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.**

Editing file

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Lecture Outline:

The main goal in this lecture is to know the approach of how to choose the appropriate antibiotic for different scenarios.

★ Introduction

- History
- Classes
- Resistance

★ Approach:

Which AB is appropriate for this patient ? it's determined based on multiple things:

- *Patient Factors*
  - Age, History, Renal and Hepatic function, Genetic variation, pregnancy and lactation, Allergies, timing, site of infection

- *Microbiological factors*
  - Empiric vs definitive
  - Identification of organism
  - Hospital vs Community acquired
  - Antibiogram

- *Pharmacological factors*
  - Pattern of action
  - Principles
  - Dosage
  - Bioavailability

- *Treatment of special resistance organisms*

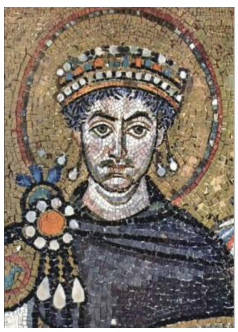
Introduction To Antibiotics

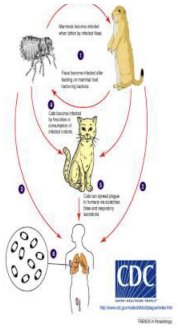
- **Why should we know about antibiotics?**

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

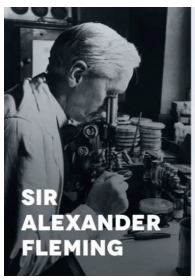
◄ History of antibiotics

- 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.





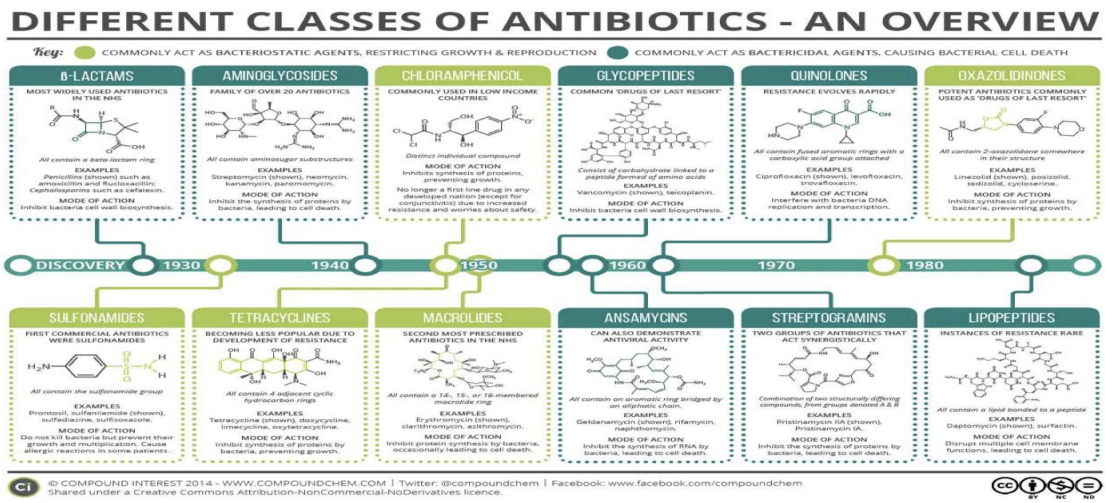
- Discovery of the therapeutic value of penicillin by Alexander Fleming from Penicillium notatum in 1928. A life saving discovery. Its discovery was by incidence, while he was eating a sandwich, a breadcrumb fell on the agar of staph.aureus, after 2 days the crumbs got moldy and he noticed an inhibition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



◄ IDSA Guidelines - Definition of Antimicrobial Stewardship

- **Antimicrobial stewardship is an activity that promotes these thongs to the right disease:**

A. The appropriate **selection** of antimicrobials

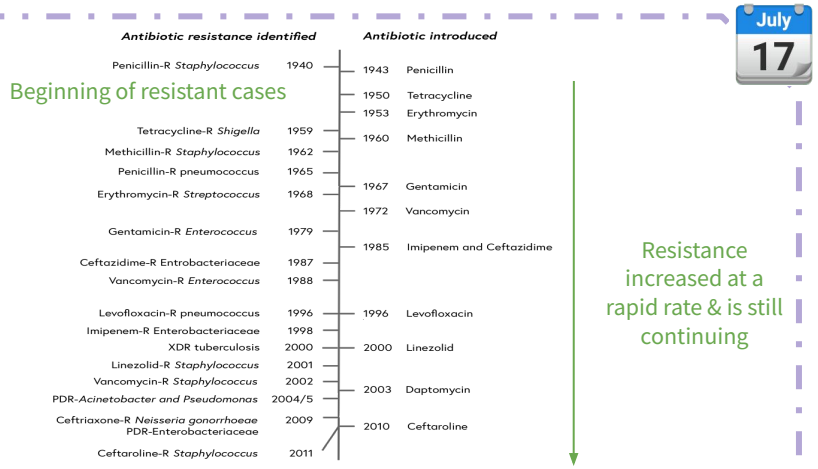
B. The appropriate **route & duration** of antimicrobials

C. The appropriate **dosing** of antimicrobials

Introduction To Antibiotics

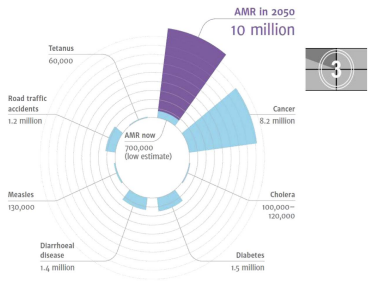
◀ Developing resistance, a timeline

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



◀ 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 if we don't take actions (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

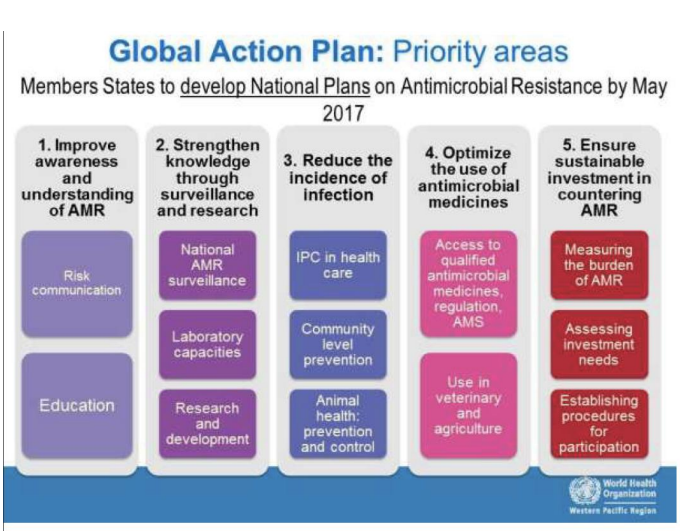


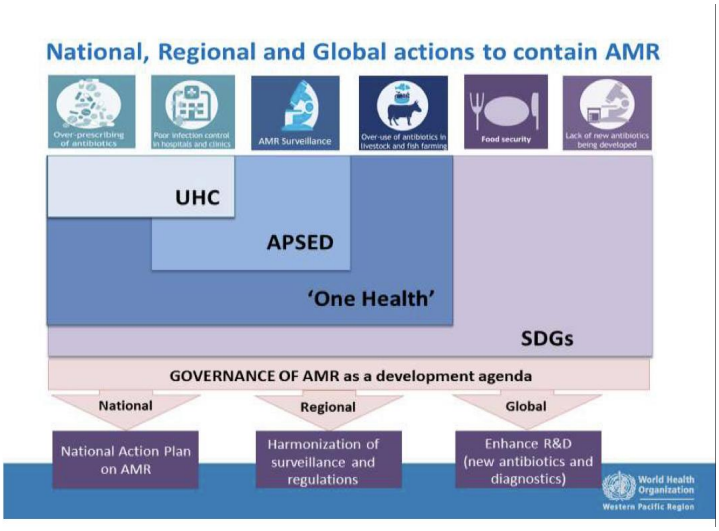
G7 2017 ITALIA

G20 GERMANY 2017

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.





Approach: 1.Patient Factors

Obtaining an accurate infectious Disease Diagnosis

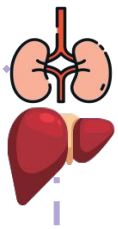
◀ History

- 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

◀ 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.

◀ 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.

◀ 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 (ARV) 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 inpatients 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 (sulfa group), such as dapsone, primaquine (Malaria treatment), and nitrofurantoin.

Approach: 1.Patient Factors

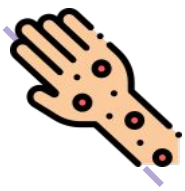
◀ Pregnancy and Lactation

- Special considerations for the use of antimicrobial agents in pregnancy relate to both the mother and the fetus and it's important to know how safe is the medication to the pregnant lady.
- 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 establis 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
Imipenem-cilastatin	C	cephalosporins not an option
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	C	clarithromycin with caution and only if benefits outweigh risks
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
Ethambutol	B	pregnancy while on tuberculosis therapy.
Pyrazinamide	C	Pyridoxine (B6) should be given with INH
Rifampin, rifabutin, rifapentine	C	during pregnancy
Bedaquiline	B	

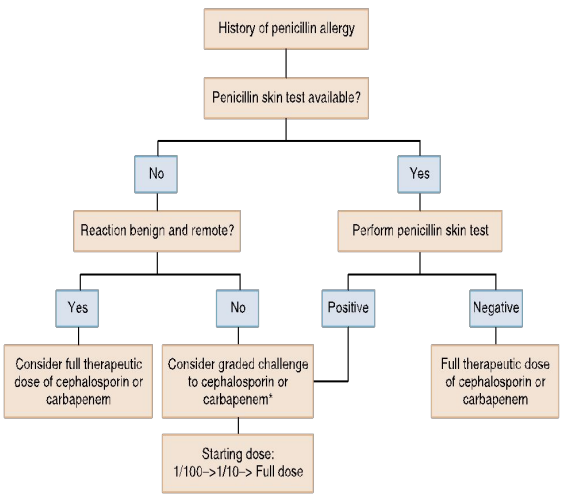
[a]Ceftolozane-tazobactam and ceftazidime-avibactam were recently approved at the time of this manuscript, but also carry a Pregnancy Category B rating.

◀ History of Allergy or Intolerance



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

- History of allergies are extremely important and one of the comments allergies is to Beta lactams (e.g.penicillin) and it's due to cross reactivity with type 1 hypersensitivity reactions and it's important to take detailed history for this allergie (is it anaphylaxis or just a skin rash? If it's rash I can go with other groups of beta-lactams but if it's anaphylaxis we have to either do skin test which doesn't have a great benefit or using in vitro test assuming there is proliferation of certain immune reactants but it's not commercially used so they go with **the gold standard** which is dose challenge test (pt allergic to Amoxicillin, give him ceftriaxone 1 over 1000 of the dose and after half an hour, we give him 1 over 100 then 1 over 10 then we give full dose and if he tolerates the full dose then he is non allergic to ceftriaxone)



*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.

Approach: 1.Patient Factors

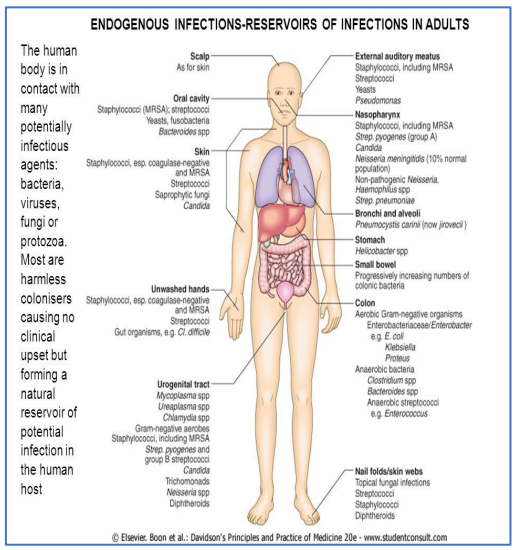
◄ Timing of initiation of antimicrobial therapy

- 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.
- Important examples of this principle are subacute bacterial endocarditis and vertebral osteomyelitis/discitis.
- 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/discitis) 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.

◄ Site of infection

1. Location: based on it, we can know if it's monomicrobial or polymicrobial organisms
   - If it's GI perforation, diabtic foot or necrotizing fasciitis we can know they're polymicrobial organisms it could be gram -ve, +ve or anaerobes
   - If it's meningitis, pneumonia or skin and soft tissue infection we can know it's monomicrobial organism

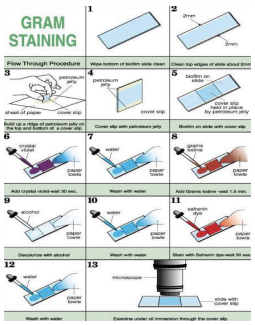
2. Source: are we dealing with community acquired infection or healthcare associated infections because if it's healthcare associated infection there must be added tests



Approach: 2.Microbiological Factors

◄ 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 (cause meningitis in young patients i.e. infants and newborns)
- Gram -ve diplococci ⟶ Neisseria
- Gram -ve rods (bacilli) ⟶ a lot of organisms
- Gram +ve rods (bacilli)⟶ Listeria monocytogenes (cause meningitis in immunocompromised and extreme ages)
- Gram -ve coccobacilli ⟶ brucella

2 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 O_2 and production of CO_2, the increasing levels of CO_2 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 we can know which type of infection he/she has) 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: <u>The organism and its susceptibility</u>**, 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.

Approach: 2.Microbiological Factors

◄ Identification of the infecting organism

3 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 and based on MIC I can interpret it if it's sensitive, intermediate or resistant

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.

Empiric vs Definitive antimicrobial therapy	Community vs HCAI	Antibiogram
◄ 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.	• 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. **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	• Every hospital makes connections to the samples that present over 6 months or 1 year to know what's the patterns of sensitivity, let's say in ICU the most common gram -ve organisms is E.coli and its sensitivity pattern is 60% resistant to carbapenems so if I have patient develop infection (e.g.pneumonia or bacteremia) with gram -ve organism I should consider the epidemiology in my ICU that shown the sensitivity to carbapenems is low so I should select agents overcome this problem **King Khalid University Hospital** **January - June 2017 Cumulative Antibiogram for Gram-Negative Organisms - (Percent Susceptible)** Only 22% is sensitive to TZP → it should not be used in a patient who is suspected to have acinetobacter.

Gram-Negative Organisms	No. of strains	β-lactams							Quinolones		Aminoglycosides		Others	
		AMP	CZ	CX	CAZ	FEP	ME	TZP	CIP	NOR	AN	GM	NIT	TMS
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: 3.Pharmacological Factors

- It's extremely important to know about drug metabolism, MOA, if it's nephrotoxic or hepatotoxic,tissue distribution, penetration to the tissue, bone, lung and CNS so you can know which antimicrobial you can use for certain diseases

Pattern 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 Fluoroquinolones Daptomycin Ketolides
Type II	Time dependent minimal PAE	T>MIC	Maximize duration of exposure	Penicillin Carbapenems Cephalosporins Linezolids E.mycin
Type III	Time dependent prolonged PAE	AUC/MIC	Maximize amount of drug	Azithromycin Clindamycin Tetracycline Vancomycin

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 and monobactams → they own b-lactam rings → antibiotic works on the cell wall production of bacteria. Vancomycin, teicoplanin and daptomycin 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 4) Aminoglycosides (but in general it's bactericidal)

- 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.
- MSSA infection: it's a common and serious infection, the best drug for it? Penicillinase resistant penicillins and 1st generation cephalosporin. Penicillinase resistant penicillins it's frequent so every 4 hours we should give a does and can cause thrombophlebitis or acute interstitial nephritis but they found that its outcome equal to 1st generation cephalosporin which are convenient we give it to the patient every 8 hours and has less side effects

Approach: 3.Pharmacological Factors

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 1/2
  - Shorter duration
- Less toxic
- Better tolerance

What is the appropriate dose?

- **The lowest dose that is effective..**
- Avoid subtherapeutic doses
- Determined by:
  - Serious Vs Non-serious infection
  - Site of infection
  - Drugs PJ/PD properties
  - Other host factors (e.g. Renal function…etc)

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
- 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.

Bioavailability

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

- The best bioavailability is when it's given through IV route (100% bioavailability)
- Examples of antibiotics with excellent bioavailability are:
  Trimethoprim-sulfamethoxazole

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) and tazocin which a very common medication in emergency but have a poor penetration 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.**
- Knowing details about each antibiotic is important to know which one to use in each situation.

Approach: 3.Pharmacological Factors

◀ 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 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:

- 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.

A) Rapid Killing is sessental:

- 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 (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.

B) Shorten the course:

- 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).

Approach: 3.Pharmacological Factors

◀ Use of Antimicrobial Combinations:

C) Critical ill patient:

- 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.

D) Polymicrobial infections:

- E.g. Intra-abdominal infections, diabetic foot
- Extend the antimicrobial spectrum beyond that achieved by use of a single agent for treatment of polymicrobial 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.
- 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

E) 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.
- e.g. 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

Approach: 3.Pharmacological Factors

◀ Antimicrobial agents as prophylactic

- **Antimicrobial prophylaxis:** the use of antimicrobial agents to prevent infection.
- **Loading does:** in certain medications we need loading does e.g. vancomycin and colistin, we give the full loading dose regardless the renal and liver function and the adjustment will be on maintenance does

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.
- Presurgical prophylaxis depends on the half life and weight of the patient

Prevent Transmission of Communicable Pathogens to Susceptible Contacts:

- Ciprofloxacin or Rifampicin for close contacts of a patient with N.meningitidis (Post exposure prophylaxis) ⟶ 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 ⟶ to prevent endocarditis or rheumatic fever (monthly injection of penicillin to reduce recurrence of rheumatic fever)
- Unrepaired congenital heart disease
- Previous infective endocarditis

Approach: 3.Pharmacological Factors

Positive culture in the absence of disease

- Generally if there is colonization we don't treat except for certain conditions because→ 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 we should treat them like:
  - Asymptomatic bacteriuria with +ve Urine culture for patient going to urological procedures like cystoscopy
  - Pregnancy

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

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.

Antibiotics

◄ 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)
VERY VERY IMPORTANT **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
★ **Acinetobacter** Mostly hospital based Very bad, fast growing problem, especially in ICU pt and it has very limited choices of abx	• Carbapenems: 70% of acinetobacter 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)
VERY IMPORTANT **Pseudomonas aeruginosa** Very famous hospital acquired infection ★★	• Piperacillin/tazobactam: From all penicillins this is the only one that cover pseudomonas. ★ 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).

EXTRA

◄ Case study 1 (is an antibiotic indicated):

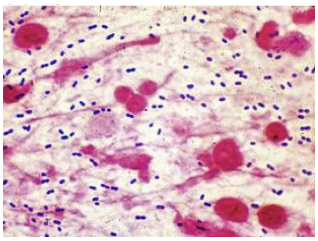
A 30-year-old male presented to an urgent care clinic with a 4-day history of dry cough, progressing to rusty colored sputum, sudden onset of chills the previous evening, subjective fever, and malaise. Originally, the man thought he had a cold, but the symptoms had worsened and he "barely slept last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

◄ 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)**



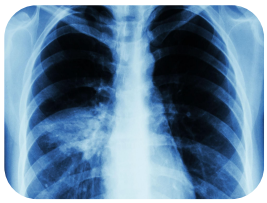
- Most likely diagnosis → pneumococcal meningitis
- Drug therapy: Only **pneumococcal** meningitis will benefit from **steroids** so it should be part of the treatment regimen. Although steroids (dexamethasone) have been proven to lower mortality only in S. pneumoniae infection, you must give them when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

You can find more EXTRA info in 438 team

Doctor's Questions

Q1: 54 years old male known case of DM , HTN, ESRD on hemodialysis presented to the ER with fever cough and S.O.B for 4 days he is conscious and oriented BP normal RR 22 CBC showed leukocytosis C-XRAY as following:

Which of the following is the best treatment option ?

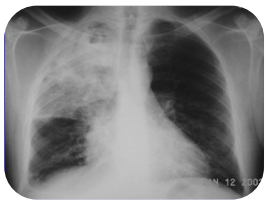


A- Admit & start IV ceftriaxone and azithromycin
B- Oral cefuroxime and azithromycin
C- tazocin and ciprofloxacin
D- Vancomycin 1gm iv bid

Q2: A 78-year-old man presents with a 4-day history of fever and cough productive of thick sputum. He has never smoked. Clarithromycin, given for the past 2 days, has been ineffective. A blood culture drawn in the office is reported to be growing gram-positive cocci in pairs.
Chest radiograph shows an infiltrate in the right lower lobe. The patient is unable to produce sputum for examination.
Which of the following antibiotics, administered intravenously, is the most appropriate initial therapy?

A- Azithromycin
B- Vancomycin
C- Ceftazidime
D-Trimethoprim-sulfamethoxazole

Q3: A 60 year-old Saudi male, heavy smoker for 40 years. Presented to ER with 4 months history of fever and yellowish sputum. He lost 10 kgs over 2 months. He was treated with antibiotics twice in another hospital over the past month. He had temporary improvement but got worse after stopping the antibiotics. He is otherwise well with no other illnesses. CXR shown.
The most likely explanation for his illness is:

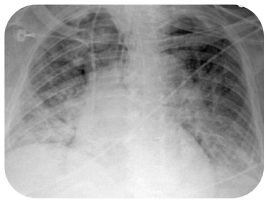


A- Recurrent aspiration
B- Atypical pneumonia
C- Post obstruction bacterial pneumonia
D- Pulmonary tuberculosis

Q4: 45 years old African man presented to the emergency room with history of low grade fever, cough with hemoptysis , decrease appetite and weight loss for the last 1 month.
Which of the following steps should be done next :

A- isolate the patient in negative pressure room and do sputum AFB
B- start INH, rifampin, pyrazinamide and ethambutol
C- start ceftriaxone and azithromycin
D- reassure the patient and book him for PFT

Q5: 54 years old patient post RTA intubated in ICU for 1 week we have been consulted for new chest infiltrate and increase in his ventilator setting and fio2 requirement for 1 day patient is hypotensive on inotropes his chest x-ray as following :
Full septic work up sent.
Which empiric AB is appropriate:



A- ceftriaxone azithromycin
B- meropenem vancomycin
C- tigecycline
D-colistin

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

Answers Explanation File!

Doctor's Questions

Q6: After 48 hours patient has increase in inotropes requirement and micro lab notified for gram-negative bacilli there is multiple cases in ICU with Stenotrophomonas maltophilia infection. Which changes in antibiotics is required?

A- continue the current treatment
B- add colistin
C- D/C vancomycin and add Bactrim
D- add aminoglycoside

Q7: A 16 year-old male patient comes to ER with a 3 days history of fever, headache, neck pain, and double vision. No history of raw milk ingestion or contact with animals. Examination revealed an uncomfortable and emaciated young aged man. He has neck stiffness.
CSF analysis showed WBC 100 cells/µL with 90% polymorph, high protein and low glucose, gram stain showed gram +ve diplococci.
Which ONE of the following empirical antimicrobial combination would you start?

A- Ceftriaxone and vancomycin
B- Ceftriaxone, vancomycin and dexamethasone
C- Doxycycline, rifampin and ciprofloxacin
D-INH, rifampin, pyrazinamide, ethambutol and dexamethasone

Temp	38.9^{O} C
BP	120/70 mmHg
Pulse rate	100 Per min
Respiratory rate	16 Per min

Q8:Which of the following is the most common organisms causing osteomyelitis in all age groups?

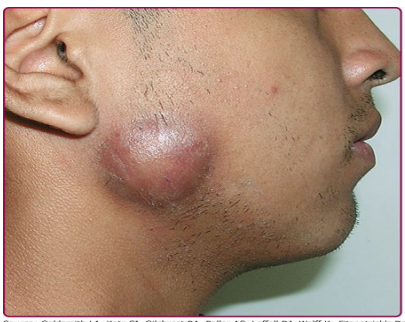
A- streptococci
B- staph aureus
C- Ecoli
D- Haemophilus

Q9: 24 years old pregnant lady in the second trimester presented to the antenatal care clinic For routine follow up , she has no complain lab test revile positive urine culture E.COLI ESBL sensitive to ciprofloxacin, trim-sulfa, meropenem. Which of the following is the beast option?

A- No treatment
B- Ciprofloxacin 500mg BID
C- cefuroxime 500mg bid
D- Ertapenem 1 gm daily

Q10: Which one of the following organisms is the most likely?

A- Prevotella melaninogenica
B- Nocardia cyriacigeorgica
C- Actinomyces israelii
D-Mycobacterium tuberculosis



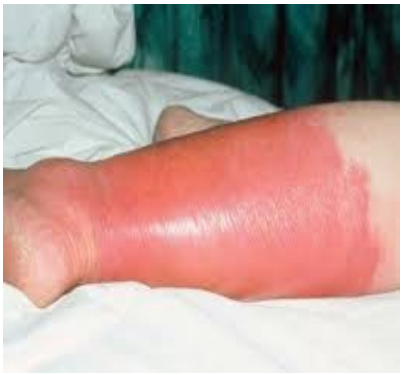
Answers: Q6:C | Q7:A | Q8:B | Q9:C | Q10:C

Answers Explanation File!

Doctor's Questions

Q11:What is the causative organism?
A- Haemophilus
B- E Coli
C-P.aeruginosa
D-Streptococci

What is the treatment?
A- Penicillin
B- Ciprofloxacin
C- Vancomycin
D- Clindamycin



Erysipelas

Q12: All of the following are antipseudomonal except :
A- Ceftazidime
B-Ertapenem
C- Cefepime
D-Meropenem

Q13:All of the following are anti MRSA except:
A- Linezolid
B- Vancomycin
C- Tigecycline
D- Cefazolin

Q14: All of the following can be used for MRSA bacteremia except :
A- Tigecycline
B- Vancomycin
C- Daptomycin
D- Linezolid

Q15: Which one of the following bacteria have a high frequency of intrinsic resistance to polymyxins (colistin)antibiotics?
A- Serratia marcescens
B- Klebsiella pneumonia
C- Pseudomonas aeruginosa
D-Acinetobacter baumannii

Answers: Q11:D,A | Q12:B | Q13:D | Q14:A | Q15:A

Answers Explanation File!

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>
<tr><td>Tetracycline</td><td>Staining of the teeth.</td></tr>
<tr><td>Fluoroquinolone</td><td>Cartilage damage to the fetus.</td></tr>
<tr><td>Thalidomide:
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!

GOOD LUCK !

This work was originally done by ***438 Medicine team:***

Team Leaders

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