Sepsis remains one of the most common causes of death in critically ill patients. It is defined as a systemic infection whose diagnosis is verified by positive blood cultures and/or identification of a primary infectious focus. This "sepsis syndrome" has been defined as the clinical presentation of a patient's response to the presence of dividing and invading organisms.

Wounds, intravascular catheters, the lungs, urinary tract, central nervous system, and the abdomen are frequently evaluated with a broad spectrum of laboratory tests and diagnostic procedures whose indications and selectivity may not have been derived from data specific to critically ill patients. As a result, the accuracy of these tests to confirm infectious diagnoses in critically ill patients may not be as good as reported in the general patient population. Inaccuracy may be further increased because of the complicity of clinical settings and the presence of multiple inter-related diagnoses and organ system dysfunction. More important, certain tests may not direct therapy or change outcome.

Most agree that the key factor in treating sepsis is identification of the source, location, and type of offending organisms. This is often not easy to accomplish, and when a thorough physical examination, routine roentgenographic studies, and appropriate culture specimens fail to identify a source, an exhaustive, but historically justified, search utilizing many imaging techniques, repetitive cultures, and a wide variety of laboratory tests is begun. It is not clear whether this approach has significantly altered outcome, or just increased hospital costs.

The purpose of this article is to review the data concerning various procedures and tests performed in evaluating the sepsis syndrome in critically ill medical and surgical patients. Guidelines for choosing certain tests are presented.

**Urinary Tract Sources**

Pyuria and bacteriuria can be found in most patients with indwelling bladder catheters after five days. Isolation of the same organism from the blood confirms urosepsis. While epidemiologic studies of nosocomial UTIs identify urosepsis as the cause of over 3,000 deaths per year and responsible for significant increases in hospital costs, the urinary tract appears to be an infrequent source for systemic sepsis in critically ill patients unless obstruction or urinary tract instrumentation has occurred.

Closed drainage systems, strict catheter care, and the liberal use of antibiotics may explain this decline of the urinary tract as a frequent source for bacteremia. Routine catheter cultures, systemic prophylactic antibiotics, and treatment of asymptomatic bacteriuria in a normal host is not indicated. Frequent catheter changes do not reduce the incidence of bacteriuria and urosepsis.

Epidemiologic studies show that catheter acquired bacteriuria is more common in orthopedic and urology patients, in patients who are catheterized after the sixth hospital day, and in patients who require catheterization for seven or more days. One consequence of such large epidemiologic studies has been the adoption of specific guidelines for preventing catheter-associated urinary tract infections in routine hospitalized patients. This information has also been utilized for specific groups such as renal transplant patients.

A recent prospective microbiologic evaluation of the urine in 100 critically ill surgery patients showed that early microbiologic monitoring of urine was unnecessary. Ninety-two patients had negative initial urine cultures and both urine and collecting bag specimens were checked daily. Mean time of catheterization was four days and only 2.6 percent of urine specimens yielded microorganisms. Of 20 patients with any...
positive culture, six had microorganisms in the collection bag alone. The remaining 14 (14.1 percent) had organisms both in the bladder and bag urine. The urine collection bag was the apparent source of microorganisms in the bladder urine in only three cases. The daily incidence of new cases and the cumulative rate of bladder bacteriuria remained below 7 percent and 22 percent, respectively, during the first week of catheterization. Life table analysis showed that the probability of remaining free of bacteriuria after one week was 0.77 by which time 74 percent of patients were no longer at risk. These rates are similar to those previously reported for various patient groups outside the ICU setting. There were no documented cases of bacteremia associated with bacteriuria in this study.18

Anaerobic UTIs, primarily from Clostridia, have been reported in critically ill patients.19 Anaerobes should be suspected if Gram stain of the urine shows Gram-positive rods or Gram-negative rods with subsequent negative aerobic cultures. Cystitis emphysematosa visible on KUB, though rare, should raise the possibility of an anaerobic UTI.19 The diagnosis is confirmed by obtaining a suprapubic needle aspirate urine specimen for anaerobic culture.

Respiratory Sources

The tracheobronchial tree of virtually 100 percent of patients intubated for greater than 48 hours become colonized with Gram-negative bacteria.20,21 It is estimated that 10 to 25 percent of critically ill patients developed a true nosocomial pneumonia,8 although estimates must be viewed cautiously due to a lack of statistical data. The percentage of true pneumonias seems to be high in patients with acute respiratory failure or direct thoracic trauma.

Gram-negative bacteria are responsible for 87 percent of nosocomial pneumonias.22,23 A review of nosocomial lung infection revealed mortality rates of 33 to 70 percent from Gram-negative pneumonia.24 The reason for this high mortality rate from theoretically reversible infections may be more a function of diagnostic accuracy than therapeutic failure. Because of rapid airway colonization, conventional bacteriologic methods for diagnosis usually provide erroneous or misleading information.44 Organisms responsible for nosocomial pneumonia come from the oropharynx24 and intestinal tract.8 Preventative alkalization of the stomach may also contribute to colonization of the upper gastrointestinal tract which may become a source of organisms due to subsequent aspiration.45 Regardless of the source, entry and proliferation of bacteria in the lower respiratory tract must occur before a true pneumonia develops.

The clinical diagnosis includes fever, leukocytosis, purulent secretions, new or progressive infiltrates on chest x-ray films, and pathogenic bacteria in tracheobronchial secretions.46 These findings are often non-specific in both medical and surgical ICU patients. Fever and leukocytosis may be due to any reason for inflammation; purulent secretions may be produced in association with tracheal intubation and repeated suctioning;46 infiltrates occur (without necessarily associated infection) in all patients who develop the adult respiratory distress syndrome (ARDS); finally, pathogenic bacteria in the tracheobronchial tree occur in 75 to 100 percent of critically ill patients.40 In fact, none of the usual criteria for diagnosis of pneumonia was significantly predictive in 24 patients with fatal ARDS.47

Sputum culture is still commonly performed in critically ill patients to guide antimicrobial therapy for pneumonia despite its reported unreliability.5,48–52 Colonization of upper airways and endotracheal tubes are responsible for this inaccuracy. Bronchoscopic aspirates and bronchial washings are also inaccurate for the same reason.5,38

Transthoracic needle aspiration may be the most accurate method for diagnosing nosocomial pneumonia, especially in immunocompromised patients,23 but this procedure is hazardous in patients requiring mechanical ventilation.

The plugged telescopic catheter (PTC) brush introduced in 197934 is a technique developed to improve culture accuracy. The PTC brush consists of a small retractable brush within a double-sheathed polyethylene catheter. The outer sheath is designed to prevent contamination from colonizing bacteria as the catheter is directed through the fiberoptic bronchoscope into the area of the infiltrate. The inner catheter is then advanced into the area of the infiltrate, and the brush is advanced to collect the culture specimen. Optimal results are achieved only with careful attention to detail,34 and quantitative cultures must be performed, with 105 colony-forming units per ml (cfu/ml) diagnostic for infection.34,58 While PTC brush cultures may give the most reliable information if properly performed, false positive results can still be as high as 41 percent.34 False negative rates cannot be assessed since there is no good comparative method to diagnose nosocomial pneumonia.

Soft Tissue Sources (Wounds)

The diagnosis of a wound infection depends on a thorough knowledge of the patient's history (including details of the operation), physical examination, and bacteriologic information from Gram-stain and proper cultures of the wound. Postsurgical and traumatic wounds should be considered possible sources for systemic sepsis following clean-contaminated or contaminated operations. Early physical examination of wounds and surgical incisions should be performed to rule out developing infections, and especially, the
occasional catastrophic, rapidly progressive infections. Most wound infections can be diagnosed by careful physical examination and confirmed with appropriate cultures.

The incubation period for staphylococcal wound infections is four to six days. Infections are usually well localized and characterized by thick, creamy, odorless pus. Staphylococcal wound infections are often erythematous, edematous, and painful and usually respond to local drainage procedures. Antibiotics are generally unnecessary unless associated cellulitis is present or systemic sepsis is documented by positive peripheral blood cultures.

Gram-negative wound infections usually result from contamination with enteric contents and may be accompanied by anaerobic streptococci or Bacteroides fragilis. The incubation period for most of these organisms is seven to 14 days. Gram-negative organisms usually produce less local inflammatory signs, but more systemic signs such as fever, tachycardia, and bacteremia. Wound infections from Gram-negative enteric organisms should be treated with antibiotics specific for these organisms as well as anaerobes, in addition to local drainage and debridement.

Patients with fever and increased pain in a traumatic wound or surgical incision during the first 48 hours postoperatively must be strongly suspected of harboring an infection with group A streptococci or clostridia. Early diagnosis and treatment with appropriate antibiotics and radical surgical debridement is necessary to prevent death which can occur as rapidly as 18 to 24 hours.

Wound infections from beta-hemolytic streptococci, and synergistic bacterial infections produced by a combination of Gram-positive cocci and Gram-negative bacilli can cause rapidly progressive infections of the subcutaneous tissues known collectively as necrotizing fasciitis. Necrotizing fasciitis is diagnosed by demonstrating fascial necrosis and widespread undermining of the skin. Soft-tissue crepitation is a frequent finding, but the overlying skin may appear normal despite widespread fascial necrosis.

Clostridial infections produce rapidly progressive life-threatening infections commonly known as gas gangrene. These infections are rare and usually follow crushing muscle injury contaminated by animal or human feces. Injury or operations to the large bowel, appendix, or gallbladder can rarely precede clostridial infections. Myonecrosis usually begins within a few hours. Severe pain is often the first sign. Careful wound inspection may show only mild local edema and irregular blanching at the wound margins, thickening of the skin and subcutaneous tissue, and a cool skin temperature. Tenderness to palpation is minimal considering the severe pain. Gaseous crepitation may not be present during the early stages of the infection, but a distinctive, putrid odor from volatile aromatic acids and hydrogen sulfide is almost always present. Spread of infection can literally progress at hourly intervals, and a fulminating septic picture rapidly develops with tachycardia and fever. A Gram-stain of the wound will show Gram-positive rods, occasionally mixed with other organisms. Spores are not routinely seen. Anaerobic cultures should be done for confirmation, but appropriate antibiotic therapy and radical surgical debridement must be initiated based on the clinical diagnosis alone.

Massive tissue destruction of extremities and large open abdominal wounds may also cause systemic sepsis. Trauma alone reduces the host's ability to combat infection, and a large wound may indeed be the source for systemic sepsis, even though it appears to be clean.

Bacteria may proliferate sufficiently in soft tissue wounds to produce the sepsis syndrome. This is more likely to occur in elderly patients, diabetics, and patients with disorders or treatment that depress immune function such as malignancy, malnutrition, steroids, and other immunosuppressive drugs.

Swab cultures taken from clean-appearing wounds do not help to confirm the source of sepsis, since almost all of such cultures will be positive. If a wound is suspected as the source, quantitative cultures should be used to confirm the diagnosis. Greater than 10⁶ organisms per gram of tissue strongly suggest wound sepsis, and aggressive topical and systemic antibiotic therapy is indicated. A rapid technique for quantitating wound bacterial counts using a slide containing a Gram-stained aliquot of a homogenized biopsy suspension has been reported. This technique may be useful in rapidly determining whether or not an otherwise clinically normal appearing wound is the source for sepsis.

**Catheter-Related Sources**

Catheter-related sepsis is an area characterized by considerable confusion because there are many different and important clinical questions but very little data specific to critically ill patients.

Part of the confusion arises from, perhaps, early erroneous interpretations of the results of clinical investigations. Catheter-infection, an imprecise term since inanimate objects cannot be infected, had been diagnosed if blood culture specimens drawn through the existing catheter (TTC cultures) were positive. Interpretations that TTC cultures represented indications of catheter-related sepsis were published in the late 1970s and early 1980s.

Maki et al popularized the concept of semiquantitative catheter segment cultures utilizing a technique in which a portion of the removed catheter was rolled on a blood agar plate. If 15 or more colonies were
identified (defining a catheter-related infection), there was a 16 percent incidence of peripheral bacteremia or local infection (catheter-related sepsis). If there were less than 15 colonies, no associated cases of catheter-related sepsis was identified. The majority of specimens cultured were short peripheral intravenous catheters; thus, the "tip" and "intracutaneous segment" were exactly the same specimen. In fact, when only long catheters were studied, the intracutaneous segment (the portion residing in the subcutaneous tract) gave the important information; the catheter tip which, in vivo, resided in the blood stream usually had fewer organisms (less than 15 or a nondiagnostic number) or were actually sterile.

Recently, 49 pulmonary artery catheters left in place for 72 hours in patients with a known source of sepsis were studied.12 Twelve TTC cultures during the course of catheterization were performed in each patient (a total of 588 TTC cultures). Fifty-eight (9.9 percent) were found to be positive for the growth of microorganisms. When compared to semiquantitative cultures of the intracutaneous portion of the catheter after removal, 55 of these 58, or 95 percent of the TTC cultures, were false positives. Only 3 (0.5 percent) of the 588 TTC cultures were true positives. The overall sensitivity was 5.7 percent and the positive predictive value 30 percent. The false positive TTC cultures contained organisms which were usually found in the patients' primary source of sepsis (usually abdominal wounds) and should probably be considered true contaminants. The TTC cultures seem to overestimate catheter-related sepsis, and are thus only misleading and expensive. Bacteria were recovered from flush solutions (2 percent), transducer domes (14 percent), transducer diaphragms (18 percent), and cardiac output fluids (24 percent), but these organisms were not found in the semiquantitative cultures of the catheter segments. Peripheral venipuncture blood cultures were positive in 10 percent although catheter segment cultures in these patients were either sterile or grew different organisms.14

Thus, confusion results from the interpretation of through-the-catheter cultures as evidence of catheter-related sepsis; the mistaken substitution of a tip culture for long catheters instead of the more appropriate intracutaneous segment which traverses the anatomic area whereby organisms gain access; and, use of broth cultures which would be positive even if there were only a few organisms present (too few to produce a catheter-related infection or catheter-related bacteremia). Semiquantitative cultures of a removed intracutaneous portion of a catheter then should be considered the appropriate method for investigation and interpretation.

There is an additional element of confusion. Should the catheter be removed and replaced to a different site, or should guidewire exchange of the catheter (and introducer) at the same site be considered both diagnostic and therapeutic for line sepsis?3 Replacement of an indwelling catheter using a guidewire exchange method and semiquantitative culture of the intracutaneous segment of the removed catheter is an appropriate diagnostic measure. However, the catheter itself is not infected so that its removal is not necessarily therapeutic; rather, the subcutaneous tissue must be considered infected (or perhaps colonized) from a bacteriologic standpoint if a positive catheter segment culture is obtained. One common theme arises from both approaches. The incidence of true catheter-related sepsis is considerably lower than the incidence of suspected cases. In the series of Sitzman et al.,20 55 percent of the total parenteral nutrition (TPN) patients were febrile at some time during their course of TPN and 27 percent ultimately had the TPN line suspected as the source of sepsis. Proven catheter-related infection occurred in only 20 percent of those patients, representing 5.7 percent of the total group. In half the cases, fever was not considered to be due to line sepsis by the clinician and in those which remained, 80 percent of the suspected cases were not confirmed by positive catheter segment cultures.

In summary, diagnosis of catheter-related sepsis can be made by (1) obvious clinical signs of local infection (this should be an infrequent means since it occurs relatively late) or (2) correlation of the same organism from peripheral venipuncture blood cultures and a positive ≥15 colonies semiquantitative culture of a removed catheter segment.

Systemic sepsis from arterial catheters is uncommon. One study showed a 4 percent incidence of bacteremia from arterial catheters left in place for greater than four days.57 In a study limited to axillary and femoral artery catheters, the duration of catheterization ranged from a few hours to 18 days (mean 6.3 days) with a 2 percent incidence of catheter-related sepsis in 350 cases.58 Although it has been recommended that arterial catheters be replaced to a different site at 96 hours,56 it is our opinion that these catheters can be maintained for longer periods if there are no signs of local infection or skin breakdown at the entry site. Constant exposure to systemic arterial pressure has been postulated to account for the frequent infectious complications.58

Neurologic Sources

Eighty percent of patients in traumatic coma will have multiple injuries.60 As a result, these patients are usually treated in surgical or combined medical/surgical ICUs even if the hospital has a separate neurosurgical unit.

Brain or spinal cord injury resulting in systemic
sepsis in multiple trauma patients has never been specifically addressed, although lumbar puncture with culture of the cerebrospinal fluid is often performed if a patient becomes febrile or develops a change in mental status. Anecdotally, meningitis associated with head or spinal cord injury is a very uncommon problem, possibly because most patients with head injuries and multiple trauma are treated with broad spectrum antibiotics for other injuries.

A review of 15,000 patients admitted to two large neurosurgical units over an eight-year period identified only 34 (0.2 percent) cases of bacterial meningitis associated with cranial or spinal cord injury or surgery. Over 70 percent of these patients developed meningitis after one week of hospitalization. Sixty-two percent of the infections were associated with contaminated traumatic injuries, with the most common organisms being Pseudomonas aeruginosa and Klebsiella species. Seventy percent of these 34 patients died; 50 percent as a direct cause of meningitis. Although Gram-negative meningitis is a highly lethal disease (mortality rates range from 43 to 91 percent), it is a very uncommon cause of systemic sepsis and death in trauma patients. The incidence may be higher in critically ill medical patients, but there are no specific data to confirm the incidence of meningitis as a cause for the sepsis syndrome in this population.

**Abdominal Sources**

The diagnosis of intraabdominal sepsis, especially in postoperative patients, is a very difficult problem. Early diagnosis and drainage is essential for improved survival.

A thorough examination may identify an obvious extraabdominal source such as an old intravenous site, sinusitis caused by use of a nasotracheal tube, a palpable perirectal abscess, epididymitis induced by prolonged bladder catheterization, or an unrecognized decubitus ulcer. If the physical examination fails to reveal a source, the abdomen, particularly in previously operated patients, must be strongly considered.

Because of the limitations associated with conventional radiographs, ultrasound, and nuclear scans, computerized tomography (CT) has become the preferred method for diagnosing intraabdominal abscess. Increased availability of CT scans which give more precise definition of anatomic details allows for successful use of percutaneous drainage methods which have significantly modified the classic approach to the management of intraabdominal abscesses. Unfortunately, clinical criteria for ordering CT scans have not developed as rapidly as technology, and similar to all diagnostic methods without specific indications, misinformation can result. The postoperative abdomen may contain air, blood, seromas, and areas of tissue necrosis that may present images indistinguishable from collections of pus.

Most CT studies for abscesses report accuracies from a broad category of patients and do not describe the temporal relationship to intervention nor examine the usefulness in arriving at a clinical decision. Further, the accuracy in critically ill patients is not usually specifically addressed. Numerous reports demonstrate that CT is effective in identifying a well-defined abscess. Large series report overall accuracy rates as high as 95 percent. Trunet et al prospectively followed 31 patients with possible intraabdominal sepsis during the postoperative period and found an overall accuracy of 94 percent with a sensitivity of 100 percent and specificity of 88 percent. Only two trauma patients were included; the overall mortality was 29 percent. Whitley and Shatney reported a 92 percent sensitivity and a specificity of 79 percent in 69 trauma patients. Details of the clinical course and timing of the CT scans were not given in either study. Although the accuracy of CT was excellent in the latter study, closer analysis of the data suggests that the information may not have been as helpful clinically. There were 31 true positive scans and ten false positive scans, seven of which were verified at surgery. Three scans were false negatives, all verified at surgery. The effect of CT in terms of clinical judgment is not addressed. This is very important since six of 38 "true negatives" were also explored. Only seven of ten fals positives had surgery, indicating that at least three patients were not re-explored despite a positive CT scan. Therefore, at least 12 (18 percent) were either operated or not operated on despite CT findings which suggested the opposite course.

Other studies have reviewed the use of CT in the decision making process. One study reviewed 135 CT scans in 111 patients and showed that the scan aided or altered the management of patients in only 55 percent of cases.

A more recent study tried to determine the impact of CT information in 53 critically ill surgical patients who were at risk for developing intraabdominal abscess. Of the 72 scans obtained, only 17 (23 percent) provided beneficial information while 55 (77 percent) provided information that was either not used or detrimental to patient care. Sensitivity and specificity was defined to extend beyond just accuracy of the test and included the impact of the information obtained from CT. Sensitivity in this study was 48 percent with a specificity of 64 percent. Calculation of personnel utilization and charges showed a figure of $28,541 for the 55 scans that were of no benefit. The authors observed that CT scanning for sepsis in critically ill patients gave little useful information; even when the scan was positive, the information did not usually influence the clinical decision-making. When the information was used to direct the clinical care of the
Evaluating patients, mortality rates did not improve. This does not mean that CT scanning is of no benefit in critically ill patients, but CT should not be employed as a tool to blindly search for a source of sepsis. The CT scans were not beneficial during the first week postoperatively, and in MSOF patients, the test was generally without benefit unless a negative scan would strongly support a decision to discontinue therapy. It had no effect upon outcome in these patients when used as a final attempt to locate an intraabdominal abscess. A CT scan should be done only if there is reasonable probability that the information will direct clinical decisions; this probability should be based upon a decision making process in which both negative and positive results actually direct therapy in different directions. As the difficulty to make a clinical diagnosis increases, the likelihood of useful CT information seemed to diminish. The CT should only be employed to confirm the clinical diagnosis of intraabdominal abscess. This should reduce the number of negative re-explorations.

Critically ill patients who develop intraabdominal sepsis eventually fall into two distinct groups. The first group consists of patients whose immunologic reserves are strong enough so that the offending organisms can be controlled, or as Fry stated, a "biological standoff" occurs with development of an intraabdominal abscess. These patients generally do not progress to MSOF, and if the timing is right, CT scanning may be beneficial.

The second group consists of patients whose defense mechanisms are so poor that they are unable to prevent the relentless onset of MSOF despite vigorous ICU care including cardiac and ventilatory support, antibiotics, and nutritional therapy. In this group, CT scanning appears to be of little benefit since these patients are essentially unable to achieve the "biological standoff" necessary to develop an abscess so that surgical drainage can be effectively undertaken.

Abdominal exploration may be the only definitive test in some instances, especially in those patients who develop unexplained single organ system failure. However, it is not clear whether reoperation significantly affects outcome in larger populations of critically ill patients with MSOF. Several recent reports have advocated early re-exploration in septic surgical patients.

A retrospective study of 50 patients who underwent reoperation for sepsis evaluated the use of available clinical and laboratory tests to predict findings at reoperation and ultimate outcome. Basic demographic data such as the diagnosis leading to primary operation, interval between primary operation, onset of fever and elevated white blood cell count, highest white blood cell count, serum albumin levels, arterial partial pressures of O₂ and CO₂, arterial pH, and serum creatinine levels, did not help to predict findings at re-exploration. In this study, 39 of 50 (78 percent) patients had positive findings at re-exploration. Thirty-seven patients (74 percent) survived hospitalization; survivors were significantly younger (41.7 ± 2.8 years) than nonsurvivors (56.0 ± 3.8 years), but there was no significant difference between the groups in terms of time intervals to re-exploration. It is not clear from this study whether all of these patients were in fact critically ill and required extensive ICU care. Fifteen patients had no organ system failure, while 19 were described as having only one organ system dysfunction. Therefore, 72 percent of the patients had one or no organ system failure and an 88 percent survival rate. Those with MSOF (16 patients), had a 56 percent mortality rate. The authors concluded that patients should be re-explored prior to the onset of MSOF, since the risk of negative re-exploration (18.2 percent mortality) was outweighed by the potential for finding and draining intraperitoneal pus.

Others have reported mortality rates following negative explorations for sepsis ranging from 19 to 71 percent. The question does not appear to be whether re-exploration is harmful to the patient, but rather, whether re-exploration significantly affects mortality rates in patients with established MSOF. The majority of critically ill septic surgical patients. There appears to be no question that a properly timed re-exploration may prevent MSOF and significantly improve the chances for survival. The question of significantly altering the course of established MSOF with re-exploration remains unanswered.

**Conclusions**

While certain diagnoses causing the sepsis syndrome are more common in critically ill patients, and the methods of evaluation sometimes too "routine" and thus overutilized, the focus for evaluation is the important issue. In past years, widespread screening evolved. This was thought to prevent omissions, required less thinking, and was perhaps "encouraged" in the era where high utilization of ancillary services was considered good for the hospital's economy.

Today none of those factors apply; omissions are eliminated by encouraging thinking and decision-making; unnecessary testing is wasteful and potentially harmful. The prevalence of the sepsis syndrome in critically ill patients therefore magnifies the need for careful re-examination of role practice to pare away unwanted overutilization and crystallize the approach, decision-making, and selection process for tests used in evaluating sepsis in critically ill patients.

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