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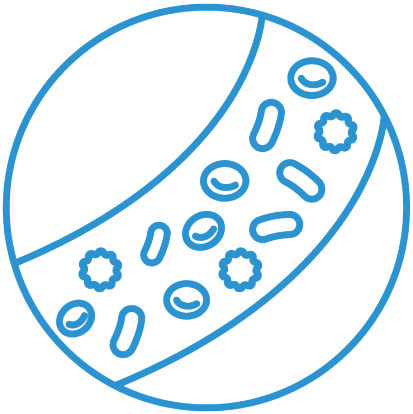

Sepsis and Septic Shock

DRIP 3

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Neutrophils

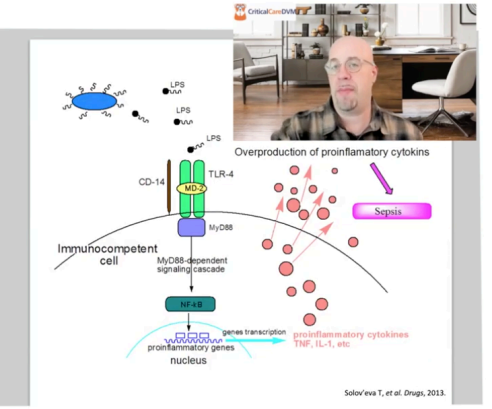
NETs

- Composed of filamentous DNA, histones, granular antimicrobial proteins, proteases
- Trap/kill pathogens – oxidative vs. non-oxidative mechanisms
- Activate factor XII via their negative charge
- DNA & histones involved in fibrin formation
- Inhibit fibrinolysis through blockade of plasminogen activator binding sites

Express TF

Neutrophils are really unique cells. And so through a process that we call NETs osis, these neutrophils shootout strands of DNA, and histones, that can trap and kill pathogens through oxidative and non-oxidative means. But these NETs contribute to pro coagulation and hyperfibrinolysis through activation of factor XII, through fibrin information itself. And through inhibition of fibrinolysis.

- LPS released & binds to LPS binding protein (via lipid A portion)
- LPS recognized by cell surface receptor (i.e.: CD14)
  - Epithelial cells, macrophages, neutrophils, endothelial cells
- CD14 transfers LPS to TLR-4 and MD-2 for cellular activation
- LPS binding to cell surface receptor activates cell
- Most common organisms:
  - *Escherichia coli*



So let's take a practical example, gram negative sepsis, a gram negative bacteria. Remember they have lipopolysaccharide in their outer membrane. In circulation, LPS, lipopolysaccharide binds to the lipopolysaccharide binding protein. And this complex gets recognized by a cell surface receptor called CD14. CD14 transfers that complex to toll-like receptor 4, TLR4-- in that process, that step, activates the cell.

Gram Positive Sepsis

Peptidoglycan

- Contains lipoteichoic acid
- Less potent than endotoxin
- Causes release of proinflammatory cytokines

May be derived from

- Skin
- Soft tissue
- IV catheters

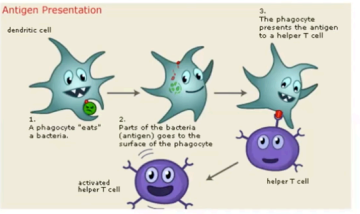
Most common organisms

- *Enterococcus* spp.
- *Staphylococcus* spp.
- *Streptococcus* spp.

Now obviously gram positive bacteria, can cause sepsis too, but lipopolysaccharide is obviously not involved. But we do have some of the other bacterial components involved like lipoteichoic acid. But gram positive bacteria interact with their own toll-like receptors. Then I interacting typically with toll-like receptor 4, they have their own and that stimulation will trigger a similar cascade of pro-inflammatory events.

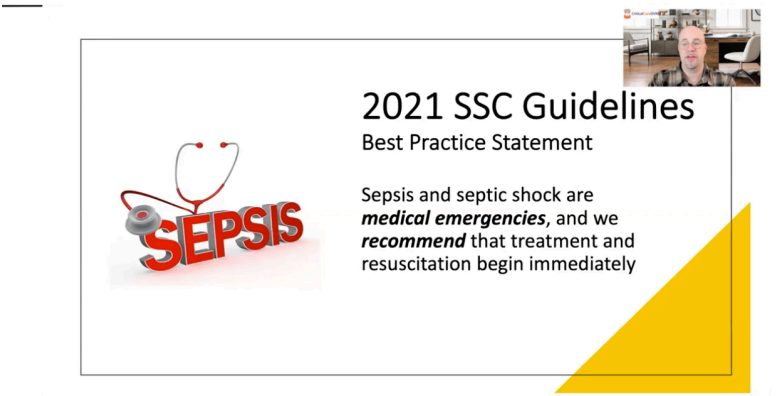
Adaptive Immunity

- Antigen-presenting cells ingest pathogen
- Naïve T cells proliferate
- Effector cells are generated
  - Th1 - TNF, IL-2, IL-12, IFN-γ
  - Th17 - IL-17A
  - Th2 - IL-4, IL-5, IL-9, IL-10, IL-13



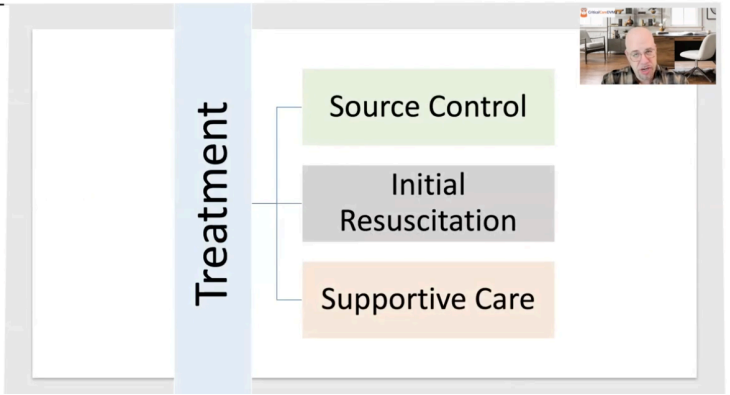
And so we have activation of cytokine production. We have initiation of inflammatory response, but we also ultimately will stimulate adaptive immunity. So dendritic cells ingest pathogens by recognizing those PAMPS. And then once a pathogen gets phagocytosed, there's an upregulation in expression of those MHC class II molecules that we learned about in immunology.

But we also get upregulation of several co-stimulatory molecules that are required for T cell activation. Things like CD40 and B7. The dendritic cells fully mature, and they move from the tissue to lymph nodes. What do they do there? They encounter and activate T cells.

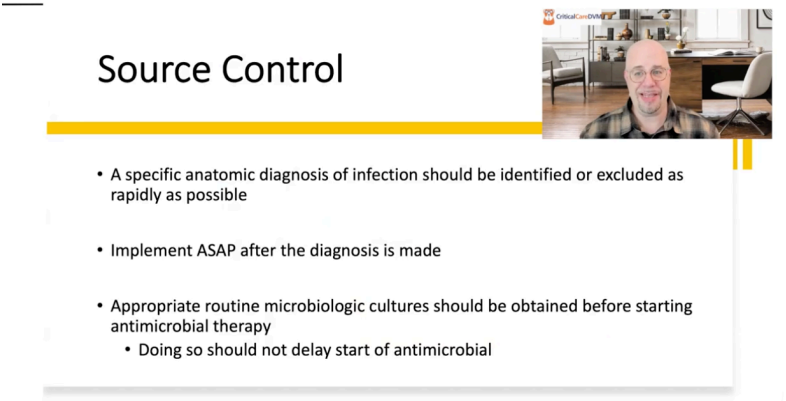


So that's it for about the physiology. Now we get to move on to the stuff that you've been waiting for, which is treating a patients, hopefully so that we can get them home to their families. And no matter any of the details about which we're going to discuss, we have to keep in mind two very simple basic premises.

Number 1, sepsis and septic shock are true medical emergencies. You drop everything and you start intervening with them, no matter how inconvenient it is, because to it is imperative-- that we begin treating these patients immediately and appropriately.

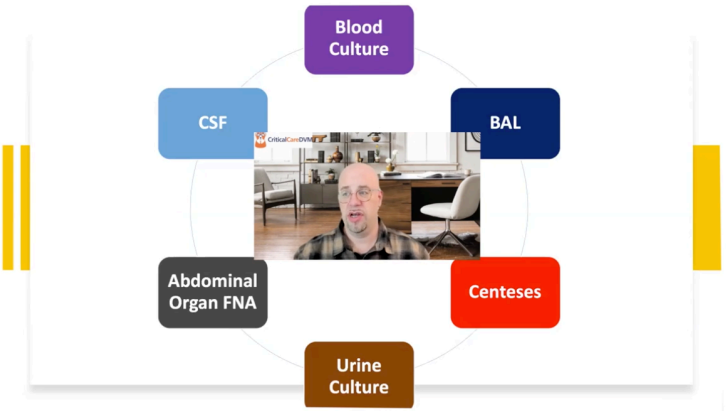


And when I think about treating my septic patients, I categorize my interventions as source control, initial resuscitation. And lastly, all the other important supportive interventions that these patients need to maximize the likelihood of a positive outcome.



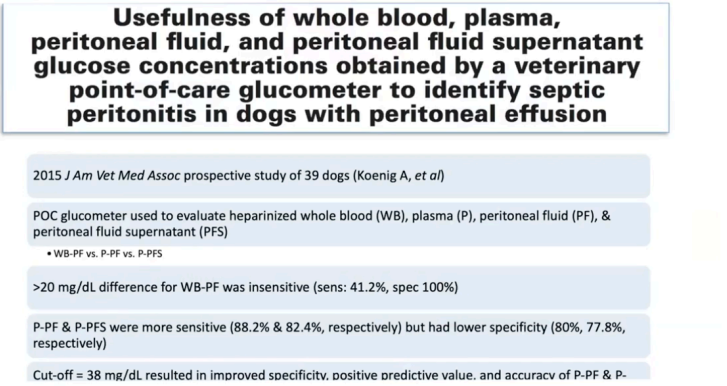
Remember the first step is, source control. Find out the origin of your patient's problem. Is it the urinary tract? Is it a bacterial translocation event from the gastrointestinal tract? Wherever it is, figure it out as soon as possible.

And as soon as you suspect or have confirmed you have a septic patient or one in septic shock, find the source and control it. Get those culture samples before starting antimicrobial therapy. As long as taking that step, doesn't delay antimicrobial therapy meaningfully.



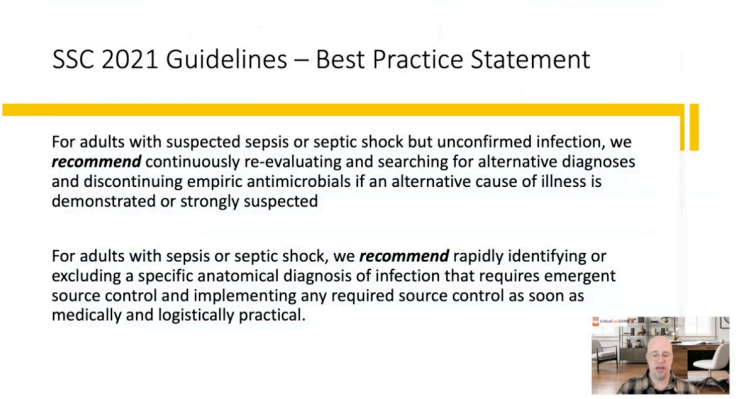
And sometimes you're going to have to think outside the box. You're going to have to do more than a urine culture. You may have to sample third space fluids. You may have to evaluate through the spinal fluid, or fluid from the lungs.

Most of the time, sampling is going to be non-invasive or minimally invasive. But I would be negligent if I didn't tell you every once in a while. You're going to have to use invasive techniques to figure out the source of infection and control it.



Now classic example, is gastrointestinal sepsis. That's caused peritoneal effusion. And so you can very simply measure and compare glucose in both the peritoneal fluid and blood. And based on this more recent study out of the University of Georgia, by Koenig and colleagues.

Using plasma and a cutoff value of 38 milligrams per deciliter-- not 20 but 38, had the highest sensitivity.



So again, here from the most recent surviving sepsis guidelines, best practice statements are essentially summarized by find the source and control it as quickly as possible.

True or false-- patients with sepsis and septic shock, should never be taken to surgery for source control?