# Late-Onset Sepsis

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## Epidemiology

Late-onset sepsis (LOS) is defined as infection of a sterile site (e.g., blood, urine, cerebrospinal fluid [CSF]) after age 72 h [1, 2]. The only exception is that the current definition of late-onset group B *Streptococcus* (GBS) infection begins after age 7 days, with the first week of life being considered early-onset sepsis [3]. The primary risk factor for LOS is prematurity; the most preterm infants are at highest risk for LOS. Approximately 25–30% of extremely low birth weight (ELBW, <1000 g) infants will have LOS during their NICU stay [1, 4]. This number decreases to about 10–15% for infants 1001–1500 g birth weight and to <2% for infants >1500 g birth weight [2, 5, 6].

The organisms responsible for LOS vary over time and between locations. Yale New Haven Hospital has produced a series of reports describing the changing patterns of organisms responsible for LOS from 1928 to 2003 showing the evolution of LOS over almost a century [7–12]. Prior to introduction of antibiotics in the 1930s and 1940s, gram-positive cocci, including *Staphylococcus aureus* and *Streptococcus pyogenes* (group A strep), were responsible for the majority of neonatal sepsis. Once antibiotics were introduced, gram-negative enteric bacilli such as *Escherichia coli* became the leading cause of serious infections in newborn.

However, over the last several decades, coagulase-negative *Staphylococcus* (CoNS) species have emerged as the most commonly identified organism in LOS (Table 1). This may be due to increased survival of the most preterm infants and a concomitant increase in reliance on indwelling catheters and other medical devices. Other gram-positives such as *S. aureus*, GBS, *Enterococcus*, and others; gram-negatives including *E. coli* and other coliforms; *Pseudomonas*, *Serratia*, and others;

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**Table 1** Organisms associated with late-onset sepsis and their approximate prevalence

| Organism | Frequency |
|---|---|
| Gram-positives | 75% |
| Coagulase-negative staphylococci | 60–70% |
| *Staphylococcus aureus*[a] | 10% |
| Group B streptococci | 3–5% |
| *Enterococcus* sp. | 3–5% |
| Group A streptococci | 1–2% |
| Gram-negatives | 20% |
| *Escherichia coli* | 5–7% each |
| *Klebsiella* | |
| *Enterobacter* | |
| *Citrobacter* | 1–2% each |
| *Pseudomonas* | |
| *Serratia* | |
| Others | |
| *Candida* sp. | 5% |

[a]In the United States, approximately 75% of isolates are methicillin-susceptible and 25% are methicillin-resistant, but proportion varies between neonatal intensive care units

and fungal species (primarily *Candida*; see chapter "*Candida*") are frequently encountered causes of LOS [1–6].

## Pathogenesis

LOS has a distinct pathogenesis compared with early-onset sepsis (Table 2). In contrast to early-onset sepsis, which is acquired during the perinatal period (see chapter "Early-Onset Sepsis") and is caused by organisms common to the delivery tract such as GBS or *E. coli*, LOS is caused by acquisition of pathogenic organisms during the postnatal period, colonization, and subsequent invasion [13]. These differences manifest as later presentation (hence the 72 h cutoff between early-onset and late-onset sepsis) and a broader range of causative organisms. Horizontal transfer of pathogenic bacteria on contaminated hands or medical equipment leads to either immediate invasion (e.g., if bacteria are infused in a contaminated infusion or procedure) or colonization of the skin, mucous membranes, or gastrointestinal tract. Colonized infants can then develop subsequent invasion either by autoinoculation (e.g., if their stool comes in contact with a central catheter hub) or translocation directly into the bloodstream [14]. Unsurprisingly, therefore, the causative organism of LOS is often one that the infant is already colonized with [15].

Once an organism reaches the bloodstream, it can cause a nonspecific sepsis syndrome or it can localize to one or more body sites and cause focal infection. In addition, some cases of LOS are caused by direct infection of a body site without preceding bacteremia; examples include ascending urinary tract infection, direct

**Table 2** Early-onset versus late-onset sepsis in neonates and young infants

| | Early-onset sepsis | Late-onset sepsis |
|---|---|---|
| Etiology | ~40% GBS<br>~30% *E. coli*<br>~30% other | 1. Coagulase-negative *Staphylococcus*<br>2. *Staphylococcus aureus*<br>3. *E. coli* and other gram-negatives<br>4. GBS and other gram-positives<br>5. *Candida* |
| Age of onset | Age ≤ 72 h | Age > 72 h |
| Time of acquisition | Before or during delivery | After delivery |
| Mode of acquisition | Perinatal (mother-to-infant transmission) | Postnatal (acquired from hospital environment and community) |
| Clinical findings | Rapid onset<br>Systemic disease more common than focal infection<br>Bacteremia/pneumonia common | Onset may be slower or fulminant<br>Focal infection (e.g., meningitis, osteomyelitis, urinary tract infection) more likely |

inoculation of skin or soft tissue during phlebotomy, or ventilator-associated pneumonia.

## Clinical Findings

The initial signs of LOS are often subtle and nonspecific such as decreased activity, poor feeding, lethargy, apnea, fever or hypothermia, respiratory distress, and jaundice [16, 17]. As a result, sepsis evaluations are often performed when clinical changes are detected, since virtually every finding has been associated with sepsis. In an effort to improve specificity, clinical prediction models that use trends in vital signs, propensity scores, or laboratory values have been used with varying degrees of success [18–20]. In some cases, more specific localizing findings may be present (Table 3). For example, osteomyelitis may present with pseudoparalysis or irritability with movement of the affected limb. Skin and soft tissue infections can present with skin changes or swelling. Meningitis may present with seizures. However, focal infection is possible even when localizing signs are absent [21].

## Diagnosis

The diagnosis of LOS based solely on clinical signs is not possible due to the nonspecific nature of the presentation [22]. The gold standard for diagnosis is isolation of a pathogen from a normally sterile site (blood, CSF, urine, pleural or peritoneal fluid, bone or joint aspirate) [23]. For non-sterile sites such as the upper respiratory tract or the skin, culture remains critical but should be used in conjunction with clinical findings and pretest probability of sepsis.

**Table 3** Clinical findings, approach to diagnosis, and treatment of common systemic and focal manifestations of late-onset sepsis

| Condition | Clinical findings | Diagnosis | Antibiotic treatment[a] |
|---|---|---|---|
| Bacteremia | • Decreased activity<br>• Poor feeding<br>• Lethargy<br>• Hypotension<br>• Apnea, bradycardia, or desaturations<br>• Temperature instability<br>• Respiratory distress or failure<br>• Jaundice<br>• Leukopenia or leukocytosis<br>• Thrombocytopenia<br>• Anemia | • Blood culture | 7–10 days |
| Meningitis | • Similar to bacteremia AND:<br>• Seizures<br>• Lethargy/unresponsiveness<br>• Bulging fontanelle<br>• Nuchal rigidity | • Cerebrospinal fluid culture | 14–21 days |
| Urinary tract infection | • Similar to bacteremia | • Urine culture | 7–10 days |
| Osteomyelitis or septic arthritis | • Decreased movement<br>• Pseudoparalysis<br>• Irritability with passive movement<br>• Swelling or redness | • Blood culture<br>• Bone or joint fluid culture<br>• Radiographic changes | 21–42 days |
| Pneumonia | • Respiratory deterioration or failure<br>• New findings on chest radiographs<br>• Changes in sputum | • Endotracheal tube culture[b]<br>• Radiographic changes | 5–7 days |
| Skin and soft tissue | • Redness<br>• Swelling<br>• Drainage<br>• Induration or fluctuance | • Wound culture[b] | Drainage procedure and antibiotics until clinical findings resolve (5–7 days) |

[a]Treatment durations are guides only; duration of therapy should take into consideration infant's clinical status, response to therapy, persistence of any infected material, etc.
[b]Culture of non-sterile sites such as upper airway and skin should be interpreted with caution

## Cultures

*Blood culture*. A blood sample of at least 1 mL ensures excellent sensitivity [24]. Sending two cultures from two different sites will help to differentiate contaminants (e.g., if CoNS grows in one culture but not the other) but requires a second blood draw and does not improve sensitivity compared to an equal volume of blood obtained from a single site. Of note, *Candida* will grow in regular blood culture media; specific fungal cultures are not required.

*Urine culture.* Urine culture should be obtained in all cases of suspected LOS; 5–10% of LOS cases are due to isolated urinary tract infection [25, 26]. Urine should be obtained by catheterization or suprapubic aspiration; bag specimens are frequently contaminated. The value of urinalysis in preterm infants has not been well studied, but the absence of leukocyte esterase, nitrites, or pyuria does not preclude the possibility of UTI in preterm infants [27].

*Cerebrospinal fluid culture.* Lumbar puncture for CSF analysis and culture is critical for infants with suspected LOS. Approximately 5% of infants with LOS have associated meningitis, and one-third of infants with meningitis have sterile blood cultures [21, 28]. Therefore, if blood cultures alone are utilized, cases of meningitis will inevitably be missed [29, 30]. Meningitis requires different antimicrobial therapy and a longer duration of treatment than other LOS, and therefore determining the presence or absence of meningitis is a critical step in the evaluation of LOS.

*Endotracheal tube cultures.* Endotracheal tubes are rapidly colonized by normal upper airway flora shortly after placement [31]. Therefore, detection of bacteria from endotracheal tube culture may represent either colonization or infection. When the pretest probability of lower respiratory tract disease is low (e.g., when another source of infection is likely or in the absence of radiographic or clinical changes), positive tracheal cultures are virtually worthless. Therefore, endotracheal tube cultures should only be considered when both clinical and radiographic findings are suggestive of pneumonia. In contrast, bronchoalveolar lavage specimens from the lower respiratory tract would be expected to be sterile and therefore are more helpful. However, bronchoalveolar lavage is not routinely available for preterm infants in most centers.

*Skin cultures.* As with the upper airway, the skin is not sterile. Normal cutaneous flora includes CoNS, *Corynebacterium* and other diphtheroids, and other gram-positives. Colonization with potential pathogens including group A streptococci, *S. aureus*, and *Candida* can also be identified and must be differentiated from active infection [32]. Interpretation of culture results should be done in consideration of the infant's clinical status.

*Other cultures.* Other sterile sites can be sampled for culture under specific situations. Infants with suspected bone or joint infections can undergo percutaneous aspiration of bone or synovial fluid [33]. Peritoneal fluid can be obtained during drain placement or laparotomy. Pericardial or pleural fluid may be obtained during drainage procedures. In general, fluid should be sent for cytology, gram stain, and culture whenever infection is suspected; providing as much detail as possible to the microbiology lab regarding patient history and sample source will ensure that the cultures are processed appropriately.

## Non-culture-Based Microbiologic Tests

PCR and nucleic acid-based testing, rapid antigen detection, direct fluorescent antibody testing, and other similar tests may be available. These tests vary in terms of

sensitivity and specificity and at present do not preclude the need for bacterial cultures. PCR in particular is becoming increasingly prevalent. Benefits to PCR include its impressive sensitivity and rapid turnaround time. However, PCR testing of blood or spinal fluid has been associated with false-positive results. PCR will also detect dead bacteria that has been previously treated or resolved, which may prompt additional, unnecessary antibiotic therapy [34]. As PCR is increasingly used and studied, our understanding of how it fits into the clinical management of these infants will grow.

### Ancillary Laboratory Testing

Ancillary lab tests such as white blood cell counts and differentials, C-reactive protein, procalcitonin, and others are often used to determine an infant's risk for infection. Although these tests have been relatively well-studied for suspected early-onset sepsis, validation for late-onset sepsis has not been as robust. In most cases, the normative values for age <72 h have been extrapolated out to older ages. The evidence suggests that these ancillary tests have reasonably good negative predictive value but poor positive predictive value [35, 36]. This means that normal ancillary testing will support discontinuation of antibiotic therapy in an infant with sterile culture results. However, abnormal laboratory tests should not be used as a reason to extend therapy for children with sterile culture results, particularly if their clinical findings are resolved or improving.

## Treatment

### Empiric Therapy

Since sepsis has significant clinical implications and can progress rapidly, empiric antimicrobial therapy should be initiated promptly when LOS is suspected. An understanding of local epidemiology (for the patient in question, within the nursery, and within the hospital or community) is essential in order to choose appropriate empiric therapy. In general, empiric therapy for LOS should include coverage against common hospital-acquired organisms such as *S. aureus* and gram-negative enteric bacilli (Fig. 1). The use of empiric antifungal therapy depends on the incidence of *Candida* in the nursery, the gestational age of the infant, and severity of presentation (see chapter "*Candida*").

Default empiric therapy with a semisynthetic penicillin (e.g., oxacillin, nafcillin) will provide coverage against methicillin-susceptible *S. aureus*, GBS, and group A *Streptococcus*. An aminoglycoside (e.g., gentamicin, tobramycin) should be used in combination to provide coverage against most gram-negative organisms. Other antibiotics should be used in certain situations:

*Vancomycin*. Although CoNS is the most common cause of LOS, it is not associated with mortality or significant morbidity, and therefore empiric vancomycin can

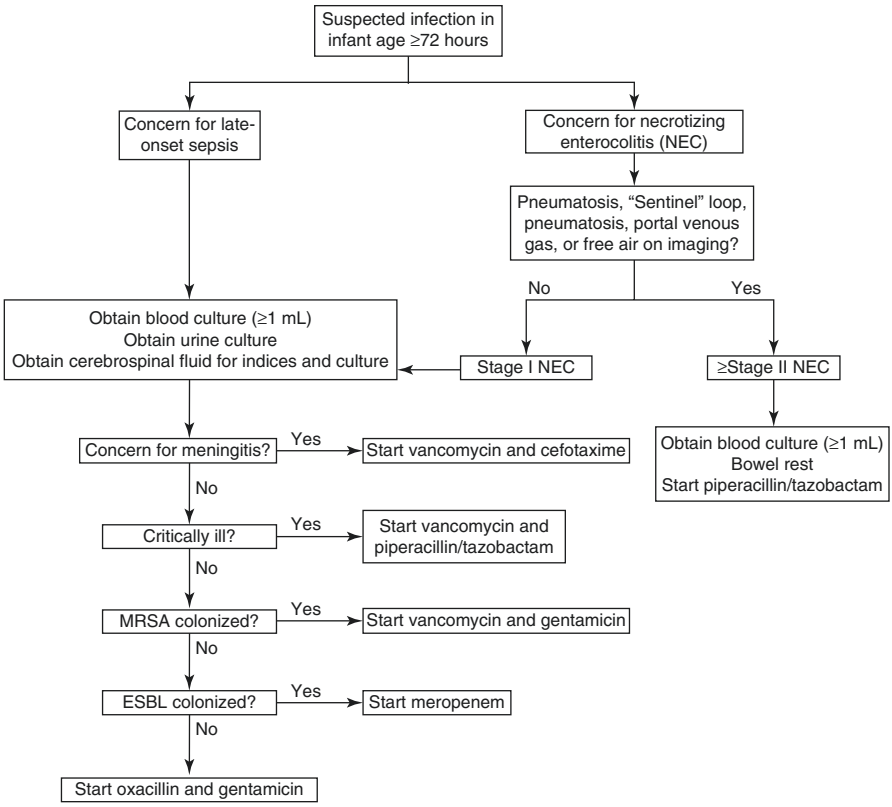


**Fig. 1** Approach to suspected late-onset sepsis in the neonatal intensive care unit. For infants with suspected late-onset sepsis or stage I necrotizing enterocolitis (NEC), which has significant overlap with late-onset sepsis, cultures of blood, urine, and cerebrospinal fluid should be obtained. *Oxacillin* (or a similar semisynthetic penicillin) and *gentamicin* (or another aminoglycoside) should then be started promptly in most cases. Exceptions include (1) when meningitis is suspected based on clinical findings or cerebrospinal fluid indices (vancomycin and cefotaxime), (2) if the infant is critically ill (generally defined as new requirement for pressors, disseminated intravascular coagulation, or acute and severe respiratory failure; vancomycin and piperacillin/tazobactam), and (3) if the infant is known to be colonized with methicillin-resistant *Staphylococcus aureus* (vancomycin in lieu of oxacillin) or an extended-spectrum beta-lactamase- (ESBL) producing gram-negative organism (meropenem in lieu of oxacillin and gentamicin). Note that if NEC is confirmed (stage II or higher), then cerebrospinal fluid and urine cultures are not required and piperacillin/tazobactam should be started once blood culture is obtained

be withheld until CoNS infection is confirmed [37]. However, vancomycin should be used empirically when an infant who is known to be colonized with methicillin-resistant *S. aureus* has suspected LOS or when an infant with suspected LOS is critically ill (e.g., hypotensive, acute respiratory failure, DIC). Vancomycin should be used for definitive treatment when required, usually for CoNS (which is usually resistant to oxacillin) and methicillin-resistant *S. aureus* [38].

*Cephalosporins*. Third- and fourth-generation cephalosporins (e.g., cefotaxime, ceftriaxone, cefepime) are associated with increased antibiotic resistance and increased risk for *Candida* in the neonatal intensive care unit [39, 40]. Therefore, their use should be restricted to three clinical situations:

1. Treatment of suspected or proven gonococcal disease (see chapter "Neonatal Conjunctivitis")
2. Treatment of suspected or proven gram-negative meningitis
3. Treatment of early- or late-onset sepsis among infants with significant renal dysfunction for whom aminoglycosides are contraindicated

*Piperacillin/tazobactam*. In addition to gram-negative coverage, piperacillin/tazobactam also provides good activity against *Pseudomonas* and anaerobes. It can be used for the treatment of proven or suspected necrotizing enterocolitis (see chapter "Necrotizing Enterocolitis") or as a first- or second-line agent for critically ill infants with suspected LOS. However, it is unnecessarily broad for routine empiric use compared with aminoglycosides.

*Meropenem*. Carbapenems such as meropenem should be reserved for infections with extended-spectrum beta-lactamase-producing gram-negative organisms.

### Definitive Therapy

If a pathogen is identified in culture, empiric therapy should be converted to definitive therapy by choosing the narrowest effective agent that will reach the infected compartment(s). Since the optimal duration of therapy has not been well established for LOS, treatment durations vary widely (Table 3). Source control is critically important in treating LOS; infected catheters or tubes should be removed whenever possible, and purulent collections should be drained.

## Prevention

Since the majority of LOS episodes are associated with nosocomial transmission of and infection with pathogenic bacteria, prevention is largely centered around appropriate infection control practices. Consistent hand hygiene practices are the single most important aspect of prevention in the NICU setting [41]. Meticulous care practices during insertion and maintenance of indwelling hardware, particularly central venous catheters, can markedly reduce the risk for late-onset bacteremia (see chapter "Principles of Infection Prevention in the Nursery") [42]. Avoiding placement of catheters and removing them as soon as they are no longer needed is critical.

Other well-studied strategies include the increased use of human milk and antibiotic stewardship programs (see chapter "Antibiotic Stewardship"). There has been increasing attention paid to the use of probiotic agents for the prevention of sepsis or necrotizing enterocolitis; early studies appear promising [43].

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