433 Teams

MEDICINE

33|Use of antibiotics

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COLOR INDEX

Slides - Step-Up medicine - Kaplan Notes - Extre explanation - Doctor Notes

Objectives

Not given

The topic is huge so we asked the doctor and he said nothing out of the slides !

❖ Introduction :

Research has shown 50% of the time , antibiotics are prescribed either:

1. when not needed

2. Misused

Evidence-based practice guidelines from :

the Infectious Diseases Society of America [IDSA] can help Direct appropriate therapy for specific infectious disease syndromes as well as for infections caused by specific microorganisms

❖ Obtaining an Accurate Infectious Disease Diagnosis :

1] Determining the site of infection >Patient comes with skin and soft tissue infection (gram positive) , Patient comes with UTI (gram negative).

2] Defining the host (e.g. immunocompromised, diabetic, of advanced age)

Age : Gray baby syndrome: A syndrome due to toxicity of the antibiotic chloramphenicol in the newborn, especially the premature newborn, because of lack the necessary liver enzymes to metabolize this drug.

3] Establishing, when possible, a microbiological diagnosis

- **It is critical to isolate the specific pathogen in many serious, life-threatening infections, especially for situations that are likely to require prolonged therapy …eg, :**

A] Endocarditis,

B] Septic arthritis,

C] Meningitis.

- **To optimize an accurate microbiological diagnosis, Diagnostic specimens should properly obtained and promptly submitted to the microbiology lab, preferably before the institution of antimicrobial therapy**
- **Example : when we take a CSF sample and check it after 12 hours , this is not a promptly submitted which might influence by temperature .**

❖ Timing of Initiation of Antimicrobial Therapy :

Urgency of the situation :

Antibiotics has to be given urgently to critically ill patients, such as those in :

1] Septic shock

2] Febrile neutropenic patients,

3] bacterial meningitis,

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

Stable clinical situation :

antimicrobial therapy should be deliberately withheld until appropriate specimens have been collected and submitted to the microbiology laboratory.

Important examples :

1] subacute bacterial endocarditis and

2] vertebral osteomyelitis/diskitis

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.

❖ Empiric vs. Definitive Antimicrobial Therapy :

- Inadequate therapy in very sick patient is associated with poor outcomes and Microbiological results do not become available for 24 to 72 hours..

This my results in :

1] greater morbidity and mortality

2] increased length of stay.

- Therefore, a common approach is: to use broad-spectrum antimicrobial agents as initial empiric therapy (sometimes with a combination)
- In a serious infection , If there is a specimen you can drain , draw it , send it to the lab and start antibiotics empirically

❖ combination?

- **The intent is to cover multiple possible pathogens commonly associated with the specific clinical syndrome…..e.g : healthy young adult with suspected bacterial meningitis: pathogens would be *Streptococcus pneumoniae* and *Neisseria meningitides*.**
- **a combination of a third-generation cephalosporin plus vancomycin**
- Remember when we give combination think about three things: it could be **additive**, **synergism** or **antagonism effects**.

synergism : a combination of two or more drugs increases the effect and making the treatment more efficient.

❖ Selecting empiric antimicrobial :

Consider the following:

(1) the site of infection and the organisms most likely to be colonizing that site (eg, intravascular catheter associated bacteremia is caused by staphylococci present on the skin.

(2) prior knowledge of bacteria known to colonize nasal cavity [currently nasal swab is conducted routinely by many hospitals before admitting patients to the intensive care unit] may indicate that the patient is colonized with MRSA.

(3) The local bacterial resistance patterns or antibiograms that are available for important pathogens at most hospitals.

- **Once the etiologic pathogen IS identified with antimicrobial susceptibility every attempt should be made to narrow the antibiotic spectrum.**

This is a critically important component of antibiotic therapy because it can :

1] Reduce cost

2] Reduce toxicity

3] prevent the emergence of antimicrobial resistance in the community.

❖ Interpretation of Antimicrobial Susceptibility Testing Results :

- **microorganism is identified in clinical cultures,..then antimicrobial susceptibility testing (AST). Antimicrobial susceptibility testing measures the ability of a specific organism to grow in the presence of a Particular drug in vitro.**
- **Data are reported in the form of Minimum inhibitory concentration (MIC):**

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

(Minimum inhibitory concentration (MIC) is useful to determine the lowest dose)

- **"susceptible," "resistant," or "intermediate,**

- **Susceptible" : The isolate is likely to be inhibited by the usually achievable concentration of a particular antimicrobial agent when the recommended dosage is used for the particular site of infection.**
- **AST has some limitations that should be kept in mind.**

Case : 23 years old man who has surgery at the base of the skull After trauma, presented few days later with meningitis CSF has revealed : WBC 1200 mainly poly Culture : staph aureus susceptible to cephazolin RX cephazolin Outcome:..Death..Why ?

✓ **Susceptible to cefazolin in vitro; But the isolate was obtained from the (CSF)…SO what ?**

✓ **cefazolin would not be an optimal therapeutic choice because it does not achieve therapeutic concentrations in the CSF. (it achieves in the blood)**

❖ 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.:**

✓ **Synergistic Activity: the combined effect of the agents is greater than the sum of their independent activities when measured separately.**

- **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 when :**

{1} Rapid killing is essential

- **(eg,: treatment of endocarditis caused by *Enterococcus* species with Penicillin and gentamicin: bactericidal, whereas penicillin alone is only bacteriostatic and gentamicin alone has no significant activity. Result in more rapid clearance of the infecting microorganism**

{2} shorten the course:

- **Endocarditis due to viridians 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).**

{3} critical ill patient :

- **Empiric therapy for health care–associated infections , Patient 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 againstgram-negative bacilli, particularly *P aeruginosa***

4} Polymicrobial Infections:

- Antimicrobial combinations, such as a third-generation **cephalosporin** or a **fluoroquinolone** plus **metronidazole**, can be used as a potential treatment option in these cases and can sometimes be more cost-effective than a comparable single agent (eg, a carbapenem)

5} To Prevent Emergence of Resistance.:

- 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.

❖ Host Factors to Be Considered in Selection of Antimicrobial Agents:

- **Renal and Hepatic Function:**
- Because the kidney and the liver are the primary organs responsible for elimination of drugs from the body,..the dose reduction to prevent accumulation and toxicity in patients with reduced renal or hepatic function.

- **Pregnancy and Lactation:**
- Special considerations for the use of antimicrobial agents in pregnancy relate to the fetus .
- many antimicrobial agents can be either teratogenic or otherwise toxic to the fetus.
- Druge prohibited in pregnancy: as sulfonamides and nitrofurantoin…….birth defect tetracyclines and chloramphenicol: well-described fetal or neonatal adverse effects

- should avoid aminoglycoside because it crosses placental barrier and cause nephrotoxicity.

- **History of Allergy or Intolerance :**
- Pencillin and anaphylaxis
- Could be IgG (from penicillin gives skin rash)or IgE (Anaphylactic shock :swelling of the tongue).

- **History of Recent Antimicrobial Use:**

- 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.

❖ Oral vs Intravenous Therapy:

- Depend on severity of the infection
- treatment mild to moderate infections can be treated with well-absorbed oral antimicrobial agents (eg, treatment of pyelonephritis with oral fluoroquinolones) and community-acquired pneumonia with 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 fluoroquinolones, linezolid, trimethoprim-sulfamethoxazole, and metronidazole. Certain infection should not be treated orally: Meningitis

❖ Efficacy at the Site of Infection:

- In addition to in vitro antimicrobial activity and achieving adequate serum levels, : the efficacy of antimicrobial agents depends on their capacity to achieve a concentration equal to or greater than the MIC at the site of infection.

- Antimicrobial concentrations attained at some sites (eg, ocular fluid, CSF, abscess cavity, prostate, and bone) are often much lower than serum levels For example, first- and second generation cephalosporins and macrolides do not cross the blood-brain barrier and are not recommended for for nervous system infections

- Fluoroquinolones achieve high concentrations in the prostate and are preferred oral agents for the treatment of prostatitis

- Daptomycin, an excellent bactericidal agent against gram-positive bacteria, is not useful for treatment of pneumonia (eg, pneumococcal pneumonia) because it is inactivated by lung surfactant.

- Vancomycin needs high concentration in the lungs , ineffective.

aminoglycosides are not good with Abscesses without drainage.

-
- moxifloxacin does not achieve significant urinary concentration because of its low renal excretion and is therefore not suitable for treatment of UTIs.

❖ Use of Therapeutic Drug Monitoring:

- for medications that have a fairly narrow therapeutic index This could be due primarily to toxicity at high levels (eg, aminoglycosides) or Therapeutic failure at low drug levels (eg, vancomycin) but is usually a combination of both (eg, voriconazole).

- In some cases, the use of serum drug level monitoring is supported by its beneficial effect on clinical outcomes (eg, voriconazole in the treatment of invasive fungal infections).

❖ Assessment of Response to Treatment:

- Response to treatment: By both clinical and microbiological parameters.

Clinical parameters

1] Decrease in fever, tachycardia, or confusion)

2] laboratory values: (eg, decreasing leukocyte count)

3] radiologic findings (eg, decrease in the size of an abscess).

microbiological parameters

- Bacteremia is the most common scenario in which microbiological response is closely assessed because clearance of the bloodstream is as important as clinical improvement. Persistent bacteremia can often be the only clue to the presence of an inadequately treated source or to the existence or development of endovascular infection (such as endocarditis or an intravascular device infection).

❖ Adverse Effects :

- Allergic or hypersensitivity reactions can be either immediate (IgE-mediated) or delayed and usually manifest as a rash .
- anaphylaxis is the most severe manifestation of IgE-mediated allergy ongoing reaction is attributed to an antimicrobial drug allergy .
- This usually requires discontinuation of the offending agent.

❖ Antimicrobial Therapy for Foreign Body Associated Infections:

- Emergence of infections associated with the placement of such devices, involving both:

1- **Temporary : (eg, urinary catheter, central venous catheter)**

2- **Permanent: (eg, prosthetic joint, artificial heart valve) implants.**

- **the important characteristics of device related infection is the formation of biofilms:**

"a structured community of bacterial cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface .

- **prolonged antibiotic treatment for these infections can be ineffective, associated with adverse effects, and result in the emergence of resistant strains of organisms**

- **However, because of the difficulty of eradicating infections with antimicrobial therapy alone, removal of the implant is often necessary for cure.**

- **As an alternative, for patients unable to tolerate implant removal, long-term suppressive antimicrobial therapy is sometimes used, with variable success.**

❖ Use of Antimicrobial Agents as Prophylactic or Suppressive Therapy:

Pre -surgical Antimicrobial Prophylaxis:

- **Antimicrobia l prophylaxis is used to reduce the incidence of postoperative surgical site infections.**
- **The antibiotic(s) should :**

1] cover the most likely organisms and be present in the tissues when the initial incision is made

2] adequate serum concentrations

- **A single dose of a cephalosporin (such as cefazolin) administered within 1 hour before the initial incision is appropriate for most surgical procedures; this practice targets the most likely organisms (ie, skin flora), Duration should not exceed 24 hours in most cases.**

Prophylaxis to Prevent Transmission of Communicable Pathogens to Susceptible Contacts:

- **ciprofloxacin can be given to close contacts of a patient with meningitis caused by *N meningitidis*,**

Antimicrobial Prophylaxis Before Dental and Other Invasive Procedures:

- **prosthetic valves, prior endocarditis, or congenital heart disease before surgical correction.**

❖ JUDICIOUS USE OF ANTIMICROBIAL AGENTS:

1- Cost Considerations in Antibiotic Selection

2- the switch from intravenous to oral therapy. Oral therapy is generally less expensive, potentially associated with fewer adverse effects, and can result in considerable cost savings .

For example : oral linezolid when compared with intravenous vancomycin for the treatment of complicated skin and soft tissue infections caused by MRSA

❖ Preventing Emergence of Antibiotic Resistance:

- The widespread—and often inappropriate use of antimicrobial agents is the single most important cause of the emergence of drug resistance, both in the community and hospital settings
- the emergence of antimicrobial resistance can be prevented or delayed through judicious prescribing, which can be characterized as follows:

1- avoidance of antibiotic treatment for community-acquired, mostly viral, upper respiratory tract infections; and use of narrow-spectrum antibiotics when possible

2- use of antibiotics for the shortest duration that is effective for the treatment of a particular clinical syndrome .

❖ Common Misuses of Antibiotics:

1-prolonged Empiric Antimicrobial Treatment Without Clear Evidence of Infection:

- One of the most common mistakes in antimicrobial use is continuing to add or switch antibiotics when a patient does not appear to be responding to therapy

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

- Colonization with potentially pathogenic organisms without any associated manifestation of disease occurs frequently in certain populations (eg, colonization of the urinary tract in women of advanced age or in the presence of an indwelling urinary catheter)

Notes

- **Identification of infecting organism by blood culture and gram stains.**

- Gram positive cocci cluster > staph aureus
- Gram negative bacilli > E.coli , klebsiella , pseudomonas …etc.
- Gram negative coccobacilli > brucella

- **Determining antimicrobial susceptibility is very important to prevent drugs resistance.**
- **De-escalation defined as a change in the initial antibiotic therapy from broad- to narrow-spectrum coverage within 14 days of the initial prescription.**

- **Penicillin :**

- Penicillinase resistant penicillins are antibiotics which are not inactivated by the penicillinase enzyme. Some bacteria produce the enzyme penicillinase that destroys the beta-lactam ring of the antibiotic, making the penicillin ineffective.
- Examples of Penicillinase resistant penicillins are : methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin.
- Piperacillin covers Gram negative infections.
- Some species of bacteria produce beta-lactamase enzymes, which cleave the beta-lactam group in antibiotics, such as penicillin, that have a beta-lactam ring in their structure. In doing so the beta-lactamase enzyme inactivates the antibiotic and becomes resistant to that antibiotic. To avoid development of resistance, beta-lactamase inhibitors are administered with the beta-lactam antibiotics so the action of beta-lactamase is inhibited. This tends to widen the spectrum of antibacterial activity.
- Examples of B-Lactamase inhibitors: clavulanate, sulbactam, tazobactam.

- **Cephalosporins :**

- It classify into 4 generations : as you go from 1st to 4th generations the gram positive activity becomes less and gram negative activity becomes more.

- **Aminoglyoside :**

- Side effect :ototoxicity, nephrotoxicity and neuromuscular blocked.

- **Tetracyclines :**

- Can't be given below the age of 18 , pregnant women and calcium containing products because it binds with calcium .
- Remember Tetracyclines have food –drug interaction and drug-drug interaction.

- **Vancomycin :**

- is purely active against gram positive.NO activity against gram negative organisms.

- **Quinolones :**

- Good for pneumococcal infection and atypical infection.Therefore it is good for treating Community acquired pneumonia.

- For Meningitis you must do a CSF study to determine the pathogen unless there is a contraindication
- No Meningitis infection treated by only one antibiotic
- Meningitis after surgery at the base of the skull after trauma = staph aureus (could be MRSA)
- Hospital acquired infections is an indication for combination of antibiotics .
- Radiologic responses sometimes lag behind the clinical improvement so even if there is still consolidation in the x-ray you could stop the antibiotics if the other clinical findings is ok in case of pneumonia
- In case of Persistent bacteraemia think about Foreign body “biofilms”

❖ summary

Appropriate use of antimicrobial agents involves obtaining an accurate diagnosis :

1- determining the need for and timing of antimicrobial therapy,

2- understanding how dosing affects the antimicrobial activities of different agents,

3- tailoring treatment to host characteristics, using the narrowest spectrum and shortest duration of therapy, and switching to oral agents as soon as possible.

4- In addition, nonantimicrobial interventions, such as abscess drainage, are equally or more important in some cases and should be pursued diligently in comprehensive infectious disease management.

MCQs

1- An 18 years old boy presented to the family physician complaining of fever, headache, painful throat, vocal hoarseness, dry cough, running nose, general malaise 3 days ago. An oral temperature was measured to be 38.8 C. The physician immediately prescribed a combination of penicillin and gentamicin for 2 weeks. 1 week later, the boy came with worsening symptoms and persisting fever. What was the mistake the physician committed?

A-Antibiotics shouldn't be combined at all.
B-He prescribed antibiotics that must not be used at the age.
C-Inappropriate use of empirical antibiotics without an evidence of a bacterial infection.
D-The physician started an oral preparation while it should be administered intravenously.

2- 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.

3- A three year old girl presents to the emergency department with a two day history of headache, nausea, vomiting and fever. She was seen by a physician two days ago who diagnosed otitis media. At ED She was conscious, alert and complains of pain over the neck area. On examination she has pain on flexion of the neck, a clinical diagnosis meningitis has been made. What is the most appropriate action to do in this case?

A-Start a regimen of empirical antibiotics then do a lumbar puncture later.
B-Start an empirical regimen of antibiotics immediately after or concurrently while taking a diagnostic CSF specimen by a lumbar puncture.
C-Start Ceftriaxone + Vancomycin immediately and LP is not needed since the clinical scenario is clear for Neisseria meningitides and S.pneumoniae especially this age group.
D-Lumbar puncture and bacterial culture should be done first to select the antimicrobial regimen based on the results.

4- Which of the following is the most important cause of the widespread emergence of antimicrobial resistance?

A-The lack of commitment in following the guidelines in selecting the appropriate agents.
B-The common use of broad spectrum antibiotics in urgent cases that need the use of empirical agents.
C-The use of antimicrobial agents for short courses.
D-The inappropriate use of antimicrobial agents.

Answers

1- The answer is (C), antibiotics use should be absolutely limited for cases with clear evidence of an infection either clinically such as in case of community acquired pneumonia or by a laboratory confirmation with a microbiological diagnosis. In this case, the patient is complaining of typical upper respiratory tract symptoms which is most of the time caused by a self-limiting viral infections. Thus the use of antibiotics here is inappropriate due to the absence of clear evidence.

2- The answer is (C), according to guidelines, prophylactic use of antibiotics is indicated before dental operations such as in A, as well as in close contacts for meningitis patients such as in B, and in pre-surgical patients to prevent surgical site infection such as in D, while there is no indication to use prophylactic antibiotics before the use of central venous catheter. In this case, following the hygiene guidelines and using sterilized instruments would be enough.

3- The answer is (B), in cases of unstable and extremely ill infected patients, the delivery of empirical antibiotics should be started immediately just after taking the specimen as it can be lethal if delayed. At the same time you need to do a microbiological diagnosis to narrow the spectrum of antibiotics once the lab results are ready. Therefor the most appropriate action would be starting the antimicrobial agents immediately after collecting the specimen. Whenever the lab results are ready, empirical agents can be exchanged by narrow spectrum agents.
This should be applied in septic shock and febrile neutropenia as well.

4- The answer is (D), the inappropriate use of antibiotics has largely contributed to the emergence of antimicrobial resistance. Bacteria are able to undergo mutations aiming to be resistant against the type of antibiotic used inappropriately. Inappropriate use of antibiotics include using them with no indications such as in viral URTIs, using them is long courses and the use of broad spectrum antibiotics while they are not needed.

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