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Diagnosis of infection in sepsis

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Introduction

Infection is a sine qua non of sepsis. Sepsis can complicate infection occurring at any site, most commonly the respiratory tract, abdomen and blood stream. More than 90% of cases of sepsis are caused by bacteria, and Gram-negative and Gram-positive organisms occur with approximately equal frequency [1]. Fungi – in particular *Candida* species – are sometimes responsible, but a wide variety of other organisms have occasionally been implicated [2].

There are several reasons why it is important to try and make a microbiological diagnosis in septic patients. First, and most important, is to ensure that effective antimicrobial therapy is given. There is good evidence to support the intuitive belief that patients given appropriate therapy are more likely to survive than those given inadequate or inappropriate treatment [3]. Secondly, obtaining microbiological information will contribute to the local epidemiological database, without which logical prescribing is difficult, if not impossible. There are substantial differences between intensive care units in the microbial ecology, including the prevalence of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis*. Antimicrobial resistance patterns also vary widely, for example, penicillin resistance in *Streptococcus pneumoniae*, and gentamicin resistance in Enterobacteriaceae. Furthermore, these patterns are constantly changing, and an up-to-date awareness of these patterns is obviously essential when considering empirical therapy. Finally, knowledge of the microbial cause of sepsis may be important in the choice of adjunctive therapies. This is not yet clinical reality but will clearly be important if, for instance, anti-endotoxin agents ever enter the clinical arena.

In this contribution we first consider the general approach to the diagnosis of infection in septic patients and then some aspects of infections at particular sites. We focus on the microbiological aspects of diagnosis, although where appropriate we also comment on other modalities such as imaging. The clinical management of these infections are discussed elsewhere.

Methods

We use where possible a systematic, evidence-based approach to provide answers to specific questions. A computer-based review of the literature was undertaken using Medline from 1991 until September 1999 as the primary database. The references obtained were searched manually for relevance. More recent clinical articles were identified by manual search of the relevant journals. Although the literature searches were not extended further back than 1991, key earlier papers are frequently cited. In reviewing this field we frequently observed that whereas there is extensive literature on microbiological aspects of infection in general, there is a paucity of data concerning sepsis in particular. Hence we have often been obliged to make recommendations based on the available literature and our own clinical experience, and that of others. The search strategies used were as follows.

Bacteremia

The primary search terms bacteremia/septicemia (diagnosis, microbiology) and blood (microbiology) were combined with secondary search terms sepsis/sepsis syndrome (diagnosis, microbiology), blood specimen collection (methods), bacteriological techniques and diagnostic tests, routine (methods). Studies addressing exclusively pediatric populations were excluded.

Central venous catheter infection

The primary search terms catheterization, central venous (adverse effects) and indwelling catheters (adverse effects) were combined with secondary search terms sepsis/sepsis syndrome (diagnosis, microbiology, etiology), bacteremia/septicemia (diagnosis, microbiology, etiology), blood specimen collection (methods), bacteriological techniques and diagnostic tests, routine (methods).

Ventilator-associated pneumonia

The primary search terms artificial respiration (adverse effects) ventilation, mechanical (adverse effects) and intensive care (methods) were combined with the secondary search terms pneumonia (diagnosis, microbiology, etiology), sepsis/sepsis syndrome (diagnosis, microbiology, etiology), bacteremia/septicemia (diagnosis, microbiology, etiology), bacteriological techniques and diagnostic tests, routine (methods).

Surgical site infections and intra-abdominal sepsis

The primary search terms wound infection (diagnosis, microbiology), abscess (diagnosis, microbiology) and abdomen were combined with secondary search terms sepsis/sepsis syndrome (diagnosis, microbiology, etiology), bacteremia/septicemia (diagnosis, microbiology, etiology), bacteriological techniques, diagnostic tests, routine (methods) and interventional radiology.

General considerations in the diagnosis of sepsis

There are three key difficulties associated with the diagnosis of infection in patients who have sepsis.

Establishing infection as the primary cause

The controversies surrounding the definition of sepsis are discussed elsewhere (see Matot and Sprung, "Introduction"). Establishing that the patient has an ongoing infection – and therefore has sepsis rather than a noninfective cause of the systemic inflammatory response syndrome (SIRS) – can be extremely difficult. An important first step is a systematic consideration of possible noninfective causes. Knowledge of other pathologies that may mimic sepsis and how they apply to the specific patient can make up for a relative paucity of clinical information in patients who may be sedated or critically ill. Noninfective causes of SIRS are the following:

- Tissue injury
  - Surgery/trauma
  - Hematoma/venous thrombosis
  - Myocardial/pulmonary infarction
  - Transplant rejection
  - Pancreatitis
  - Erythroderma
- Metabolic
  - Thyroid storm
  - Acute adrenal insufficiency
- Therapy related
  - Blood products
  - Cytokines, especially granulocyte-macrophage colony stimulating factor
  - Anasthetic-related malignant hyperpyrexia, especially halothane
  - Neuroleptic malignant syndrome, for example, caused by haloperidol
  - Opiates/benzodiazepines
- Malignancy
  - Hypernephroma/lymphoma
  - Tumor lysis syndrome
- Neurological
  - Subarachnoid hemorrhage

Tissue infarction or hematoma, for example, may need to be actively sought in a surgical or trauma patient who develops signs of SIRS and precipitation of thyroid storm or adrenal insufficiency should be considered in at-risk patients following trauma or surgery.

Localizing the site of infection

This may be straightforward, but frequently it is confounded by the fact there are multiple pathological processes occurring concurrently or by the frequent use of antibiotics which undermine microbiological diagnosis. Occasionally the site of infection is occult, for instance, when there is sinusitis or deep intra-abdominal infection.

Interpreting the microbiological findings

Conventional microbiology has several limitations in hospitalized patients who may be septic:

- Distinguishing colonization from infection
- Prior antibiotic therapy
- Correctly identifying unfamiliar organisms
- Determining the significance of mixed culture results
- Interpreting the importance of organisms normally of low virulence

Principal among these is the fact that many organisms isolated from nonsterile sites may represent either colonization or infection – microbiology alone cannot answer this question. Conversely, the microbiology laboratory may report negative findings in samples from sites that are in fact infected, either because antibiotics have sterilized the specimen, or because special procedures need to be carried out (e.g., immunofluorescence to detect *Pneumocystis carinii*).

A clinical approach

Fever is a common sign in hospitalized patients and is often the first indication of sepsis. Practical guidelines for the evaluation of fever on the ICU have recently been published [4]. Focused clinical examination, guided by risk factors relevant to the individual patient, often reveal potential sources of sepsis and guide subsequent investigation. Surgical and traumatic wounds should be exposed and examined for signs of infection. Particular attention should be paid to vascular access sites for signs of phlebitis or cellulitis and to pressure areas or injection sites for evidence of soft tissue infection. Evidence of sinusitis should be sought, and fundoscopy is invaluable in detecting candidal endophthalmitis, a pathognomic feature of systemic fungal sepsis. Urine in the catheter may be frankly purulent, and the presence of diarrhea may indicate *Clostridium difficile* associated colitis. The importance of repeated, complete physical examination to detect the emergence of new signs cannot be overstated.

Nonspecific markers of infection

Traditional markers of infection such as neutrophilia lack sufficient sensitivity among hospitalized patients to be of value in distinguishing sepsis, although marked neutrophilia or failure to mount a neutrophil response may be of prognostic value. Levels of procalcitonin (PCT) and C-reactive protein (CRP) are straightforward to assay. The evidence that these acute-phase markers have specificity in differentiating infection from other causes of an inflammatory response has recently been reviewed [5]. Levels of CRP and PCT are correlated well with the degree of inflammatory response and are of particular value in monitoring response to treatment [6]. PCT may have some advantages over CRP in that it rises more quickly at the onset of inflammation and is cleared more quickly as inflammation resolves [7]. Levels of PCT are correlated more closely with severity of sepsis [8] and also are predictive of mortality [9]. A prospective study of ICU patients found that a CRP level of 50 mg/l or higher had a sensitivity of 98.5 % and specificity of 75 % in identifying probable or definite sepsis [10]. De Werra et al. [11], also in an ICU population, found PCT levels of 1.5 ng/ml or higher to have a sensitivity of 100 % and specificity of 72 % in identifying sepsis. Such markers therefore cannot alone differentiate sepsis from other causes of SIRS; rather they are a part of a systematic evaluation that includes clinical examination and directed diagnostic techniques. Daily, sequential measurement of inflammatory markers is likely to be of more value in diagnosis of infection than single measurements [10].

Detection of circulating endotoxin might be expected to be a specific test for sepsis. Assays differ in the sensitivity, cutoffs are not established, and the transient nature of endotoxemia makes timing of measurements essential. For these reasons measurement of endotoxin levels in sepsis patients remains experimental.

Figure 1 outlines an algorithm for investigation of suspected sepsis into which may be fed data from clinical examination and nonspecific investigations along with the appropriate specific microbiology and imaging investigations discussed in detail below.

Discussion: literature-based recommendations

To answer each of the following important clinical questions, a review of the literature was performed as previously described.

Bacteremia

Are there specific indications for obtaining blood for culture?

Answer: yes; grade D.

Recommendation

Fever, chills, hypothermia, leukocytosis, left-shift of neutrophils, neutropenia, and when infection is suspected, hypoalbuminemia, development of renal failure or signs of hemodynamic compromise are specific indications for obtaining blood for culture. Blood cultures should be taken as soon as possible after onset of fever or chills.

Rationale

Blood should be obtained for culture whenever there is reason to suspect blood stream infection, commonly when a patient develops a new fever. In practice, as a noninvasive, safe, and low-cost investigation, blood culture is often performed when there a few specific indications. However, a number of clinical and laboratory parameters are independently correlated with the presence of bacteremia in patients in whom infection is suspected, notably, chills, hypoalbuminemia, development of renal failure, and a diagnosis of urinary tract infection [12]. Other criteria are fever, hypothermia, leukocytosis, left-shift of neutrophils, neutropenia and signs of hemodynamic compromise [13]. Ideally patients should not be receiving parenteral antibiotics when blood cultures are performed. While we are aware of no published

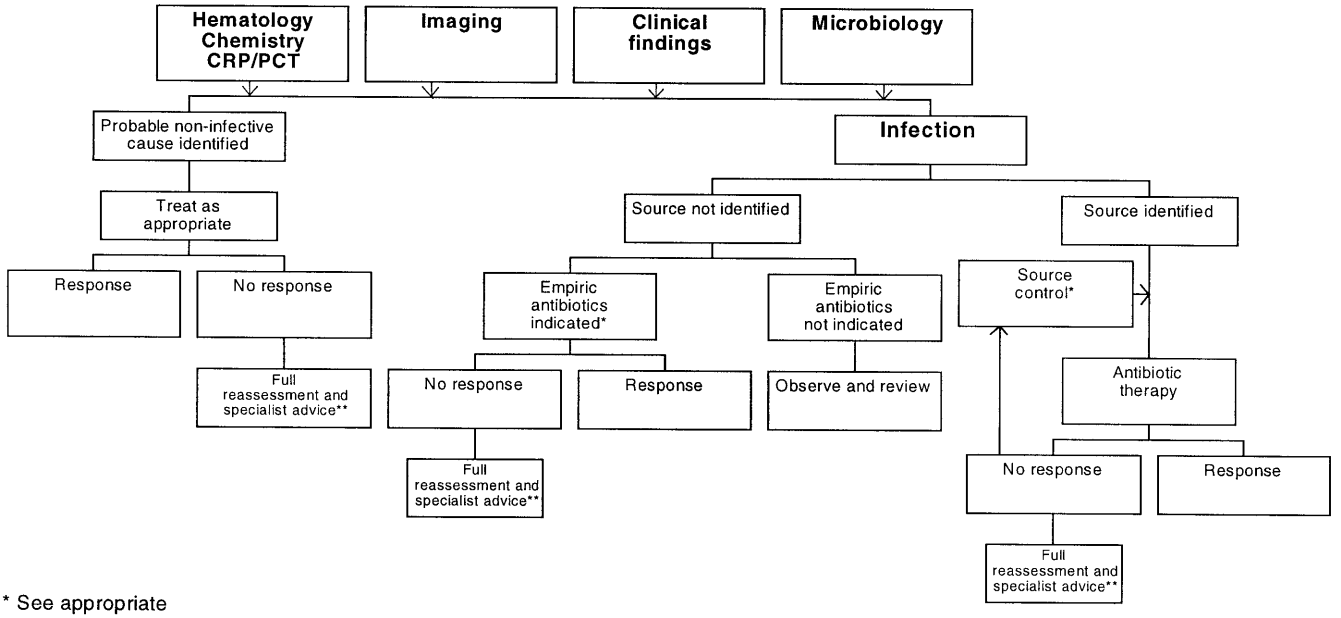

Fig. 1 Algorithm for systematic evaluation of nonneutropenic patients with suspected sepsis

data which directly address this issue, blood cultures should be taken, where possible, immediately before a regular dose of antibiotic so that blood levels are minimized. In suspected fungemia, therapy with antibacterial agents clearly should not impact on yield. Otherwise the indications for performing blood culture are the same irrespective of whether the patient is receiving antibiotics or not. In this group of patients, media containing antibiotic adsorbing substances such as BacT/Alert FAN and BACTEC Plus/F should be used since they are associated with increased recovery of significant pathogens, particularly among patients on appropriate antibiotic regimes [14].

The literature contains no clinical data relating to timing of blood cultures with respect to timing of fever or chills. Nevertheless, bacteria are rapidly cleared from blood, and development of fever usually follows an episode of bacteremia by 30–90 min. Published expert opinion is that blood cultures should be taken as soon as possible following onset of fever [15].

Does the technique employed in obtaining blood cultures influence the sensitivity and specificity of this investigation?

Answer: yes; grade D.

Recommendation

Blood should be obtained by fresh venipuncture. Sites associated with skin contamination (e.g., femoral site) or loss of skin integrity (e.g., burns or dermatological disease) should be avoided. Skin should be swabbed twice with either 70% isopropyl alcohol or with an iodine containing solution prior to venipuncture. The blood culture stopper should also be sterilized prior to inoculation. An adequate volume (20–60 ml) of blood should be obtained per culture (10–30 ml per bottle). If insufficient blood is available, only the aerobic bottle should be inoculated. The needle used for venipuncture should be changed prior to inoculation of blood into culture bottles.

Rationale

When a decision has been made to take blood for culture, adherence to a protocol for obtaining the specimen results in lower contamination rates and improved yield [13, 16]. The cost of additional investigations, treatment and in-patient stay associated with each contaminated blood culture has been estimated as between U.S. $1,000 and $5,000 [17, 18]. Furthermore, with Gram-positive organisms making up an increasing proportion of significant blood culture isolates, identifying such isolates as contaminants is more difficult than ever.

Blood taken from a central venous catheter (CVC) is significantly more likely to be contaminated by skin flora [19], as is blood taken from previously placed periph-

Table 1 Trials comparing skin sterilization techniques

Protocol	Conclusion	Reference
10% povidone iodine and 0.2% chlorine peroxide	No benefit	21
Alcohol then povidone iodine compared with alcohol alone	No benefit	22
70% iodophore compared with tincture of iodine	Tincture of iodine associated with 50% fewer contaminated cultures	23
70% isopropyl alcohol/70% povidone iodine compared with isopropyl alcohol, 10% acetone and povidone iodine dispenser	Isopropyl alcohol and 10% acetone and povidone iodine dispenser associated with 50% fewer contaminated cultures	24

eral cannulas, although contamination rates may not be higher for blood obtained through a peripheral cannula at the time of insertion, and this is acceptable as a means of minimizing number of venipunctures [20]. It may be possible to minimize contamination of blood obtained through venous catheters by adherence to meticulous sterile technique [21], but this approach should only be used when no site for venipuncture is available.

Definitive evidence that skin disinfection reduces blood culture contamination rates is lacking, but this conclusion has been inferred from the findings of controlled trials which demonstrated superiority of one skin preparation agent over another. Two other trials have shown no benefit. One concluded that contamination occurs during laboratory specimen handling [22], a second found unexpectedly low contamination rates in both patient groups. The relevant trials since 1990 are summarized in Table 1. We are aware of no reason to revise our earlier recommendations that skin should be swabbed twice with either 70% isopropyl or ethyl alcohol or with an iodine-containing solution [25]. The blood culture stopper should also be sterilized prior to inoculation of the blood sample. While we are aware of no data that directly address this issue, it is the recommendation of previously published expert opinion [15].

Inoculation of 3 cfu into blood culture is required to give 100% culture positivity [26]. The concentration of bacteremia in adult patients is frequently less than one viable organism per milliliter [27] and may be less than 0.1 organisms per milliliter [28]. For these reasons it is not surprising that the volume of blood inoculated into culture is an important variable determining culture yield [13, 29]. This effect has also been demonstrated in clinical studies, although not specifically in sepsis patients [30, 31]. While the blood culture system employed determines the volume of blood that may be utilized, in adults a minimum sample size of 20 ml is required per venipuncture (10 ml per bottle) [15, 32] while increasing the sample volume above 30 ml is not associated with significantly improved culture rates [13]. In infants, in whom bacteremia is associated with higher number of colony-forming units per milliliter, a smaller volume of blood (0.5– ml or < 1% of circulating blood volume) can be used for culture [33]. Anaerobic organisms now make up fewer than 5% of blood culture isolates [34, 35]. Furthermore, aerobic culture bottles are more successful in culture of the overwhelming majority of organisms identified in blood [36]. Therefore, if insufficient blood is available to inoculate two culture bottles, only the aerobic bottle should be inoculated.

Contrary to earlier reports [37, 38, 39], a recent meta-analysis has demonstrated lower contamination rates if a needle change is performed [18]. Guidelines regarding resheathing of needles must be strictly adhered to in order that the associated increased risk of needle-stick injury be avoided.

Is there evidence to determine how many sets of blood cultures should be taken?

Answer: yes; grade E.

Recommendation

A minimum of two and maximum of three sets of blood cultures should be obtained for each episode of suspected bacteremia.

Rationale

When bacteremia is associated with endocarditis, if one culture is positive, the probability of any subsequent culture being positive exceeds 95%. In bacteremia associated with other sources of infection, sensitivity exceeding 99% is reached with either two [40] or three [41] cultures. The taking of only one culture is rarely permissible since the rate of contamination of an individual set of blood cultures is finite, ranging from 1% to 4.5% [22, 23, 24]. Interpretation of a single isolate of a potentially contaminating organism may therefore be exceedingly difficult.

Is there evidence that temporal separation of blood cultures is valuable?

Answer: no; grade D.

Recommendation

In critically ill patients, in whom it may not be possible to delay treatment, no interval is required between taking sets of blood cultures.

Rationale

In patients who are not critically unwell, published expert opinion has been that a 30- to 60-min interval should be allowed between obtaining sets of blood cultures [42]. However, the only published study directly to address the efficacy of serial versus simultaneous blood cultures, demonstrated that drawing blood cultures simultaneously or at intervals over a 24-h period did not effect yield [31].

Central venous catheter infection

Definition of terms

It is clinically important to distinguish catheter-related bacteremia (CRB) from catheter-related sepsis (CRS). CRB is defined by the presence of three criteria [43]:

- Positive catheter culture.
- Positive peripheral blood culture taken before catheter removal.
- The same micro-organism is identified in each of the above.

A positive catheter culture has been defined [44] as the presence of 15 colonies or more on semiquantitative culture of the catheter tip [45] or of 10 colonies or more on quantitative culture [46]. The various laboratory techniques used to culture CVCs is beyond the scope of this article but have recently been reviewed [47].

CRS is defined as a positive catheter culture when this is considered to be the source of the patient's sepsis, but bacteremia does not occur [44]. The term catheter-related blood stream infection is sometimes used, and refers to cases in which peripheral cultures are positive, but catheter tip cultures do not need to meet culture criteria as long as there is indirect evidence that the catheter is the source of infection, for example, defervescence following catheter removal.

Unfortunately, many of the studies pertaining to diagnosis of CVC infection do not strictly adhered to definitions of CRB and CRS. In particular, most published studies that appear to show that it is possible to diagnose catheter infection without catheter removal for culture in reality only address cases of CRB.

Can CVC infection be identified as a source of *bacteremia* without resorting to catheter removal for culture?

Answer: yes; grade C.

Recommendations

When a CVC is suspected as a source of bacteremia, diagnosis of CVC infection may be made by blood culture based techniques if (a) the patient's clinical condition permits a potentially infected line to be left in place, (b) treatment of CVC infection is to be attempted, or (c) other potential sources of bacteremia are apparent. While the acridine orange leucocyte cytospin (AOLC) test offers the possibility of virtually immediate diagnosis, on the basis of currently available data its use should remain experimental.

Rationale

When a patient who has a CVC in place develops bacteremia, the likelihood that the CVC is the source of the bacteremia depends on the organism cultured. One study of 311 patients who had CVCs found that 73 % of bacteremias were related to CVC infection, and that if the culture was of *S. aureus*, this figure rose to over 92 % [48]. Other organisms that are particularly associated with CVC infection as a source are coagulase-negative staphylococci, *Corynebacterium* (especially JK-1), *Bacillus* species and fungi, in particular, *Candida* species [49]. Two approaches to diagnosing CVC infection as a source of bacteremia, without catheter removal for culture, have been reported in the literature: (a) culture of CVC and peripheral blood and (b) AOLC test.

Culture of central venous catheter blood

This approach is based on the fact that the concentration of bacteria drawn through an infected catheter is between 4 [50] and 30 [51] times higher than the concentration in peripheral blood drawn simultaneously. The use of this approach in clinical diagnosis has been assessed in two ways. First, by quantitative or semiquantitative blood culture and, secondly, in continuous monitoring blood culture systems. Both methods rely on it being possible to aspirate at least 20 ml blood through the

Table 2 Studies of continuous blood culture monitoring (*CRB* catheter-related bacteremia)

Population	Finding	Reference
Retrospective review of 7 patients with suspected line related infection	Time to positivity shorter for central catheter cultures than cultures from peripheral sites	59
Retrospective study of 11 patients in whom CRB was diagnosed	Time to culture positivity 1–24 h earlier for central peripheral catheter cultures	61
Retrospective analysis of 64 cancer patients with suspected CRB	28 cases of CRB were identified; a cutoff of +120 min had 100 % specificity and 96.4 % sensitivity	62
Prospective study of 93 cancer patients on an ICU	28 cases of CRB were identified; a cutoff of +120 min had 91 % specificity and 94 % sensitivity	63

Table 3 Studies of acridine orange leukocyte cytospin *(AOLC)* in adult patients (*CRB* catheter-related bacteremia, *CVC* central venous catheter, *HDU* high dependency unit)

Setting	Finding	Reference
100 patients with suspected CRB, most on parenteral nutrition	35 cases of CRB, AOLC positive in 2/17; when used in conjunction with endoluminal brushing, AOLC identified 15/18 and was 100 % specific	64
55 CVC tips from ICU patients	4 cases of CRB, AOLC positive in 2; 10 colonized catheters, AOLC positive in 2	65
49 patients with suspected catheter-related blood-stream infection; mixed ICU/HDU	12 cases of catheter-related blood-stream infection identified, AOLC negative in all	66
128 surgical patients with suspected CRB	50 cases of CRB, AOLC was 96 % sensitive and 92 % specific	67

catheter in question, and it is estimated that blood cannot be aspirated from 12–50 % of potentially infected catheters [43, 52]. Furthermore, being culture based methods, both involve a delay of up to 48 h before cultures can be expected to become positive, time when a potentially infected catheter remains in situ.

Quantitative blood cultures

A series of studies in the 1980s demonstrated that quantitative cultures of central and peripheral blood can be used to diagnose CRB [53, 54, 55]. In the literature since 1991 two studies have attempted to determine the ratio of colony-forming units per milliliter that gives optimal sensitivity and specificity. Capdevila et al. [50] found that using a cutoff of 1:4 for the ratio of bacterial colonies in peripheral to central blood, sensitivity and specificity of 94 % and 100 %, respectively, could be achieved. Quilici et al. [56] used a ratio of 1:8 and found sensitivity of 92.8 % and specificity of 100 % in a prospective study of critical care patients. Published expert opinion is that quantitative culture of central and peripheral blood samples showing a greater than 5:1 ratio suggest CRB [57, 58]. A meta-analyis of various catheter culture techniques concluded that quantitative blood cultures were more cost effective than any culture technique involving the catheter itself [47].

Continuous blood culture monitoring

In this approach the time taken for a blood culture to become positive is related to the number of micro-organisms initially present. The higher the initial concentration, the faster the cutoff point is be reached to determine positivity [59]. Four clinical studies have been performed using paired central and peripheral blood samples and one of the commercially available continuous monitoring blood culture systems (e.g., BacT/Alert) which employs a colorimetric CO_2 sensor [60]; findings are summarized in Table 2.

Acridine orange leukocyte cytospin test

This is currently the only good candidate for a rapid diagnostic test for CRB. The test requires only 50 μl blood to be withdrawn from a CVC and takes around 30 min and minimal specialist laboratory expertise. We are aware of four clinical trials in adults (Table 3). Two have yielded positive results [64, 67], both from the

Table 4 Factors associated with risk of central venous catheter *(CVC)* infection (*CRB* catheter-related bacteremia)

		References
Catheter site	Subclavian lines are associated with significantly less catheter site colonization and infection than jugular or femoral lines although less CRB has not been demonstrated.	71, 74, 75, 76
Catheter insertion	Difficult catheter insertions with multiple attempts are associated with higher rates of infection.	77
Catheter type	It has been suggested that multilumen catheters may be associated with a higher risk of infection than single lumen catheters possibly because they are handled more frequently. This effect is not apparent in critical care patients. Tunnelled lines are associated with delayed and fewer incidences of CRB.	72, 74, 78, 79, 80
Antiseptic impregnated and antibiotic coated catheters	There are conflicting studies assessing the extent to which incorporating antimicrobial agents into the manufacture of catheters reduces infection rates. When assessed in critical care patients, such catheters are associated with rates of colonization, local infection and CRB reduced by up to 70%.	81, 82, 83, 84
	When CVCs are used for parenteral nutrition this benefit may be lost.	85, 86
Catheter use	In an ICU setting the use of CVCs for parenteral nutrition has been shown to increase colonization rates. In a non-ICU setting higher infection rates have been found in CVCs used for parenteral feeding.	74, 87
Duration of catheterization	The risk of a central venous catheter being infected increases as duration of catheterization increases beyond 1 week.	74, 88, 89
Previous catheters	Meta-analysis data suggest that "guide-wire" replacement of CVC may be associated with a higher infection rate than replacement to a new site.	90
	The infection rate for a patient's first CVC is significantly lower than for any subsequent catheter whether replaced by "guide-wire" or at a distant site.	91
Underlying disease	Trauma and burns patients at high risk, neurosurgical patients at lowest risk.	71

same group in Leeds, while two from elsewhere [65, 66] both produced disappointing results. None has specifically investigated sepsis patients, and only one specifically involved critical care patients [65]. Two small studies, again from the group in Leeds, have demonstrated that culture of a wire brush passed down the lumen of a potentially infected catheter is correlated well with subsequent culture of the catheter tip. The first looked at 115 CVCs used for parenteral nutrition in general surgical patients [68]. The second reported 95% sensitivity and 84% specificity among 22 surgical patients subsequently diagnosed with CRB [69].

Can CVC infection be identified as a source of sepsis in *nonbacteremic* patients without catheter removal for culture?

Answer: no; grade E.

Recommendation

When a CVC is suspected as a source of sepsis in nonbacteremic patients, definitive diagnosis requires that the CVC should be removed and sent for culture.

Rationale

Only a proportion (10–72% depending on organisms involved) of infected CVCs are associated with bacteremia [70]. When critical care patients develop signs of sepsis, even in the absence of bacteremia, replacement of central venous catheters is frequently advised. However, using standard culture techniques, rates of proven catheter infection range from 8.9% to 26% [66, 71, 72], and therefore many more catheters are removed than are infected [66, 69, 73]. The decision whether to remove a CVC in this setting, where blood cultures are negative, is essentially a clinical one, and involves weighing up risk of catheter replacement against risk of leaving in place a potential source of infection. To help guide this decision a range of clinical parameters have been suggested as possible correlates of catheter infection. A number of individual associations have been identified, summarized in Table 4, and these have been used to make recommendations concerning CVC insertion and care [44]. Two studies have assessed the use of such parameters in guiding clinical judgement and have failed to show they are of value in increasing the proportion of removed CVCs that are infected [66, 92]. Clinical criteria have been incorporated with microbiological data and clinical response to catheter removal into a scoring system [93] which appears more sensitive and no less specific than the Hospital Infection Control Practices Advisory Committee diagnostic criteria [94]

but nevertheless requires removal of the catheter for culture.

Is infection at the catheter insertion site indicative of CVC infection?

Answer: yes; grade C.

Recommendation

If infection is suspected at the catheter site, swabs should be taken from the insertion site for culture. The presence of purulence at the CVC site should prompt catheter replacement at a distant site irrespective of culture results.

Rationale

We are unaware of any studies of insertion site skin culture as a predictor of catheter-related infection in sepsis patients. In patients with long-term nutrition catheters, negative site cultures had a negative predictive value for line infection of 98 % [95] while positive culture, particularly of organisms other than coagulase-negative staphylococci is predictive of CVC infection [96]. In patients with nontunneled CVCs, quantitative skin cultures at the time of removal for suspected infection had a sensitivity of 75 %, a positive predictive value of 100 % and a negative predictive value of 92 % in detecting CVC infection [97].

Expert opinion in the literature is generally that inflammation and frank purulence around a catheter insertion site is a predictor of CVC infection [43, 57, 98]. Reed et al. [44] recommend that "if the site appears to be infected, the catheter is removed." While local evidence of infection is predictive of systemic infection, it is possible to find marked local signs of infection with no evidence of systemic infection [48].

Ventilator-associated pneumonia

This section addresses specifically the diagnosis of ventilator-associated pneumonia (VAP) in sepsis patients. The diagnoses of community-acquired pneumonia [99, 100, 101] and pneumonia in the immunocompromised host [102] have recently been reviewed by others. The merits of various invasive diagnostic approaches to VAP have also been the subject of several recent editorials and reviews [103, 104, 105, 106, 107]. We therefore specifically exclude from this discussion a review of the extensive literature, which assesses the different modes of invasive airway sampling. Nevertheless, the question "Is the lower respiratory tract the source of this patient's sepsis?" will, particularly in the ICU frequently apply to patients who develop sepsis while ventilated. We focus then on the evidence to support the recommendation of particular diagnostic tests in management of sepsis patients in whom VAP is suspected as the source.

Can clinical parameters be used to diagnose pneumonia as a source of sepsis in a ventilated patient?

Answer: uncertain; grade D.

Rationale

The clinical diagnosis of pneumonia in the non-ICU patient is usually based on the presence of fever, leukocytosis, purulent sputum and new radiographic infiltrates in such patients these criteria are sensitive and specific. In intubated patients these parameters are too nonspecific to be of diagnostic value. Purulent secretions, for example, are almost inevitably found in patients receiving prolonged mechanical ventilation and do not specifically indicate the presence of pneumonia [108].

A range of risk factors for the development of VAP have been identified. Cumulative incidence of VAP increases with time following intubation, but the daily increase in risk diminishes over time [109], such that rates are approximately 3 % per day in the first week, 2 % per day in the second and 1 % per day thereafter [109]. Other independent risk factors recently reviewed include witnessed aspiration, neurological disease and administration of a paralyzing agent impairing airway reflexes, presence of a nasogastric tube, enteral feeding and drugs used to raise gastric pH [110]. One study used by multivariate analysis of clinical parameters to generate a scoring system for risk of developing nosocomial pneumonia in ICU patients. In the patients studied the scoring system had a sensitivity of 85 % and a specificity of 66 % [111]. We are not aware of any prospective, comparative data to assess the usefulness of such a system in clinical practice; hence the answer to the question remains "uncertain."

Should blood cultures be obtained in patients in whom VAP is suspected?

Answer: yes; grade E.

Recommendation

Two sets of blood cultures should be sent in patients with suspected VAP.

Rationale

Blood cultures are neither sensitive nor specific in the diagnosis of VAP. Between 3 % and 12 % of bacteremias which occur in ICU patients have a respiratory tract source [112, 113], but only one-quarter of cases of VAP are associated with bacteremia [114]. Bacteremia in patients with suspected VAP, in reality, usually arises from outside the chest [114, 115]. Meduri et al. [115] have demonstrated that two-thirds of patients with nosocomial pneumonia have at least one other focus of infection, usually urinary or CVC related. For this reason published expert opinion is that blood cultures are an essential part of the work up of a patient with suspected VAP [116].

Are new chest radiographic infiltrates diagnostic of pneumonia in a ventilated patient?

Answer: no; grade D.

Recommendation

A chest radiography should be performed.

Rationale

The development of a new chest radiographic infiltrate in a ventilated patient may have many causes other than infection [104, 117]. When assessed against diagnosis by bronchoscopy [118], final clinical diagnosis [104] or postmortem histology [119], chest radiographic changes alone are insufficiently specific for diagnosis of pneumonia in this group of patients. Computed tomography (CT) is more sensitive in detecting lung parenchymal changes than plain radiography and may better demonstrate fluid collections [120]. Even so, most causes of diffuse air-space shadowing cannot be reliably differentiated on CT, which therefore adds little diagnostic information in suspected VAP over and above plain radiography [121]. Not withstanding this lack of diagnostic specificity, chest radiography may provide valuable information, for example, to guide invasive diagnostic approaches and detect pleural effusion.

Should thoracocentesis be performed in patients with pleural effusions in whom VAP is suspected?

Answer: yes; grade E.

Recommendation

Pleural effusions larger than 10 mm should be aspirated. Samples should be sent for immediate Gram and fungal stains, culture and biochemistry including protein, lactic dehydrogenase and glucose. Paired blood chemistry samples should also be sent for comparison.

Rationale

Pleural effusions are uncommon in VAP, and empyema develops rarely. We are not aware of any data which determine rates at which diagnostic information is gained from analysis of pleural fluid in the context of VAP. Our recommendation is in line with published guidelines of the American Thoracic Society [116]. The presence of a parapneumonic effusion larger than 10 mm warrants diagnostic thoracocentesis. Parameters suggestive of an underlying pneumonia include: white blood cells higher than 5×10^9/l, more than 50 % polymorphonuclear cells, organisms seen on Gram stain, low glucose (< 40 g/dl), pH less than 7.3 and biochemical criteria of an exudate (protein > 3 g/l, raised lactic dehydrogenase) [122].

Do serological tests have a role in diagnosis of VAP?

Answer: no; grade E.

Recommendation

Serology is not routinely indicated in the diagnosis of VAP.

Rationale

With the possible exception of *Legionella* infection, "atypical" organisms are not causes of VAP. Although nonepidemic *Legionella* infections made up 22 out of 286 episodes of hospital acquired pneumonia in one study, none developed in patients who were already ventilated [123]. *Legionella* infection developing in a ventilated patient would raise the possibility of acquisition from within the ICU. In rare cases in which *Legionella* infection is suspected, urinary antigen testing provides rapid and accurate diagnosis and is now beginning to replace serology.

Should tracheal aspirates be obtained in patients in whom VAP is suspected?

Answer: yes; grade C.

Table 5 Studies assessing diagnostic accuracy of endotracheal aspirates *(ETA)* in diagnosis of ventilator-associated pneumonia *(VAP)* (*BAL* bronchoalveolar lavage, *PSB* protected specimen brush)

Protocol	Finding	Reference
12 patients with suspected VAP; compares semiquantitative culture of ETA, PSB and BAL	Similar range and quantities of organisms recovered by all techniques	127
52 patients with suspected VAP; compares ETA (cutoff 10^6 cfu/ml) and PSB	Sensitivity 82 % vs. 64 %; specificity 83 % vs. 96 %	128
26 patients with "definite VAP," 48 "possible VAP," 28 controls; compares ETA (cutoff 10^5 cfu/ml) and PSB/BAL	Sensitivity 70 % vs. 60 %/57 %; specificity 72 % vs. 93 %/87 %	129
28 patients with suspected VAP; compares ETA (cutoff 10^5 cfu/ml) and PSB/BAL to postmortem histology	Sensitivity 63 % vs. 57 %/47 %; specificity 75 % vs. 88 %/100 %	130

Recommendation

A sample of secretions aspirated via the endotracheal tube should be sent for Gram stain and for bacterial and fungal culture.

Rationale

Studies which assess different approaches to the microbiological diagnosis of VAP have been hampered by the fact that there is no accepted diagnostic "gold-standard." Postmortem histology and quantitative tissue culture (10^4 cfu/g tissue) are generally regarded as the most precise techniques available but are often not practicable for use in clinical studies. Furthermore, characteristic histological changes in pneumonia may be found in lung which is sterile in culture, and bacterial counts up to 10^4 cfu/g lung tissue may be found in the absence of histological changes in pneumonia, due to rapid proliferation of organisms after death (reviewed in [124]). Published studies therefore frequently make comparisons between different techniques or use clinical response as confirmation of the diagnosis.

The microbiology of endotracheal aspirates (ETA) exemplifies the problem of distinguishing colonization from infection in an ICU setting. Bacterial colonization of the lower respiratory tract is almost universal following intubation [125]. Consequently, negative ETA cultures have powerful negative predictive value in the diagnosis of VAP. When pneumonia is present, the causal agent is usually present in nonquantitative culture of ETA [126, 128, 129]. True pathogens may, however, be missed in culture if more numerous but possibly less pathogenic organisms over-grow the plates. Gram staining is an essential component of the evaluation of respiratory tract specimens. The presence of squamous cells (> 10 per high power field) and the absence of leukocytes (< 25 per high power field) suggests the specimen is contaminated with saliva and unsuitable for culture. The finding of certain organisms may influence initial choice of antibiotics. For example, large numbers of clustered gram positive cocci may emphasize the need to cover *S. aureus* pending culture results.

Table 5 summarizes the studies of ETA in diagnosis of VAP since 1991. What is clear from these data is that ETA has the advantages of not only being the least invasive means of sampling the respiratory tract but also the most sensitive. This is a crucial point in favor of use of ETA in that the outcome of VAP is correlated with the adequacy of the initial antibiotic regimen used. Where the initial antibiotic regimen fails to cover pathogens subsequently identified by microbiology, changes aimed at broadening coverage of pathogens does not improve outcome [131]. ETAs may be of particular value combined with clinical and radiographic parameters in a formal scoring system [132].

Should lower respiratory tract specimens be obtained routinely for microbiology in suspected VAP?

Answer: yes; grade B.

Recommendations

Samples from the lower respiratory tract should be obtained for microbiology. No significant advantage of one invasive diagnostic approach over another has been consistently demonstrated. Choice of technique depends in practice primarily on available expertise and equipment.

Rationale

Sampling of lower respiratory tract secretions for microbiology may impact on the management of VAP in several ways. First, the range of bacteria which cause VAP, and their susceptibility patterns, varies widely between different hospitals [133]. For this reason knowledge of

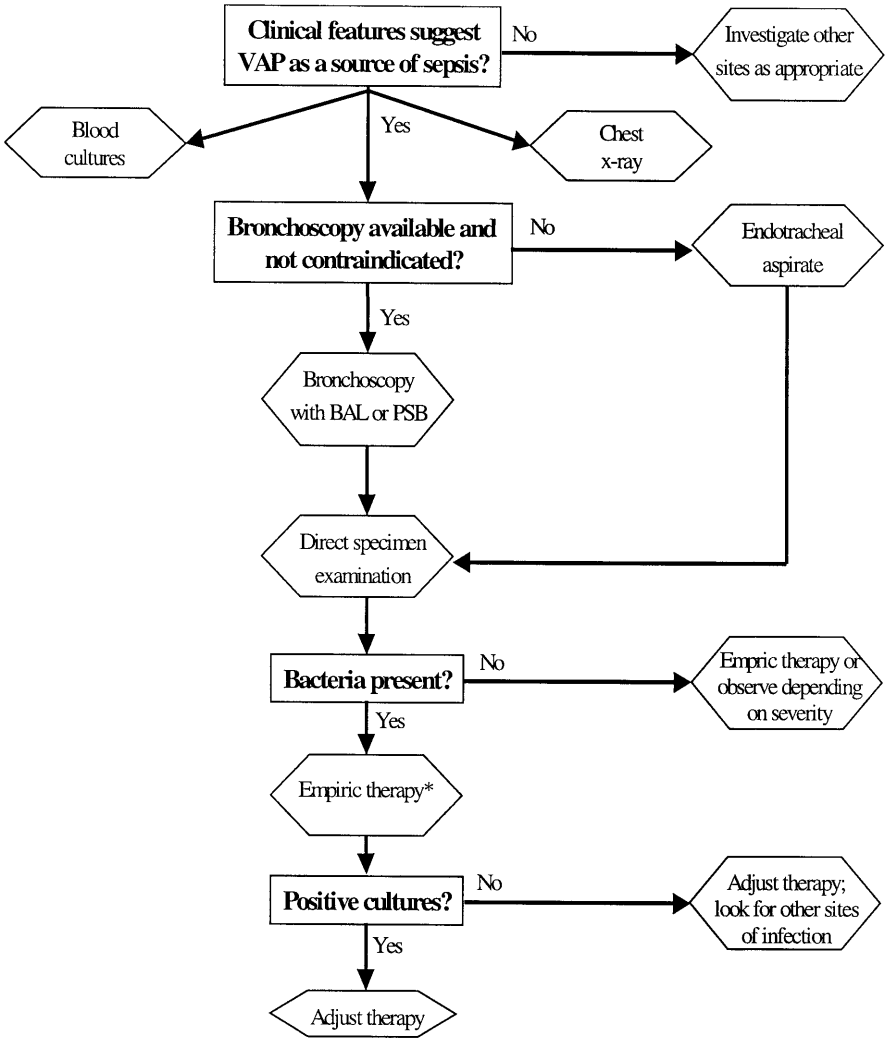

Fig. 2 Algorithm for diagnosis of ventilator associated pneumonia

pathogens present in an individual hospital has great importance in choice of empirical antimicrobial regimens. Secondly, the microbiological data may alter the outcome. A number of studies on the impact of invasive diagnostic techniques on mortality of VAP have demonstrated that invasive techniques often trigger a change in the antibiotic regimen but have failed to provide conclusive evidence of associated improvement in outcome [131, 134, 135, 136, 137]. However, the balance of evidence is beginning to accumulate in favor of invasive sampling. A preliminary report of a prospective randomized controlled trial comparing invasive to noninvasive strategies demonstrated that the invasive approach is significantly better [138]. A large randomized controlled trial recently been completed in France has demonstrated reduced 14- and 28-day mortality and reduced antibiotic use associated with invasive as oppose to noninvasive diagnosis of VAP [139]. Direct examination of a good-quality specimen helps to guide initial empirical therapy, and culture results allow subsequent modification of antibiotic regimen.

The information obtained by invasive sampling of the lower respiratory tract secretions might be expected to allow use of broad spectrum antibiotics to be restricted. The studies cited above, however, show that in clinical practice this is rarely the case. Only in a small minority of cases do the changes in antibiotic regimen, which follow lower respiratory tract sampling, result in the use of narrower spectrum drugs. This need not be so. Where appropriate cutoff values for quantitative culture are set, sensitivity of bronchoalveolar lavage and protected specimen brush has exceeded 90%. Two studies addressing outcome in patients with suspected VAP who have had antibiotics withdrawn on the basis of bronchoscopy findings showed that there was no increase in mortality associated with this strategy [140, 141].

A systematic approach to the diagnosis of VAP in sepsis patients is described in Fig. 2. When a ventilated

patient develops sepsis, blood cultures should be drawn and chest radiography performed. A diagnostic bronchoscopy should be performed without delay unless either facilities or expertise are not available, or the procedure is contraindicated. In such cases diagnostic endotracheal aspiration is indicated. Respiratory samples should be sent for direct examination and the result used to guide choice of antibiotic therapy. When culture results become available, the antibiotic regimen may be modified.

Surgical site infection and intra-abdominal sepsis

National Nosocomial Infections Surveillance definitions for surgical site infection (SSI) have been in use in the United States for a decade [142]. These are as follows [143]:

- Superficial SSI: Occurs within 30 days, involves skin or subcutaneous tissue of the incision, and any one of the following; purulence, organisms cultured from aspirate or biopsy specimen, clinical signs of local infection, diagnosis as SSI by attending clinician. *Not* stitch abscess.
- Deep SSI: Occurs within 30 days, or up to 1 year if implant in place, infection appears to relate to surgery and involves fascia and deep muscle layers and any one of the following; purulence, dehiscence of deep incision, abscess found at reoperation, radiology or histology, diagnosis as deep SSI by attending clinician.
- Organ/space SSI: Occurs within 30 days, or up to 1 year if implant in place, infection appears to relate to surgery, involves any part of the body other than the incision, and any of the following; purulence, organisms cultured from aspirate, abscess found at reoperation, radiology or histology, diagnosis as organ/space SSI by attending clinician.

Similar definitions have recently been adopted in Europe and the United Kingdom [144]. The literature on microbiological diagnosis of surgical site and wound infection has recently been reviewed [145], and we know of no more recent, relevant data. In brief, while culture of bacteria from an aseptically collected sample of deep fluid or tissue is diagnostic of infection, the contribution of qualitative culture of wound swabs is limited by inevitable contamination of any open wound. Certain organisms such as β-hemolytic streptococci can be considered as pathogenic when present at any concentration. Otherwise, on culture of tissue biopsy, growth of more than 10^5 bacteria per gram of tissue is considered diagnostic of wound infection.

Should blood cultures be obtained in cases of suspected surgical site infection or deep abdominal collection?

Answer: yes; grade E.

Recommendation

Two sets of blood cultures should be obtained.

Rationale

Superficial SSI rarely causes sepsis and uncommonly bacteremia. Although making up fewer than 5% of all causes of bacteremia among hospitalized patients [113, 146], cases of deep SSI and localized intra-abdominal sepsis are frequently associated with bacteremia. Furthermore, empirical antibiotics may need to be given before samples from the suspected site of infection itself are available. However, such deep infections are frequently polymicrobial, comprising fecal organisms, and blood cultures may not identify the full range of organisms involved, particularly anaerobes.

Are there specific indications for obtaining wound swabs or specimens of drain fluid?

Answer: yes; grade E.

Recommendations

The presence of purulence or spreading cellulitis are indications for taking wound swabs. Infection should be suspected particularly at "contaminated" or "dirty" surgical sites

Rationale

Certain clinical changes imply that a superficial surgical site has become infected. Discharge of purulent fluid is diagnostic of SSI, and spreading inflammation, in excess of that seen in normal healing, is present. The development of these features in the first 48 h after surgery or trauma ("early infection") suggests the presence of infection by virulent organisms such as β-hemolytic streptococci or *Clostridium* species. Most surgical site infections appear between the 4th and 6th postoperative days ("late") and are polymicrobial. The National Research Council wound definitions set out in 1964 continue to be of value in risk assessment of wound infection. The category of wound is correlated well with the rate of wound infection (Table 6).

Table 6 Wound categories and infection rates (modified from [147])

Wound category	Definition	Infection rate
Clean	Elective surgery, primary closure, no breach in sterile technique, no contamination from potentially colonized body sites	1.5 %
Clean contaminated	Nonelective surgery, controlled opening of colonized body site, minimal breach in sterile technique, reoperation through clean wound with-in 7 days	7.7 %
Contaminated	Nonpurulent inflammation at first surgery, major break in sterile technique or contamination from colonized body sites; penetrating trauma < 4 h old	15.2 %
Dirty	Purulent inflammation at first surgery, preoperative perforation of colonized body sites; penetrating trauma > 4 h old	40 %

Can the contribution of anaerobic organisms to surgical site infection be determined in routine practice?

Answer: no; grade D.

Recommendation

When contaminated or dirty abdominal wounds develop, features of wound infection, a diagnosis of anaerobic coinfection should be assumed irrespective of whether anaerobes are identified by routine microbiology.

Rationale

Detection of anaerobic organisms in clinical specimens is technically demanding. If anaerobic organisms are to be cultured, specific measures may need to be taken in obtaining samples, such as transporting pus in anaerobic conditions. In the laboratory, culture techniques are specialized and time consuming. For these reasons routine processing of samples in most microbiology laboratories does not include an extensive search for anaerobes.

While infections which develop in clean wounds are frequently caused by skin flora such as *S. aureus*, when contaminated or dirty wounds become infected it is possible to identify, at least one anaerobic organism in 65–94 % of samples [148]. Similarly, over 50 % of abdominal abscesses are polymicrobial, and almost 80 % involve at least one anaerobic species [149, 150]. Consequently, while data from randomized controlled trials are lacking, it is accepted best practice to cover anaerobic organisms when treating sepsis arising contaminated or dirty surgical sites [151].

Gas liquid chromatography to detect bacterial short-chain fatty acids is a technique that allows rapid identification of anaerobes in a mixed culture. Although cost currently limits the availability of gas liquid chromatography, it may in future replace culture-based methods of anaerobe identification.

Is there evidence to support the preference of particular imaging modalities in the diagnosis of intra-abdominal infection?

Answer: yes; grade E.

Recommendation

In most situations ultrasound is be the modality of first choice. When ultrasound is not diagnostic, CT should be considered.

Rationale

Plain radiography of the abdomen may reveal free gas within the abdomen suggesting bowel perforation, or demonstrate the presence of gas within an abscess, but is only rarely yield definitive diagnostic information [152]. In most patients further imaging, usually by ultrasound or CT, is necessary to localize a source of infection within the abdomen [153]. Ultrasound is readily available, if necessary as a bed-side investigation. Its limitations are that gas-filled loops of bowel, commonly present in postoperative ileus may obscure underlying pathology. Wounds and drains may make access to the abdominal wall difficult. The sensitivity of ultrasound is particularly operator dependent. CT, by comparison, is more sensitive than ultrasound in detecting small foci of infection, but in certain areas of the abdomen, particularly the pancreas, distinguishing an abscess from inflammation may be difficult by CT [154].

Magnetic resonance imaging is in turn more sensitive than CT; a recent study reported 100 % sensitivity and 94 % specificity in detecting intraperitoneal abscess [155]. In many situations, for example in ventilated patients, the use of magnetic resonance imaging is limited in the diagnosis of sepsis by the need to keep all metallic instruments away from the scanner's magnetic field.

Should abdominal fluid collections identified by imaging be aspirated as a matter of routine?

Answer: yes; grade E.

Recommendation

Collections identified by radiology should, where technically possible, be aspirated and drained under radiological control, samples being sent for Gram-staining and culture.

Rationale

Differentiation of infected material from hematoma or inflammatory fluid is not possible on the basis of radiology alone [154]. Confirmation that infection is present and identification particularly of any drug-resistant organisms depends on obtaining samples for microscopy and culture [156, 157]. The pH of fluid obtained at ultrasound-guided aspiration (< 7.1) was found in one study to be a sensitive marker (92%) of the presence of infection [158] and has been suggested as a bed-side means of identifying collections which require formal drainage.

Acalculous cholecystitis

Acute acalculous cholecystitis (ACC) is an infrequent but probably underdiagnosed complication in critically ill patients [159, 160]. It is caused by spontaneous gangrene of the gall bladder which without prompt diagnosis and treatment progresses to perforation. The cause appears to involve infection by *Clostridium perfringens* [161]. Although reported as a complication of a wide range of critical illnesses, the majority of cases of AAC follow trauma or biliary surgery [162, 163]. High doses of narcotic agents may be a contributory factor [164].

Is there a standard approach to the diagnosis of acalculous cholecystitis?

Answer: no; grade E.

Recommendations

ACC should be suspected in any sepsis patient, particularly postoperatively, when there are either signs relating to the right upper quadrant of the abdomen or obstructive liver function tests. When ACC is suspected, ultrasound should be ordered urgently. If an initial ultrasound examination is not diagnostic, CT should be performed. If CT is unavailable, a repeat ultrasound should be performed after 24 h.

Rationale

Localizing right upper quadrant pain and tenderness is often absent in sedated or ventilated patients suffering from ACC. Diagnosis therefore requires a high index of suspicion. The only differentiating features in a sepsis patient may be elevation in alkaline phosphatase or γ-glutaryl transferase, in an at risk patient [165].

Although the ultrasound appearances of ACC (gallbladder distension, wall thickening and free fluid suggestive of perforation) are well established [166], such changes are not diagnostic and are frequently demonstrable in critically ill patients who do not go on to develop ACC [167]. The value of a single ultrasound study in diagnosis of ACC has been assessed in three retrospective studies. Two studies of ICU patients estimated sensitivity at 76% [168] and 92%, with a specificity of 96% [169]. More recently among 27 cases of ACC, only half of which occurred in critically ill patients, a sensitivity of 29% was found [165]. Two prospective studies looking specifically at the use of serial ultrasound examinations in patients with suspected ACC have demonstrated that when initial diagnosis is uncertain, failure of any abnormalities to progress on follow-up scans has excellent negative predictive value [170, 171]. The role of CT in diagnosis of ACC has not been thoroughly evaluated. Superior sensitivity of CT over ultrasound has been suggested by three retrospective studies of patients with a surgical diagnosis of ACC [165, 169, 172].

We are aware of two studies which examine the role of laparoscopy in diagnosis and treatment of ACC. Neither study compared diagnostic accuracy with radiology. In both the procedure was well tolerated. Laparoscopy has the advantage over CT that it may, in some units, be performed at the bedside and, if the diagnosis of ACC is confirmed, can proceed directly to laparoscopic cholecystectomy [162] or cholecystostomy [173].

Sinusitis

Since being first reported in 1974 [174], ventilator-associated sinusitis has become an increasingly well recognized cause of sepsis. It occurs usually but not exclusively in patients who have nasotracheal, as opposed to orotracheal intubation [175, 176]. The true incidence of sinusitis among critical care patients is hard to establish since published estimates vary widely depending on the population studied and the diagnostic techniques used. In the only study to directly address the issue, one of 19 patients with occult sepsis on a surgical ICU had si-

nusitis as the sole focus of infection [177]. This topic has recently been the subject of a general review [178].

Is there a standard approach to the diagnosis of ventilator-associated sinusitis?

Answer: no; grade E.

Recommendations

Acute sinusitis should be suspected in any sepsis patient who has either a nasotracheal tube or a fine-bore nasogastric feeding tube, or who has suffered a head injury. When sinusitis is suspected, radiography of the maxillary sinuses should be performed to detect the presence of fluid. When radiography does not demonstrate fluid in the maxillary sinuses, CT should be performed. If either radiography or CT demonstrates the presence of fluid, antral puncture should be performed to allow definitive diagnosis and therapeutic drainage before antibiotic therapy is initiated.

Rationale

If sinusitis is the source of sepsis, specific physical signs are likely to be absent, although a mucopurulent nasal discharge may be noted. For this reason the diagnosis should be suspected in any patient who has a nasotracheal tube or an indwelling nasal device of any sort (even a fine-bore nasogastric feeding tube), or who has had a head injury.

The definitive investigation of antral sinus disease is considered to be direct endoscopic examination [179]. In general the diagnosis is made on the basis of culture of bacteria from purulent material obtained from the sinus cavities [180]. Because clinical evidence to support a diagnosis of sinusitis is generally lacking in ICU patients, the first supportive evidence often comes from radiology, either plain radiographic sinus views, ultrasound or CT. For each of these modalities there is a discrepancy between radiological diagnosis of sinusitis (presence of fluid) and microbiological confirmation on any subsequent aspirate. While plain radiography is of value in diagnosis of maxillary sinusitis [181], five views are required to achieve 88 % sensitivity [182]. Similarly, ultrasound detected accumulation of fluid in the sinuses of 15 of 100 patients in a consecutive prospective series of intubated ICU patients but in only one of these patients could aspiration confirm sinusitis [183]. CT has two advantages over sinus radiography and ultrasound. CT is able to distinguish mucosal thickening from fluid within the sinuses [184] and can assess the other paranasal sinuses which may, albeit less frequently, be infected in isolation [185]. The principal disadvantage is that CT usually requires the patient to be moved from the ICU. Although the ability of CT to detect mucosal abnormalities improves diagnostic accuracy, the discrepancy between CT diagnosis and diagnosis by antral puncture remains significant [184, 186].

Since the discrepancy between radiological diagnosis of sinusitis and confirmation on aspiration is unavoidable, abnormalities on radiology indicate further investigation by antral puncture to obtain fluid for culture. Interpretation of culture results, however, requires caution. Hospitalized patients have heavy colonization of the nose, and contamination of samples is virtually unavoidable [184]. In addition, while true infective sinusitis is frequently caused by mixed Gram-negative and anaerobic infections, fluid obtained from antra that do not have signs of infection quite frequently produces an apparently significant culture result [187].

Invasive *Candida* infection

As a result of widespread use of broad-spectrum antibiotics and intravascular catheters, an increase in the incidence of nosocomial infection by *Candida* species has occurred in both the United States and Europe [188, 189, 190, 191]. Although *C. albicans* remains the most frequently isolated species, the incidence of other, potentially more drug-resistant species is also rising [192]. The importance of invasive fungal infection is further underlined by the considerable attributable mortality, 38 % in one study [193] and 21.7 % in another [194].

Invasive *Candida* infections begin by colonization of the gastrointestinal tract or skin [195]. Suppression of indigenous intestinal bacteria allows overgrowth of *Candida* in the gastrointestinal tract and mucosal adhesion. Once a critical level of colonization has been reached translocation, across intact small bowel mucosa may occur. In an ICU setting, where a range of physiological stresses may impair small bowel mucosal integrity, such translocation may occur at much lower concentrations. Similarly, skin colonization provides a source for invasive disease when integrity is breached either by intravascular catheters or burns. Finally, any disease or drug which inhibits cellular immunity, for example, diabetes mellitus, or corticosteroids, predisposes to invasive *Candida* infection [196].

Is there a standard approach to the diagnosis of invasive candidiasis?

Answer: no; grade E.

Table 7 Examples of suggested risk factors for invasive *Candida* infection and associated mortality (*APACHE II* Acute Physiology and Chronic Health Evaluation II) (data summarized from: [194, 201, 202, 203, 204])

Examples of risk factors for development of invasive *Candida* infection	Examples of risk factors for mortality associated with invasive *Candida* infection
Colonization with *Candida* species.	APACHE II score > 20
Prior treatment with multiple antibiotics	Delay between onset of candidemia and start of antifungal therapy > 48 h
Total number of different antibiotics > 2	
Total number of days on antibiotics > 14	
Prior Hickman catheter	
Prior hemodialysis	

Recommendations

There are no data to support a policy of routine screening of hospitalized patients for *Candida* colonization. However, in sepsis patients invasive fungal infection is more likely in patients who are heavily colonized. When sepsis develops in patients colonized by *Candida* species at two or more sites, blood cultures should be sent and lysis centrifugation performed if available. Isolates of *Candida* species from sterile sites should be sent for speciation and sensitivity testing.

Rationale

Clinical features of invasive *Candida* infection are in most cases nonspecific, ranging from unexplained fever to sepsis [197]. Specific clinical manifestations are rare. Candidal chorioretinitis occurs in fewer than 15 % of candidemic patients [198], but when found is an absolute indication for initiation of antifungal therapy. Skin lesions and septic arthritis occur less frequently still [199]. Retrospective studies have demonstrated a range of risk factors for invasive *Candida* infection (Table 7). One small prospective study has suggested that after 4 days of persisting fever despite antibacterial antibiotics, antifungal agents should be started empirically [200]. We are not aware of any studies that address a risk stratification approach to diagnosis of fungal infection.

Development of invasive *Candida* infection is correlated with preceding colonization [201]. Sites at which colonization may be detected include urine, rectum, gastric aspirate, vascular access sites, sputum/throat swab, wounds and surgical drains. The number of sites has been found to be correlated with the risk of developing invasive fungal infection [202, 203] A cutoff of two sites colonized, as an indication for beginning empirical antifungal therapy, has a high sensitivity but low specificity, 22 % in one study [203]. This may in part be because using the number of colonized sites alone as a measure of infection risk fails to take into account the intensity of colonization. Using semiquantitative culture techniques to produce a "corrected *Candida* colonization index"; sensitivity and specificity of 100 % was achieved in a retrospective analysis of 29 critical care patients [203]. No evidence exists regarding how frequently samples should be taken to detect colonization in at-risk patients. Five days would seem a reasonable interval. At present there is no consensus on the value or use of routine screening for *Candida* in hospitalized patients, and the data are inadequate to support a general recommendation that it should be instituted.

Conventional blood culture techniques are insensitive in detecting blood-borne *Candida* infections. For example, only 50 % of patients with disseminated candidiasis have positive blood cultures [196], but lysis centrifugation of blood cultures increases yield by 30–40 %. While growth of *Candida* species in blood is a clear indication for initiation of antifungal agents, failure to confirm candidemia in an at-risk patient in no way disproves the diagnosis.

Candiduria in patients who have not had instrumentation of the renal tract is strongly suggestive of renal involvement in disseminated candidiasis [195]. The practical value of this is limited by the fact that the majority of ICU patients will have been catheterized at some stage. Furthermore, up to 50 % of patients who have disseminated candidiasis do not have candiduria [205]. In an ICU setting the finding of candiduria in a catheterized patient is no more significant an indicator of invasive disease than isolation from any other single site [206].

While a single colony of *Candida* species isolated from a sterile site such as blood or cerebrospinal fluid must be regarded as significant, the greatest obstacle to the diagnosis of invasive *Candida* infection by culture from nonsterile sites is distinguishing infection from colonization. Cut-off values for quantitative diagnosis of *Candida* infections are much less well established than for bacterial infections. Diagnosis of *Candida* infection by tissue biopsy is made on the basis of either quantitative culture of more than 10^5 organisms per gram of tissue or the presence of yeasts on microscopy pending culture results [196].

Although *C. albicans* continues to make up the majority of clinical isolates, the incidence of other species is increasing. When *Candida* is cultured from nonsterile sites or urine, differentiation of *C. albicans* from other species using the germ-tube technique is generally sufficient. However, when *Candida* is identified at sterile sites, speciation and sensitivity testing should be routine [157]. Relative sensitivity of these species to azole anti-

fungals varies. In certain cases the use of azoles may be possible in place of amphotericin, with its associated toxicity (see Bochud et al., "Antibiotics in sepsis") [157, 207]. In addition, knowledge of the species and resistance patterns within a particular hospital is essential to choice of empirical antifungal agents.

A number of PCR [208] and serological [209, 210, 211] assays have shown promise in preclinical trials, but two clinical trials in hospitalized patients have found that such techniques are unlikely to replace culture based diagnosis [212, 213].

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