric therapy**, based on: • predicted susceptibility of likely pathogens • local antimicrobial policies
Laboratory investigations: microbiological diagnosis	• infecting organism • likely antimicrobial susceptibility	**targeted therapy**, based on: • predicted susceptibility of infecting organism • local antimicrobial policies
Antimicrobial susceptibility results	antimicrobial susceptibility of infecting organism	susceptibility-guided therapy, based on: • susceptibility testing result



Antibiotics *(cont.)*

2 Empiric and definitive therapy *(cont.)*

◀ Timing of initiation of anti-microbial therapy

1 Urgent cases

Abx are life-saving, and any delay will affect patient's mortality and morbidity.

01 **Acute meningitis**

02 **Septic shock**

03 **Febrile neutropenia** (Immunocompromised)

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

- Why empiric? Microbiological results do not become available for 24 to 72 hours. Sample will be sent to the lab → put in incubator → whenever there is growth there will be consumption of O_2 & production of CO_2 → gram stain is done (It'll be the first time you see the organism) → sample is inoculated in 3 agars for 24 hrs → wait for colonies to grow → take colony for dilution → put in machine for detection → run biochemical and sensitivity testing → report gets out with results of resistance → lastly, manually do the testing for confirmation.
- Empiric antimicrobial therapy -guided by the clinical presentation- is selected to treat a suspected infection (e.g. meningitis) before the microbiological cause is known.
- Inadequate therapy for infections in critically ill, hospitalized patients is associated with **greater morbidity and mortality** there is a grey zone (critical zone) between sending workup & getting results, so we should have a careful selection of broad-spectrum antibiotics.
- **Use broad-spectrum antimicrobial agents as initial empiric therapy**, regimens need to have activity against the range of pathogens that could be causing the infection in question ; because broad-spectrum agents affect many more bacteria than needed, they select for antimicrobial resistance.
- Optimum empiric therapy depends on the site of infection, patient characteristics and local antimicrobial resistance patterns. National or local guidelines are often used to inform antimicrobial prescribing decisions.
- Considerations that should be documented when choosing an initial antibiotic regimen include:

01 route of administration.

02 frequency

03 duration of treatment.

04 monitoring for potential toxicity.

05 where appropriate, drug levels (e.g. pre-dose gentamicin or amikacin levels).

06 dose adjustment in renal/hepatic failure.

07 need for adjuvant therapy (rifampicin or fusidic acid for severe S. aureus infection).

08 alternative antibiotics for severe or non-severe penicillin allergy.

Antibiotics *(cont.)*

2 Empiric and definitive therapy *(cont.)*

Non-Urgent cases

In more stable clinical circumstances, hold antibiotics until appropriate specimens have been collected and submitted.

Example:

- subacute bacterial endocarditis → multiple sets of blood cultures
- Wound infection, diabetic foot, chronic ulcers. Patient's discharging for 2-3 weeks and stable → debridement → then deep tissue culture (because treatment could extend for 3 months so we should know the organism and choose the appropriate antibiotic accordingly) → then follow up the response
- Febrile and stable patient with fever for several days with no clue to diagnosis.

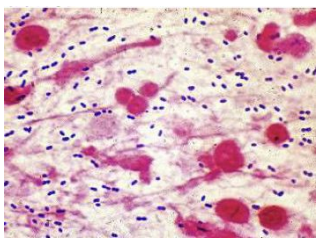
Harms of premature initiation of antimicrobial therapy: Can be as harmful as delaying the treatment, eg. a diabetic foot patient who is relatively stable and culture came negative after 5 days, but antimicrobial therapy was started before the result → this increases the chance of antimicrobial resistance + impacts the renal and hepatic functions.

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.

◀ Case study 2 (urgent vs non-urgent):

- 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. if there will be delay
  b. Arrange for urgent CT-scan brain
  c. Perform urgent LP and give the first dose of antibiotics. best answer if there will be no delay
  d. perform urgent LP and if csf is abnormal, start RX

- **Answer is: C**
- The time of CSF analysis is the determinant of the first step. This pt has Meningitis, if the LP and CSF analysis will take time (>30min) then start CS followed by abx and arrange for CSF study later. If <30min then you can do LP and CSF analysis then start CS and abx. Prophylaxis is indicated for those who were in contact with the pt.
- **Management:**
  - Patient was prescribed a dose of:
    - Ceftriaxone
    - Vancomycin → To cover ceftriaxone-resistant strep. pneumo
  - Urgent LP is done, Result:
    - WBC : 1230 cells/mm, 90% polymorph
    - RBC : NILL
    - Gram stain: Gram positive intracellular diplococci. **(Strep. pneumoniae)**



- Most likely diagnosis → pneumococcal meningitis
- Drug therapy: Only **pneumococcal** meningitis will benefit from **steroids** so it should be part of the treatment regimen. Although steroids (dexamethasone) have been proven to lower mortality only in S. pneumoniae infection, you must give them when you see thousands of neutrophils because you will not know the culture results for several days.

Antibiotics *(cont.)*

Once:

1. Microbiology have identified the etiologic pathogen
2. Antimicrobial susceptibility data are available.

Then:

3 Identify opportunities to **switch to narrow-spectrum**

Every attempt should be made to narrow the antibiotic spectrum and de-escalate depending on the sensitivity test, as much as possible - why?

1. Reduce cost and toxicity
2. Prevent the emergence of antimicrobial resistance in the community

◀ Steps in switching antibiotics:

- Sign for the narrowest spectrum and shortest duration of therapy
- **switch to oral agents as soon as possible.** Route of administration depends on what you're treating, eg.
  - simple UTI
  - bacteremia: also note that dosing will differ in Bacteremia, certain antibiotics are not suitable for bacteremia because the concentration will not be enough
  - osteomyelitis

In addition

- Non antimicrobial interventions by controlling the focus which is as important as narrowing the spectrum, such as abscess drainage **concurrently** with antibiotics (except lung abscesses, which are treated with antibiotics only without draining), are equally or more important in some cases and should be pursued diligently in comprehensive infectious disease management.

An area for your notes

Antibiotics *(cont.)*

4 **Cost-effective** oral agents for the **shortest duration** necessary

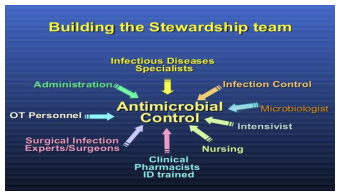
◀ Definition of antibiotics stewardship

➔ Antimicrobial stewardship (AMS) refers to the systems and processes applied to a population to optimise the use of antimicrobial agents.

➔ AMS aims to improve patient outcomes and reduce antimicrobial resistance (AMR), needs collaboration from all departments in order to reach the goal.

➔ Elements of AMS include treatment guidelines, antimicrobial formularies and ward rounds by infection specialists.

➔ Antibiotics stewardship is an activity that promotes:



A The appropriate **selection** of antimicrobials

B The appropriate **route & duration** of antimicrobials

C The appropriate **dosing** of antimicrobials

Relationship between AMS and IPC (infection prevention and control):

- AMS: effective AMS reduces health care-associated infections.
- IPC: effective IPC reduces the need for antimicrobials.

◀ What is the appropriate dose?

➔ **The lowest effective dose** → avoid sub-therapeutic doses

Determined by:

Serious vs non-serious infections

Site of infection[1]

01 02 03 04

Drug PK/PD properties[2]

Other host factors (e.g. renal function)

1: Eg. usual dose of meropenem is 1 mg/kg (in patients with normal kidney function) but with patients who have meningitis we have to increase the dose to 2 mg/kg.
2: Elderly, morbidly obese, GI problems (no PO), NGT...

Antibiotics *(cont.)*

4 **Cost-effective** oral agents for the **shortest duration** necessary *(cont.)*

◀ Any modification needed?

1. Narrow vs broad spectrum antibiotics (Narrow spectrum is always better)
2. Least toxic agent
3. Cheaper

◀ Criteria for Use of New Agent look for all of these factors

Antimicrobial activity is superior

Have a therapeutic advantage

Better pharmacokinetics
- Site penetration[1]
- Longer t ½
- Shorter duration

Less toxic

Better tolerance

Side effects | Dosing frequency | transfusion reaction problems

◀ Use of Antimicrobial Combinations:

➔ **when to use combination therapy?**

- when there is need to increase clinical effectiveness (e.g. biofilm infections)
- when no single agent's spectrum covers all potential pathogens (e.g. polymicrobial infection)
- when there is a need to reduce development of antimicrobial resistance in the target pathogen, as the organism would need to develop resistance to multiple agents simultaneously (e.g. antituberculous chemotherapy, antiretroviral therapy (ART)).

Exhibits synergistic activity is used in the treatment of serious infections: **Used in very limited situations**

A) Rapid killing is essential:
- Endocarditis caused by **Enterococcus species** with a combination of **penicillin and gentamicin**: bactericidal activity (In vivo enterococcus species are tolerant to penicillin alone so we add gentamicin to improve the bactericidal activity of penicillin)

B) Shorten the course:
- 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).

C) Critical ill patient:
- Empiric therapy
- If septic shock and blood cultures are reported to be growing-negative bacilli, it would be appropriate to provide initial therapy with 2 agents that have activity against gram-begative bacilli, particularly P aeruginosa.

1: 1st generation cephalosporins and tazocin have poor penetration into CSF (cannot penetrate BBB) → not used in CNS infections

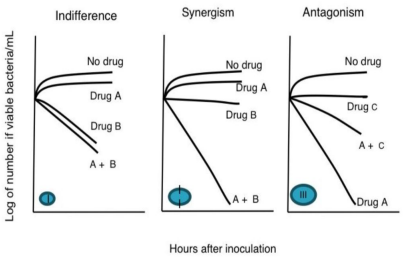
Antibiotics *(cont.)*

4 **Cost-effective** oral agents for the **shortest duration** necessary *(cont.)*

◀ Use of Antimicrobial Combinations *(cont.)*

D) Polymicrobial infections:
- Eg. Intra-abdominal infections, diabetic foot
- Antimicrobial combination, such as third-generation Cephalosporin or a fluoroquinolones **plus** metronidazole.
- in severe gram -ve pseudomona infection → we give 2 antipseudomonal therapy because of the variation of colonies on culture (some strains produce different colonies on culture)

Medications when combined could:



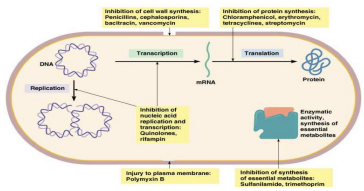
E) To prevent resistance
- Eg. In the treatment of TB, we use a combination of 4 anti-TB drugs in the first 2 months, then 2 anti-TB drugs for the rest of the course of treatment, to prevent resistance

5 Understanding drug **pharmacodynamics and efficacy** at the site of infection.

◀ Bactericidal vs Bacteriostatic Therapy

Bactericidal	Bacteriostatic
Cause death by cell rupture and disruption of the bacterial cell. **Drugs act on:** 1) **The cell wall** (b-lactams most famous) eg. penicillins & cephalosporins & carbapenems & monobactams → they own b-lactam rings → antibiotic works on the cell wall production of bacteria. 2) **Cell membrane** (daptomycin) 3) **Bacterial DNA** (fluoroquinolones) - Preferred in the case of serious infections such as: - endocarditis - meningitis to achieve rapid cure	- Inhibit bacterial replication without killing the organism. Most common MOA - Act by inhibiting protein synthesis such as: 1) Sulfonamides: 2) Tetracyclines 3) Macrolides

Sulfonamides competitively inhibit the incorporation of PABA into folic acid, thereby preventing the synthesis of folic acid. Trimethoprim binds reversibly to and inhibits dihydrofolate reductase, an enzyme that reduces dihydrofolic acid to tetrahydrofolic acid, decreasing folic acid synthesis. Bacterial intelligence can develop resistance against any of the mechanisms in the picture, which is why it's a continuous problem.



➔ In severe infections and/ or immunocompromised patients, it is customary to use bactericidal agents in preference to bacteriostatic agents.

Antibiotics *(cont.)*

5 Understanding drug **pharmacodynamics and efficacy** at the site of infection *(cont.)*

◀ Oral vs IV therapy

➔ Oral → for more stable patients providing that patient is tolerant to oral medications.
➔ IV → bacteremia, septic shock, infective endocarditis, severe meningitis...
➔ Candidates for treatment mild to moderate infections

- well-absorbed oral antimicrobial agents :
  - **Pyelonephritis**
    - Fluoroquinolones .
  - **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 as well as fluoroquinolones

◀ Efficacy

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. Not a well drug for CNS infections and should **not** be used to treat them. eg. meningitis, endophthalmitis (similar to BBB)
  - **Aminoglycosides:** are less active in the:
    - low-oxygen, low-pH, of Abscesses → Not good for abscesses
  - **Fluoroquinolones** achieve high concentrations in the prostate preferred oral agents for the treatment of **Prostatitis**. Excellent penetration → excellent for UTIs
  - **Moxifloxacin** does not achieve significant urinary concentrations therefore not suitable for treatment of UTIs because it is not excreted in the urine (low conc. in the urine).
- Knowing details about each antibiotic is important to know which one to use in each situation.

◀ Assessment of response to treatment

Response to treatment of an infection:

01 **Clinical parameters:**
improvement of symptoms and signs (e.g. fever, tachycardia, or confusion)
We assess the patient at least daily to 3 times a day:
- How is the treatment going? (especially empiric treatment)
- Is the patient improving
- Is the patient stable?
- When should I shift patient from IV to oral?
- Is the foreign body that is causing the infection removed?
- Can I remove the central line/catheter?

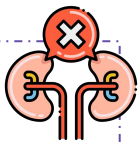
02 **Laboratory values** e.g. Procalcitonin is important for bacterial infections

03 **Decreasing leukocyte count**

04 **Radiologic decrease in the size of an abscess**

Antibiotics *(cont.)*

6 **Host characteristics** that influence antimicrobial activity:



Renal and Hepatic Function (Adjust dose)

Pregnancy and Lactation

special considerations, teratogenicity or otherwise toxic to the fetus:

- **Sulphonamides**: A risk to develop **kernicterus** (brain damage that occurs in a newborn with severe jaundice especially when used in the third trimester) especially in preterm infants. It can be used in the 2nd trimester. However, it's contraindicated in the 3rd trimester
- **Tetracycline: Staining of the teeth**
- **Fluoroquinolone: Cartilage damage**
- **Thalidomide: Phocomelia**
  - Thalidomide was released in the late 1950's
  - It was very effective: antiemetic and used to treat morning sickness and emesis in pregnant women
  - The biggest man-made medical disaster ever, over 10,000 children were born with a range of severe and debilitating malformations.

Note: If you check the biodata of each drug you will find its risk in pregnancy: A= Very safe, B= Acceptable to use, C= Shouldn't be used

Antimicrobial agents in pregnancy
Contraindicated
• Chloramphenicol: neonatal 'grey baby' syndrome – collapse, hypotension and cyanosis • Fluconazole: teratogenic in high doses • Quinolones: arthropathy in animal studies • Sulphonamides: neonatal haemolysis and methaemoglobinaemia • Tetracyclines, glycylcyclines: skeletal abnormalities in animals in first trimester; fetal dental discoloration and maternal hepatotoxicity with large parenteral doses in second or third trimesters • Trimethoprim: teratogenic in first trimester
Relatively contraindicated
• Aminoglycosides: potential damage to fetal auditory and vestibular nerves in second and third trimesters • Metronidazole: avoidance of high dosages is recommended
Not known to be harmful; use only when necessary
- aciclovir - glycopeptides - clarithromycin - meropenem - cephalosporins - linezolid - clindamycin - penicillin - erythromycin

Antibiotics *(cont.)*

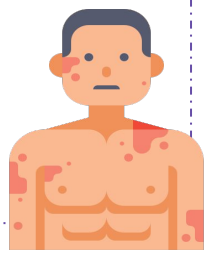
6 **Host characteristics** that influence antimicrobial activity *(cont.)*

History of Allergy or Intolerance.

- **Penicillin and anaphylaxis**

Anaphylaxis to penicillins or any antibiotic can be fatal, so careful evaluation is required. The timing of the reaction is of paramount importance:

- *Immediate hypersensitivity reactions*, which include anaphylaxis, are immunoglobulin E (IgE)-mediated and classically begin within 1 h of the dose, and often within minutes. Typically, they are characterized by facial swelling, rash and severe shortness of breath.
- *Delayed reactions* appear after multiple doses of treatment, typically after days or weeks. While they may be immune- mediated, they are not associated with anaphylaxis, although in some rare cases they can lead to severe or life-threatening conditions such as Stevens–Johnson syndrome and toxic epidermal necrolysis



Consider Special Host Factors

- Genetic e.g, G6PD → avoid sulfa group in G6PD patients as it may lead to hemolysis
- Drug interactions are important to consider

Old Age

- problem with antimicrobial therapy in old age:
  - **Clostridium difficile infection:**
    - all antibiotics predispose to some extent, but second- and third-generation cephalosporins, co-amoxiclav and fluoroquinolones (e.g. ciprofloxacin) especially so
  - **Hypersensitivity reactions:**
    - rise in incidence due to increased previous exposure.
  - **Renal impairment:**
    - may be significant in old age, despite 'normal' creatinine levels
  - **Nephrotoxicity:**
    - more likely, e.g. first-generation cephalosporins, aminoglycosides.
  - **Accumulation of β-lactam antibiotics:**
    - may result in myoclonus, seizures or coma.
  - **Reduced gastric acid production:**
    - gastric pH is higher, which causes increased penicillin absorption.
  - **Reduced hepatic metabolism:**
    - results in a higher risk of isoniazid-related hepatotoxicity.
  - Quinolones: associated with delirium and may increase the risk of seizures.

Antibiotics *(cont.)*

◄ Organisms and the antibiotics to use

Organism	Antibiotics
MRSA Methicillin Resistant Staph. Aureus (R mechanism: PBP2a penicillin binding protein)	• Vancomycin (Glycopeptide) • Teicoplanin (Glycopeptide) • Linezolid, Tedizolid • Daptomycin (Lipopeptide) • Telavancin (Glycopeptide) • Dalbavancin (Glycopeptide) • Oritavancin (Glycopeptide) • Ceftaroline (5th generation cephalosporins) • Tigecycline: cannot be used for pneumonia or bacteremia, only for intra-abdominal infections and skin and soft tissue infections • Delafloxacin: new fluoroquinolone agent • **Ceftobiprole** : 5th generation cephalosporins
VRE Vancomycin Resistant Enterococcus (common inside hospitals)	• Teicoplanin • Linezolid • Oritavancin • Tedizolid Daptomycin • Tigecycline and Eravacycline (new agents used only for intra-abdominal infections and skin and soft tissue infections, not UTIs since it isn't excreted in urine)
ESBL Extended Spectrum Beta-Lactamase ★	• **Carbapenems: drug of choice** • Piperacillin/tazobactam: increases mortality if given to severe infections. • Nitrofurantoin and fosfomycin (**UTI**): for very mild infections only. • Tigecycline and Eravacycline: for intra-abdominal infections and skin and soft tissue infections only • Colistin • Plazomicin • fluoroquinolones: like cipro and bactrim (depends on what you're treating)
CRE Carbapenem-Resistant Enterobacteriaceae Challenging infection, that carries high mortality and morbidity, need to produce new agents for treatment	• Nitrofurantoin and fosfomycin (UTI): for simple cystitis • Tigecycline and Eravacycline: for intra-abdominal infections and skin and soft tissue infections only. • **Colistin**: only one used for **NDM and OXA-45** → MOA of bacteria (covers BOTH MOAs) • Ceftazidime/avibactam and Meropenem/vaborbactam (new agents for OXA-45) • Plazomicin (used for OXA-45 only) Perform PCR to see what's the mechanism of resistance, based on this we choose the abx
Actinobacter Very bad, fast growing problem, especially in ICU pt and it has very limited choices of abx	• Carbapenems: 70% of actinobacter are carbapenem resistant, use if sensitive • Tigecycline and Eravacycline : for intra-abdominal infections and skin and soft tissue infections only (This organism mostly causes pneumonia in ICU, these two abx cannot be used for pneumonia) • Aminoglycosides, Colistin (only saving agent, but has many problems including dosing, they are nephrotoxic and not enough alone)
Pseudomonas aeruginosa Very famous hospital acquired infection ★	• Piperacillin/tazobactam: From all penicillins this is the only one that cover psuedomonas. ★ Ceftazidime (3rd) and cefepime (4th) and **Ceftobiprole** (5th generation cephalosporins) These are the only cephalosporins that cover pseudomonas • Meropenem, imipenem and Doripenem (carbapenem group) • Aztreonam • Some fluoroquinolones (only **ciprofloxacin** and levofloxacin) • Aminoglycosides • Colistin • Ceftolozane/tazobactam and Ceftazidime/avibactam (new agents).

Antimicrobial agents as prophylactic

◀ Antimicrobial agents as prophylactic

➔ **Antimicrobial prophylaxis:** the use of antimicrobial agents to prevent infection.

1. **Primary prophylaxis:** used to reduce the risk of infection following certain medical procedures, following exposure to a specific pathogen (e.g. *Bordetella pertussis*) or in specific situations such as post-splenectomy .

2. **Secondary prophylaxis**: used in patients who have been treated successfully for an infection but remain predisposed to it.

Presurgical Antimicrobial Prophylaxis:

- is used to reduce the incidence of postoperative surgical site infections. We should dictate our aim when giving prophylactic antibiotics.
- A single dose of a cephalosporin (such as cefazolin) administered within 1 hour before the initial incision is appropriate for most surgical procedures. Most of the times it's just a single dose, very limited times beyond that is indicated.

Prevent Transmission of Communicable Pathogens to Susceptible Contacts:

- Ciprofloxacin or Rifampicin for close contacts of a patient with N.meningitidis → need to give prophylaxis, eg. during Hajj

i 6.18 Recommendations for antimicrobial prophylaxis in adults

Infection risk	Recommended antimicrobial
Bacterial	
Diphtheria (prevention of secondary cases)	Erythromycin
Gas gangrene (after high amputation or major trauma)	Penicillin or metronidazole
Lower gastrointestinal tract surgery	Cefuroxime + metronidazole, gentamicin + metronidazole, or co-amoxiclav (single dose only)
Meningococcal disease (prevention of secondary cases)	Rifampicin or ciprofloxacin
Rheumatic fever (prevention of recurrence)	Phenoxymethylpenicillin or sulfadiazine
Tuberculosis (prevention of secondary cases)	Isoniazid ± rifampicin
Whooping cough (prevention of secondary cases)	Erythromycin
Viral	
HIV, occupational exposure (sharps injury)	Combination tenofovir/ emtricitabine and raltegravir. Modified if index case's virus known to be resistant
Influenza A (prevention of secondary cases in adults with chronic respiratory, cardiovascular or renal disease, immunosuppression or diabetes mellitus)	Oseltamivir
Fungal	
Aspergillosis (in high-risk haematology patients)	Posaconazole (voriconazole or itraconazole alternatives if intolerant)
Pneumocystis pneumonia (prevention in HIV and other immunosuppressed states)	Co-trimoxazole, pentamidine or dapsone
Protozoal	
Malaria (prevention of travel-associated disease)	Specific antimalarials depend on travel itinerary (p. 278)

Antimicrobial Prophylaxis Before Dental Procedures:

Dental prophylaxis indications:

- Prosthetic valves
- rheumatic heart
- Unrepaired congenital heart disease
- Previous infective endocarditis

→ to prevent endocarditis or rheumatic fever (monthly injection of penicillin to reduce recurrence of rheumatic fever)

Positive culture in the absence of disease

➔ Colonization without any associated manifestation of disease occurs frequently in **certain populations:** → leads to over treating with antibiotics when there is no need to do anything because it's a colonization and the patient is asymptomatic. **No need to treat colonization** except in special cases like UTI +ve culture, if patient is pregnant or symptomatic or going for a procedure → treat

1. **Old women**
   with **indwelling urinary catheter**:
   Active infection are absent (asymptomatic bacteriuria)

2. **Endotracheal tubes**
   In mechanically ventilated patients

3. **Chronic wounds**

◀ Antimicrobial decision making ★

antimicrobial decision-making at 72 hours, when most culture results are available, one of the following five decisions should be made:

- **Stop antibiotic treatment**: cessation of antibiotics is the appropriate action when patients are thought not to have had an infection after all.
- **Step down to an oral alternative**: For uncomplicated infections, e.g. pneumonia or pyelonephritis, treatment can normally be switched from intravenous to oral after 2–3 days if the patient is clinically stable and is showing signs of clinical improvement.
- **Switch treatment**: This may be necessary because of an unanticipated site of infection (e.g. infective endocarditis requiring prolonged intravenous antibiotic treatment) or unanticipated resistance (such as urosepsis and bacteraemia caused by an **ESBL-producing E. coli requiring treatment with an intravenous carbapenem**).
- **Continue with intravenous treatment**: The patient has a more complicated or difficult-to-treat infection, such as meningitis or septic arthritis.
- **Discharge on outpatient parenteral antibiotic treatment**: This is defined as the provision of intravenous antibiotics to patients out of hospital in either the community or an ambulatory care setting. For conditions such as skin and soft tissue infection, urinary tract infections and bone and joint infection, where the patient is otherwise well, treatment may be continued in the community.

An area for your notes

Summary

<table>
<tr><td>Definition</td><td colspan="2">Antibiotic : chemical that produced by a microorganism that kills or inhibits the growth of another microorganism.</td></tr>
<tr><td>Indications</td><td colspan="2">• Clinical diagnosis of bacterial infection: Pneumonia (CAP) treated empirically (macrolide or fluoroquinolone antibiotic) without performing specific diagnosis test.
• Prophylactic: Before surgeries and dental procedures (single dose of a cephalosporin administered within 1 hour before most surgical procedure) - Prevent Transmission of Communicable Pathogens to Susceptible Contacts (Ciprofloxacin for close contacts of a patient with N.meningitidis).</td></tr>
<tr><td rowspan="2">Timing of Initiation of Antimicrobial Therapy</td><td>Urgent</td><td>Non urgent</td></tr>
<tr><td>1) Acute meningitis.
2) Septic shock.
3) Febrile neutropenia.
• Empiric therapy should be initiated immediately after or concurrently with collection of diagnostic specimens</td><td>• Febrile and stable patient with fever for several days or months with no clue to diagnosis.
• In more stable clinical circumstances, hold antibiotics until appropriate specimens have been collected and submitted.
• Example: subacute bacterial endocarditis must multiple sets of blood cultures</td></tr>
<tr><td>Organisms responsible</td><td colspan="2">Based on:
• History & physical examination.
• Epidemiological data: Hospital-acquired vs community-acquired & Prior antibiotic
Examples :
• Patient with dyspnea and cough: Streptococcal pneumonia and atypical organism
• Patient with fever and urinary symptoms: E. coli
• Patient with erythema over the right leg associated with pain and tenderness: Group A streptococcus and Staphylococcus</td></tr>
<tr><td>Use of Antimicrobial Combinations</td><td colspan="2">Used in the treatment of serious infections:
• Rapid killing is essential: Endocarditis caused by Enterococcus species with a combination of penicillin and gentamicin: bactericidal activity.
• Shorten the course: 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
• Polymicrobial Infections</td></tr>
<tr><td>Host factors that influence antimicrobial activity</td><td colspan="2">• Renal and Hepatic Function
• Pregnancy and Lactation
• History of Allergy or Intolerance</td></tr>
<tr><td rowspan="5">Antibiotic risks</td><td>Drug</td><td>Risk</td></tr>
<tr><td>Sulphonamides</td><td>A risk to develop kernicterus, especially preterm infants.</td></tr>
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very effective antiemetic that was used to: - treat morning sickness
- emesis in pregnant women.</td><td>Phocomelia:
The biggest man-made medical disaster ever, Over 10,000 children were born with a range of severe and debilitating malformations.</td></tr>
</table>

Lecture Quiz

Q1: A 59-year-old man undergoes coronary bypass surgery. He receives cefazolin prophylactically for 24 hours. On the ninth postoperative day, he develops a fever of 39.8°C with a heart rate of 115 beats/minute and a blood pressure of 105/65 mmHg. The surgical site is healing well with no redness or discharge. His white blood cell count is 14,000/mm3 and urinalysis reveals many white blood cells per high power field. Blood and urine cultures grow a non-lactose fermenting oxidase-positive gram-negative rod. Which of the following antibiotics is most appropriate to treat this infection?

A- Moxifloxacin.
B- Ceftriaxone.
C- Doripenem.
D- Trimethoprim-sulfamethoxazole.

Q2: A female arrives at the emergency department with complaints of high fever, malaise, painful urination and severe flank pain. Lab tests indicate the presence of white blood cells and E.coli in her urine. A diagnosis of kidney infection (pyelonephritis) is made, and the decision is made to use a beta-lactam antibiotic that has both an appropriate antibacterial spectrum of activity, and good tissue penetration, yet is more resistant to beta-lactamases than narrow spectrum penicillins. The drug that best fits these characteristics is?

A- Ceftriaxone
B- Daptomycin
C- Fosfomycin
D- Nitrofurantoin

Q3: Which one of these cases is not a clear indication for the use of prophylactic antimicrobial agents to reduce the risk of developing infection?

A- A 68-year-old male with a prosthetic heart valve who will undergo an invasive dental procedure.
B- A susceptible close contact person with a meningitis patient infected with Neisseria meningitides.
C- A 35-year-old woman with a central venous catheter placed to deliver chemotherapy for treatment of breast cancer.
D- A 70-year-old woman with a brain tumor, which is going to be removed surgically tomorrow,

Q4: A 35-year-old previously healthy man develops cough with purulent sputum over several days. On presentation to the emergency room, he is lethargic. Temperature is 39°C, pulse 110, and blood pressure 100/70. He has rales and dullness to percussion at the left base.There is no rash. Flexion of the patient's neck when supine results in spontaneous flexion of hip and knee. Neurologic examination is otherwise normal. There is no papilledema. A lumbar puncture is performed in the emergency room. The cerebrospinal fluid (CSF) shows 8000 leukocytes/μL, 90% of which are polys. Glucose is 30 mg/dL with a peripheral glucose of 80 mg/dL. CSF protein is elevated to 200 mg/dL. CSF Gram stain is pending. Which of the following is the correct treatment option?

A- Begin acyclovir for herpes simplex encephalitis.
B- Obtain emergency MRI scan before beginning treatment.
C- Begin ceftriaxone and vancomycin for pneumococcal meningitis.
D- Begin ceftriaxone, vancomycin, and ampicillin to cover both pneumococci and Listeria.

Q5: An 18-year-old high school student presents to the emergency room with 1-day history of right knee pain, swelling, and redness. He is a quarterback in the school's football team.He remembers falling on the knee while practicing 2 days ago. The knee is tapped and 15 mL of cloudy fluid is sent for cell count, Gram stain, and culture. The Gram stain shows gram-positive cocci in clusters. Which of the following is the best course of action?

A- Start vancomycin and consult orthopedic surgery.
B- Consult orthopedic surgery.
C- Start linezolid awaiting culture results.
D- Start ceftriaxone.
E- Start telavancin and order MRI of the knee.

Answers: Q1:C | Q2:A | Q3:C | Q4:C | Q5:A

Answers Explanation File!

THANKS!!

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Send us your feedback:
We are all ears!