

Bacteriology -1- ☺

The following are the topics discussed in this sheet:

⊗ Bacteremia

⊗ Septicaemia & Septic Shock

⊗ Bacteremia

♦ **Definition:** The presence of microorganisms, **viable bacteria** mainly - hence the name - in the blood, which is -the blood- normally sterile (with no associated illness) .

▼ How can the bacteria be introduced to the sterile blood? Sometimes by cleaning your teeth or by having a dental procedure (like tooth extraction).

♦ **Clinical Course:** Usually, there are no symptoms of disease -there is no disease at all- & the patient is ok & eventually the blood will get rid of the bacteria.

▼ Exceptions regarding the usual asymptomatic clinical course:

In case of people who have valvular heart disease (disease of the valves of the heart), they can be susceptible to infections by these microorganisms (bacteria) that access to their blood, now, this type of infection is known as **sub-acute bacterial endocarditis** ... what does it mean?

Endocarditis (inflammation of the heart valves) is of 2 types:

1) Acute endocarditis: occurs in cases of normal heart valves; due to a bacterial infection mainly by *Staphylococcus aureus*.

2) Sub-acute endocarditis: occurs in cases with valvular heart disease,

For example; some people who have rheumatic fever, have damaged heart valves - these valves are rough & there is turbulence of blood flow over them - & this damage allows the settlement of bacteria on these valves, followed by bacterial multiplication & causation of the disease (the offending organism here doesn't have to be a highly pathogenic one *strep. viridans* or *enterococcus* might cause the sub-acute endocarditis)

- That's why people with valvular heart disease should have antibiotic coverage when they go to the dentist to have any dental procedure (prophylactic Antibiotic)

{**Conclusion:** A simple bacteremia in normal people doesn't do anything harmful/ no disease, but in cases of valvular heart diseases, the patient may end up with sub-acute bacterial endocarditis...}

⊗ Septicaemia

♦ **Definition:** the presence of **viable bacteria or their products (like exotoxins or lipopolysaccharides)** in the blood & it's associated with disease.

♦ **Clinical Course:** The patient is ill & there is an infection going on.

♦ **Another terminology for septicaemia:** **Sepsis.**

▼ What is sepsis? It's an infection that results from bacterial (or its products') presence in the blood, which gives rise to profound changes in the patient.

Note (1): Sepsis can be associated with any microorganism; it can be associated with viruses, bacteria, fungi or even protozoa, but most commonly it's associated with bacteria.

Note (2): Usually, gram negative bacteria "most commonly E.Coli & Pseudomonas Aeruginosa" are the ones associated with sepsis more than gram positive bacteria; due to the presence of LPS (LipoPolySaccharides) on gram -ve bacteria as a part of their outer membrane, **don't forget** that LPS are endotoxins, however, if there's sepsis resulting from gram +ve bacterial infection, then the causative agents are most commonly Staphylococci - especially Staph. Aureus - & streptococci pyogenes

{**Conclusion:** when there is sepsis, always think first of gram negative bacteria causing it.}

▼ Degrees of sepsis: There are various degrees of sepsis; mild, moderate & severe sepsis & towards the end of the severity – when sepsis is severe & goes untreated– there will be septic shock which is a medical emergency, that might lead to death.

▼ How does sepsis occur? Usually, there is a source –focus - of infection,

Where could this source –focus- of infection be? Anywhere in the body, but here are the major sources of infection:

Most commonly, it's in the lungs (40% - 50% of sepsis cases are associated with lung infections), i.e. if there is an infection in the lungs, then the patient is more likely to have sepsis > then the urinary tract, again, any infection in the urinary tract can be associated with sepsis > then the GIT & system, any infection in the gall bladder, peritonitis, appendicitis infection in the gut or the liver can also be associated with septicaemia > also meningitis can be associated with sepsis.

(Note : of course not any patient with a UTI for example is going to have sepsis)

▼ What causes the symptoms associated with sepsis?

- To answer that, we need at first to tell the difference between sepsis & an ordinary infection:

Ordinary infection >> elicits an immune response & then the body cures itself & the person is alright.

Sepsis >> elicits an immune response with the production of all kinds of cytokines that lead to **excessive** reaction of the immune response, this excessive reaction causes the problems of sepsis.

- Now, let's answer with details:

(I) Sepsis associated with gram negative bacteria: here are the steps from A to Z:

(1) LPS are present in the blood - after the death of the bacteria for example and so called in this case "disintegrated bacterial LPS" - .

(2) LPS have receptors for them known as LPS-binding proteins, which these LPS will bind to.

(3) After binding to LPS- binding proteins, LPS will go to a receptor –designed for them- that's present on macrophages mainly, dendritic cells & also neutrophils, this receptor is known as **CD14**.

Associated with CD14, there is a Toll Like Receptor - 4 (**TLR 4**) ... don't forget that TLRs are 13 in number, one of them is TLR 4, which serves as a receptor for LPS.

(4) Once LPS bind to TLR 4, there will be a signal sent to the inside of the macrophages & dendritic cells to produce various cytokines.

(5) Release of IL-1 & TNF –the main cytokines that are associated with sepsis - from macrophages.

(6) The previous cytokines will now function, producing the manifestations of sepsis.

➤ Effects of TNF (how it produces the symptoms of sepsis):

(A) It acts on the hypothalamus causing fever, **but be careful**; sometimes, sepsis in the very young & the very old patients might present with hypothermia, but as a rule, sepsis is present with high fever up to 39° - 40°.

(B) It causes DIC (Disseminated Intravascular Coagulation) by:

(a) Stimulating the endothelial cells & making them produce adhesion molecules, which in turn will adhere neutrophils to the endothelial cells, neutrophils then degranulate releasing harmful enzymes which will harm the endothelium & this injury will now give rise to coagulation.

(b) Promoting the coagulation system to function too, resulting in the end with DIC!

All in all, this process mainly occurs in the small blood vessels.

- **Consequences of DIC:**

(1) There will be a tendency for bleeding afterwards, why?

Because in DIC, the coagulation uses up all the proteins concerned with coagulation (the clotting factors), so there will be no more coagulation during the depletion of these factors, ending up with bleeding.

(2) There will be a compromised blood supply (ischemia) to many organs in the body, why? Due to DIC. >> this will lead to organ failure .

(C) It (TNF) increases the vascular permeability & so the vasculature resistance becomes less, i.e. there will be a drop in the blood pressure, now the heart will function (pump) more trying to keep the B.P normal , ending up having tachycardia but still >>> the patient ends up with shock –septic shock-.

Note: IL-1 has similar properties/ effects to TNF, but with less dramatic effects.

(II) Sepsis associated with gram positive bacteria, again how do they produce sepsis?

- Here, instead of having LPS as a bacterial product, there is: Lipoteichoic acid in the cell wall of the gram +ve bacteria, which isn't present in gram -ve bacteria.
- This Lipoteichoic acid like LPS is received by a Toll Like Receptor & then will produce the SAME effects, however, TLR here is **TLR 2** not TLR 4 as in the case of LPS.

(III) Sepsis associated with bacterial DNA, peptidoglycans or even flagellar proteins
(despite whether the bacteria is gram +ve or -ve):

Some Toll Like Receptors can receive such bacterial components & thus, these components can stimulate the TLRs producing the features of sepsis & septic shock.

(IV) Sepsis associated with Super Antigens:

There are secreted products –from bacteria- that are actually super antigens & cause septic shock too as in case of exotoxins like:

(a) TSST 1 –Toxic Shock Syndrome Toxin – produced by Staph. Aureus which produces septic shock mainly but not exclusively in menstruating women.

(b) The pyrogenic exotoxin produced by streptococcus pyogenes in scarlet fever.

- Now, how do these exotoxins – SUPER ANTIGENS – work?

You have to know that super antigens don't bind to or work upon TLRs, **instead**, they stick to MHC II molecules on macrophages (without being processed first by these macrophage into smaller epitopes) >> then they are introduced to TCRs (specifically to the β chain of the TCR)... So the activation of T helper cells here isn't specific; why?

Usually the stimulation of TCRs is done by the antigen present on MHC II (the antigen is first processed by the APC & then expressed on MHC II) & that is specific.

But again in this case, the MHC II is linked to the TCR through the super antigen (not processed) >> this leads to polyclonal activation of the T helper lymphocytes >> activated T helper lymphocytes in turn will produce lots of cytokines like interferon γ >> interferon γ will stimulate the macrophages >> macrophages in turn will produce lots of TNF & IL-1 >> resulting in sepsis which if not treated ends up in septic shock.

****** Most probably, you won't understand what I just wrote above, it needs a bit of animation to understand & it's wonderfully illustrated in this video: [Http://m.youtube.com/watch?v=hqv8w4Tc-Xo](http://m.youtube.com/watch?v=hqv8w4Tc-Xo) ****** ☺

▼ Role of the complement system in sepsis:

The complement system can lead to activation of the kinin system, which in turn leads to coagulation of blood (so, the complement system contributes to DIC & exaggerates its effects).

⊗ **Septic shock**

♦ **Definition:** shock means that there is a very low B.P resulting from various causes & here in our subject: it results from sepsis; hence the name “septic shock”... another example of shock is the anaphylactic shock.

Note: Septic shock is a medical emergency, where you have to act very quickly to avoid death of the patient.

♦ **Manifestations of septic shock:** (please note that many of the symptoms appear actually during sepsis & go on during the shock):

▼ **Organ failure** (either one organ failure or more than one major organ failure); like:

*Lung failure: where the lungs become deprived from oxygen resulting in hypoxia and the body tries to compensate for this hypoxia by hyperventilation .

*Myocardial failure.

*Renal failure: in this case, the patient’s kidneys won’t be able to produce urine & the patient is **anuric** –no or very little amount of urine is passed daily-.

*Liver failure: no production of many important proteins including the clotting factors.

*Endocrine glands’ failure: one of the consequences is the reduced insulin production in case of affected beta cells of the pancreatic langerhans’ islands, which leads to elevated blood sugar levels (hyperglycemia) ...Also, failure of the adrenal glands, in case of meningococcal septicaemia for example, will lead to no production of cortisol.

(Waterhouse–Friderichsen syndrome)>> by N.meningiditis.

*Brain failure.

▼ **Changes in skin temperature:**

At the beginning of the septic shock, the patient’s skin is warm; because of tachycardia – a sort of compensation by the heart for the drop in the B.P - **except** at the extremities which might be a bit cold, but as the patient progresses in the septic shock, the heart starts failing & there will be severe & excessive vasoconstriction & the patient’s skin is now cold.

In contrast to the cardiac shock in which the patient feels cold from the beginning due to the impaired blood circulation .

▼ **Confused patient:**

The patient in the beginning will be completely conscious, but as the blood supply to the brain is being more compromised by time (due to DIC), the patient will become confused & disoriented.

▼ Hypoxia:

Due to: A) Compromised blood supply to the tissues due to DIC. B) Respiratory failure.

▼ Hyperventilation (tachypnea):

Due to:

A) Hypoxia.

B) Fever\pyrexia (it causes tachypnea).

C) As a compensation for the metabolic acidosis – accumulation of lactic acid - that occurs in tissues & muscles as a result of anaerobic respiration which resulted from hypoxia in the first place, so by hyperventilation, the body is trying to wash out as much as possible of CO₂.

BUT the problem with tachypnea is that it may result in respiratory alkalosis which is also a bad condition.

Clinical Case: if there is a person who is feverish, anuric, has a low B.P & any of the previously mentioned symptoms of sepsis, then you should suspect that this person is having sepsis or even a septic shock ... what to do?

- 1) Very quickly, you have to take a blood sample to make sure about your diagnosis & at the same time, you have to identify the source –focus- of infection causing the sepsis –since you have suspected sepsis in the first place - by taking multiple tissue samples (like urine sample, sputum sample, skin sample if there's an infection there or even a bone sample if you see it necessary) & also doing CT-Scan & MRI will help in the investigation... but most importantly, DON'T WASTE TIME; because you have to give the antibiotic straight away IV - it's a life threatening situation after all -.
- 2) Administration of antibiotics, what type of antibiotics should be administered?

Wide spectrum antibiotics; since the lab results will take time & the case can't wait until then, like: Vancomycin to cover the gram +ve infections, Gentamicin & aminoglycosides to cover the gram -ve infections, also cephalosporins (3rd & 4th generations) can be helpful.

- 3) Provide fluids intravenously.
- 4) You have to exclude surgical emergencies, for example, in case of appendicitis or cholecystitis followed by rupture of the appendix or the gall bladder respectively, the patient will have peritonitis in addition to sepsis & this even requires further treatment.

Note (1): The treatment should be in the ICU, since it's a life threatening case & requires monitoring.

Note (2): Mortality in cases of septic shock is very high especially if the treatment is delayed & may reach up to 75%.

Keep Smiling Despite All ☺

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