Bacterial Sepsis

I. The Concept of Sepsis

A**. Introduction.** Sepsis is one of those topics that pathologists have a hard time talking about. We generally like to see specific, visible, palpable lesions in specific organs, like liver abscesses, thyroid neoplasms, lung consolidations, etc. At autopsy, we have hard time seeing "sepsis." Anatomic findings in cases of sepsis can be very vague and nondescript, sometimes limited only to a soft, mushy spleen, so-called "**septic splenitis**." Accordingly, a student fresh from the sophomore pathology course is often surprised when he or she ventures out to the hospital wards as a third year and encounters the clinicians' obsession with the diagnosis and treatment of sepsis. Preventing, recognizing, and treating sepsis is a very large part of managing the sick patient in the hospital. The importance of recognizing sepsis is especially underscored by the fact that, unlike many other diseases, sepsis can often be cured, leaving no permanent medical abnormality or risk of future deterioration.

B. **Definition**. Sepsis can be defined as a **constellation of clinical and laboratory findings from which an experienced physician concludes that the patient may have a serious infection**. I have purposely made this a nebulous, subjective, and tautological definition, because attempts to define "sepsis" in the literature have stirred a great deal of disagreement and qualification. Probably the late Justice William O. Douglas would have provided the most useful definition, had he been a physician defining sepsis, and not a jurist defining pornography: "I can't define sepsis, but I know it when I see it." So, if sepsis is a constellation, let us look at the individual stars:

C. **Manifestations of sepsis**. Unfortunately for pathologists, sepsis cannot be diagnosed by biopsy. There is really only one general anatomic manifestation of sepsis, and that one is available only at autopsy. We will deal with that one first, and then go into those pointers which hopefully lead to the diagnosis before the patient comes under the purview of the autopsy prosector.

Most of the following manifestations are mediated by various **cytokines** produced by the immune system reacting to components of the microbial pathogens. But since all the various cytokines have never been successfully memorized, except by a few institutionalized *idiots savants*, I will not go into them in detail. If anyone ever asks you about cytokines and sepsis, act irritated and mumble something about "TNF-α," and they'll probably leave you alone.

1. **Septic splenitis**. This finding (referred to in Robbins as "nonspecific acute splenitis") is seen at autopsy only, as no one in his or her right mind takes out a patient's spleen to diagnose an infection. The spleen is

enlarged and soft. The cut surface is “diffluent,” i.e. very soft and runny. Microscopically, neutrophils infiltrate the red and white pulp. Occasionally there are foci of necrosis.

2. **Bacteremia**. This is the gold standard of sepsis from a clinical diagnostic standpoint. Although organisms other than bacteria can cause sepsis, the detection of bacteria is of utmost importance, because 1) you can often treat and cure a bacterial infection with drugs, 2) bacteria are most common cause of life-threatening sepsis in hospitalized patients, and 3) bacteria grow fast enough in culture to allow the physician to respond rapidly with specific treatment. In contrast, **viremia** is typically either self-limited or noncurable (or both). **Fungemia** is very serious and can be treated, but fungi grow so slowly in culture that the patient is either dead or recovered by the time the organisms are identified in culture. **Parasitemia** (such as in filariasis, malaria, and trypanosomiasis), is usually diagnosed by direct microscopic exam of a blood film, rather than by culture. Also, parasitemia tends to occur in clinically stereotypical situations (e.g., in those who have visited certain endemic areas outside the U.S.), while bacteremia can be much more subtle, arising in a multitude of clinical scenarios.

   The detection of bacteremia is so fundamental to the diagnosis of sepsis, that ordering “blood cultures times three” is a pontine-level reflex of the sleepy intern when partially roused from his or her hypnagogic state by the gleeful nurse who reports a fever spike in a hospitalized patient. The reasons that the cultures are done “times three” are 1) in most patients, the bacteremia is only transient, and 2) occasionally one of the cultures is contaminated by normal skin flora. Some inexperienced physicians get carried away and order blood cultures “times six” or “times nine,” but this is rather excessive and is considered poor resource management.

3. **Fever or hypothermia**. These are signs of systemic reaction to infections. Since one involves abnormally high body temperature, and the other low body temperature, one can consider these as two sides of the same coin of abnormal temperature regulation.

4. **Leukocytosis or leukopenia**. Abnormally high or abnormally low white blood cell counts can signal an infection. In either case, immature neutrophils, such as bands, metamyelocytes, and myelocytes can be kicked out of the marrow into the circulating blood and onto the microscope, where eagle-eyed laboratorians wait to detect them and report them out to you. In especially severe cases of bacteremia,

phagocytosed bacteria may be seen in neutrophils in the peripheral blood smear.

5. **Hypotension**, or low systemic arterial blood pressure, can be caused by a lot of diseases, and sepsis is one of them. If the hypotension persists despite adequate intravenous fluid replacement, the diagnosis of **septic shock** can be made. Sometimes shock is the only manifestation of a systemic infection.

6. **Disseminated intravascular coagulopathy** (DIC). You will study this in more detail later on in the course, but briefly this is a condition in which the coagulation cascade *and* the fibrinolytic system are activated by cytokines. The resulting consumption of platelets and plasma coagulation factors, and the generation of natural anticoagulants by the fibrinolytic system, leave the patient without normal hemostasis, causing abnormal bleeding. Also, the diffuse production of blood clots throughout the microcirculature causes ischemia at the tissue level and contributes to the end-organ damage described below.

7. **End organ damage**. The results of unchecked sepsis are diverse and potentially deadly. Some of the damage is directed at specific organs and produces specific clinical manifestations. Sometimes the patient presents with end-organ damage as the initial manifestations of sepsis, so you have to delve deeply to uncover the offending infection.

   a. **Diffuse alveolar damage (DAD)**. We have already discussed this, and its clinical correlate **adult respiratory distress syndrome** (ARDS), in the Pulmonary block. Briefly, damage to pulmonary alveolar endothelial cells results from the action of cytokines arriving by way of the pulmonary circulation. Radicals and neutrophil products also appear to play a role in the damage. Endothelial cells and type 1 pneumocytes are destroyed, and their detritus build up on the alveolar walls, where they become visible as hyaline membranes. Clinically the patient develops hypoxia which is refractory to oxygen therapy due to shunting of pulmonary blood flow through relatively oxygen-poor areas of the lung.

   b. **Acute renal failure**. This is more fully discussed in the Renal block. Briefly, hypotension, DIC, and possibly the direct or indirect effects of bacterial toxins and cytokines produce damage to renal tubular epithelium and vasoconstriction of pre-tubular blood vessels. This eventuates by a variety of mechanisms as decreased glomerular filtration rate and resulting oliguria and azotemia. Sometimes, the pathologist can see **acute tubular necrosis** at autopsy, but more

commonly the kidney, despite severe functional problems, looks normal under the microscope.

c. **Heart failure** can occasionally be seen, presumably as a result of toxic damage and/or ischemia at the microscopic level.

d. The **liver** may also be damaged by sepsis, producing clinical **jaundice**.

8. **Evidence of a primary infection**. In many cases, you will be able to find the seat of the infection that has produced the systemic manifestations of sepsis. In other cases, the actual site of infection will never be found, even at autopsy. We will finish out this discussion with coverage of the various clinicopathologic paradigms that fall under the purview of sepsis, but first, consider the two following patients:

   Ms. Doe, a 23-year-old previously healthy woman, came to the clinic complaining of shaking chills, fever, and a cough productive of rust-colored sputum. Your physical examination reveals rales in the left lower chest, as well as dullness to percussion and vocal fremitus. Her temperature is 103.2°F. Chest x-ray shows a consolidated left lower lobe. The white blood cell count shows 18,000 cells/µL, with immature neutrophils seen on the smear. Sputum Gram stain shows a pure population of Gram-positive diplococci.

   Mr. Roe, a 77-year-old nursing home patient who has been left aphasic by a stroke over a year ago, is brought into the hospital emergency room by ambulance. His blood pressure is 70/38. His temperature is 96°F. He is cyanotic and tachypneic. The chest x-ray shows a diffuse bilateral infiltrate consistent with diffuse alveolar damage. The white blood cell count is 4,000 cells/µL, with 20% neutrophils.

   Since I am writing from the point of view of an omniscient author, I can tell you that both patients are septic. In real life, however, it will be very clear to you that Ms. Doe is an infected patient, but getting a handle on what Mr. Roe's problem is will be no small challenge. Yet, as a physician, you will be expected to make an accurate diagnosis on both of these types of patients. You will eventually be able to do this, but some diagnoses will scream loudly in your face, while others will continually slink away and hide.

II. The Primary Lesions of Sepsis

A. **Urinary tract infections** (UTI) are very common lesions that lead to bacterial sepsis. When faced with a septic patient, this is going to be one the first places you are going to look to as a source of the infection. By the time a patient becomes septic from a urinary tract infection, the infection has usually traveled upstream from the bladder to cause **acute pyelonephritis**. In practice, it is usually not necessary to exactly pinpoint the site or sites of the infection; *i.e.*, it is enough that there are signs of sepsis to pull out the big guns in the form of intravenous antimicrobial drugs.

The most common cause of UTI by far is a Gram-negative rod, *Escherichia coli*. [1] Other Gram-negative rods are frequent offenders as well, especially in hospitalized patients and in outpatients with multiple recurrent UTIs. These organisms include *Proteus* spp., *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*.[2] One Gram-positive coccus, *Enterococcus fæcalis*, is also not uncommon. *Enterococcus* is noteworthy in that although it is Gram-positive, it acts like a Gram-negative rod, especially in its pattern of sensitivity to antimicrobial drugs. More recently, the pathogenic qualities of *Staphylococcus saprophyticus* and *Corynebacterium* group D2 have been appreciated, but these only very rarely produce sepsis. Instead, they tend to stay in the bladder, producing cystitis that does not progress to sepsis. The cell wall deficient bacteria *Mycoplasma hominis* and *Ureaplasma urealyticum*, may possibly cause UTI, but this is unproven.

B. **Pneumonia**. Bacterial pneumonia either causes complete consolidation of a whole lobe (lobar pneumonia), or a multifocal pattern of smaller consolidations in one or more lobes (lobular pneumonia or bronchopneumonia). In either case, the diagnosis of acute bacterial pneumonia is accomplished by x-ray. Bronchoscopic biopsies are reserved for chronic pneumonias or in the case where a mass is complicated by pneumonia. Accordingly, the pathologist does not usually see acute bacterial pneumonias except at autopsy. Grossly the lung, rather than

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[1]But "Escherichia" is so infrequently spoken that I'm not sure how to pronounce it myself. Perhaps *no one* knows how to pronounce it, so no one attempts to do so, which would otherwise risk revealing ignorance, a cardinal sin in academic medicine. So, "*E. coli*" is the universal sobriquet for this organism.

[2]I don't guarantee that any of these species names are current. Bacterial taxonomists seem to take delight in continually changing genus and species names, depending on the hottest DNA sequence data available (or so they say, and no physicians ever challenge them). Linnaeus would be appalled. I refuse to be drawn in. I say let them have their fun with clinically insignificant bacteria, like *Methanobacterium somethingorotherii*, and leave our pet bugs alone.

being light, airy and spongy, is heavy, wet and firm. In cases of lobar pneumonia, the lung becomes so consolidated that its texture resembles that of normal liver. This is called **hepatization**. There may also be a pleural effusion which is rich in protein and inflammatory cells, a so-called **exudative effusion** (Cf., **transudative effusion**, which is a thinner fluid with less protein and cells; it results usually from hydrostatic abnormalities caused by congestive heart failure and nephrotic syndrome). Microscopically, acute bacterial pneumonia is characterized by an intra-alveolar accumulation of neutrophils and fibrin. Bacterial pneumonia can be complicated not only by sepsis, but also by serious local lesion that require invasive techniques for resolution. These are **empyema**, or accumulation of frank pus in the pleural space, which must be surgically drained, and **lung abscess**, which basically trashes an entire lobe, which must then be surgically removed.

The classical cause of acute pneumonia (leading to sepsis) in previously healthy adults is the “pneumococcus,” *Streptococcus pneumoniae*, which in the past accounted for between 50% and 90% of cases, but this proportion appears to have dropped somewhat in recent years. Loss of the function of the spleen, either by splenectomy or infiltrative disease, is known to prominently increase the risk for pneumococcal pneumonia.

Between 4% and 15% of community-acquired pneumonias are caused by *Hemophilus influenzae*. This is especially difficult to diagnose, since the organisms are not readily isolated by sputum cultures, and normal flora of the upper aerodigestive tract includes multiple species that look like "H. flu" on sputum Gram stain.

The next most common offender is *Staphylococcus aureus*. Known better as the cause of wound infections and osteomyelitis, “Staph” is more prone to cause pneumonia in the elderly and debilitated, and in people who have influenza. Most of the remainder of acute bacterial pneumonias are caused by facultative Gram-negative rods (like *Klebsiella pneumoniae*) and *Legionella* spp. Legionellosis is especially prone to produce systemic effects, such as acute renal failure.

A fairly large proportion of community-acquired pneumonias are caused by *Mycoplasma pneumoniae*, as well as chlamydiae (*C. trachomatis, C. psittaci, C. pneumoniae*) and rickettsiae (*Coxiella burnetii*). These “atypical pneumonias,” however, do not produce a systemically ill, septic patient as frequently as does bacterial pneumonia.

C. **Acute meningitis** is a much feared source of sepsis. Patients may have nothing more specific than a fever and a headache but can head down the tubes quite rapidly. In terms of diagnosis, the anatomic pathologist can offer little help, but the clinical lab saves the day by detecting white blood

cells, protein, and lack of glucose in the cerebrospinal fluid. Rapid methods for detection of bacterial antigens in the csf can give an etiologic diagnosis right away, and even the old traditional Gram stain of the csf can reveal the smoking gun: visible bacteria.

The etiology of bacterial meningitis depends largely on the age of the patient. In neonates, the chief causes are *Streptococcus agalactiae* (a.k.a. "group B Strep"), *E. coli*, *Klebsiella pneumoniae*, *Listeria monocytogenes*, *Enterococcus* spp., and *Salmonella* spp. Older children more often face *H. influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*, while adults also contend with meningococcus and pneumococcus, but not *H. flu*.

D. **Cellulitis** is an acute, spreading infection of the skin and subcutaneous connective tissue. Although penetrating trauma is certainly a predisposing factor for the development of the infection, it can also occur following nonpenetrating trauma, and it may even arise when no predisposing lesion is identifiable. The affected area exhibits the classic signs of acute inflammation, described by Celsus[3], namely *tumor* (swelling), *rubor* (redness), *calor* (heat), and *dolor* (pain). Although you might think, "Big deal. This doesn't involve a vital organ, such as the heart or brain," cellulitis is a serious condition that may require hospitalization and intravenous antibiotics. As in other infections that can lead to sepsis, the effects of sepsis may be seen before there is evidence of the local infection. For instance, a patient with postoperative cellulitis at the site of the incision may present with hypotension even before you can see the classic signs of inflammation at the wound.

The overwhelming majority of cases of cellulitis are caused by *Streptococcus pyogenes* (= "group A Strep") and *Staph. aureus*. There are several special scenarios, though, in which other bacteria are prone to show up. **Erysipeloid**, caused by *Erysipelothrix rhusiopathiae*, is a type of cellulitis seen in individuals who handle saltwater fish, shellfish, poultry, meat, and hides. *E. coli* causes a spontaneous cellulitis in children with nephrotic syndrome. Swimming in fresh water may lead to cellulitis due to *Aeromonas hydrophila*, while exposure to saltwater can be followed by infections due to *Vibrio vulnificus* and other *Vibrio* species. **Gangrenous cellulitis** occurs when extensive necrosis of skin and subcutis accompanies the inflammatory response. There are several clinical syndromes that feature this process, but the most notable ones are 1) **necrotizing fasciitis**, caused by *Strep. pyogenes* (and other Strep

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[3]Or another one of those old-timey guys who believed in humors, etc., back before we geniuses of the Present discovered Real Science and figured everything out the way it really is.

species), and 2) **gas gangrene**, caused by gas-forming anaerobic bacteria, especially *Clostridium perfringens*.

As with some of the other infection already discussed, you, as a primary care physician or surgeon, are pretty much on your own to make a diagnosis of acute cellulitis. Biopsies do not show specific diagnostic findings, and x-rays show only nonspecific soft tissue swelling. Even the clinical microbiology lab is not much help: only about one-fourth of cultures made from aspirates of the affected area will yield the offending microbe. Again, you have to rely on honed clinical skills to pick up the sometimes very subtle findings on physical examination.

E. **Peritonitis**, or inflammation of the peritoneal lining of the abdomen/pelvis, may occur as a primary infection or as a secondary lesion by direct extension of an infection based in an abdominal or pelvic viscus.

1. **Primary peritonitis** is uncommon, but individuals with ascites are especially prone to develop it. In children, the classic etiologic agents were *Strep. pneumoniae* and *Strep. pyogenes*, but the incidence of these organism has declined considerably, possibly as a spin-off of physicians' liberal use of antibiotics in children with minor upper respiratory infections and demanding parents. Nowadays, the villain is more likely to be one of a number of organisms, especially Gram-negative enteric bacilli (*e.g.*, *E. coli*) and *Staph. aureus*. Exactly how bacteria get into the normally sterile peritoneum is unclear, but hematogenous, lymphogenous, and transenteric (through the gut wall) migration of pathogens have been postulated. In females, organisms may enter the peritoneal cavity by way of the Müllerian tract.
2. **Secondary peritonitis** follows contamination of the peritoneum by organisms released from infected organs (as from acute salpingitis), or perforated "dirty" viscera, such as the large intestine. When the latter is the case, the etiologic organisms reflect the normal flora of the ruptured organ. Accordingly, you would expect to see a large contingent of Gram-negative coliform bacilli (e.g., *E. coli, K. pneumoniae, Enterobacter cloacae*) and obligate anaerobes (e.g., *Bacteroides fragilis, Prevotella melaninogenicus*[4], *Clostridium perfringens*) in the septic soup.

F. **Other primary infections** leading to sepsis include infective endocarditis, osteomyelitis, and septic arthritis. These are covered more fully elsewhere.

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[4]Previously *Bacteroides melaninogenicus*...Thank you, Mr Taxonomist with nothing better to do! And I just know the Prevot family is endowing your chair anyway. Happy tenure!