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ANTIBIOTIC USE IN NEONATAL SEPSIS*

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Neonatal sepsis is a life-threatening emergency and any delay in treatment may cause death. Initial signs of neonatal sepsis are slight and nonspecific. Therefore, in suspected sepsis, two or three days empirical antibiotic therapy should begin immediately after cultures have been obtained without awaiting the results. Antibiotics should be reevaluated when the results of the cultures and susceptibility tests are available. If the cultures are negative and the clinical findings are well, antibiotics should be stopped. Because of the nonspecific nature of neonatal sepsis, especially in small preterm infants, physicians continue antibiotics once started. If a baby has pneumonia or what appears to be sepsis, antibiotics should not be stopped, although cultures are negative. The duration of therapy depends on the initial response to the appropriate antibiotics but should be 10 to 14 days in most infants with sepsis and minimal or absent focal infection.

In infants who developed sepsis during the first week of life, empirical therapy must cover group B streptococci, Enterobacteriaceae (especially E. coli) and Listeria monocytogenes. Penicillin or ampicillin plus an aminoglycoside is usually effective against all these organisms. Initial empirical antibiotic therapy for infants who developed sepsis beyond the first days of life must cover the organisms associated with early-onset sepsis as well as hospital-acquired pathogens such as staphylococci, enterococci and Pseudomonas aeruginosa. Penicillin or ampicillin and an aminoglycoside combination may also be used in the initial therapy of late-onset sepsis as in cases with early-onset sepsis. In nosocomial infections, netilmicin or amikacin should be preferred. In cases showing increased risk of staphylococcal infection (e.g. presence of vascular catheter) or Pseudomonas infection (e.g. presence of typical skin lesions), antistaphylococcal or anti-Pseudomonas agents may be preferred in the initial empirical therapy.

In some centers, third-generation cephalosporins in combination with penicillin or ampicillin have been used in the initial therapy of early-onset and late-onset neonatal sepsis. Third-generation cephalosporin may also be combined with an aminoglycoside in places where aminoglycoside-resistance to this antibiotic is high. However, third-generation cephalosporins should not be used in the initial therapy of suspected sepsis, because 1) extensive use of cephalosporins for initial therapy of neonatal sepsis may lead to the emergence of drug-resistant microorganisms (this has occurred more rapidly as compared with the aminoglycosides), 2) Antagonistic interactions have been demonstrated when the other beta-lactam antibiotics (e.g. penicillins) were combined with cephalosporins.

Infections due to gram-negative bacilli can be treated with the combination of a penicillin-derivative (ampicillin or extended-spectrum penicillins) and an aminoglycoside. Third-generation cephalosporins in combination with an aminoglycoside or an extended-spectrum penicillin have been used in the treatment

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of sepsis due to these organisms. Piperacillin and azlocillin are the most active of extended-spectrum penicillins against Pseudomonas aeruginosa. Among the third-generation cephalosporins, cefoperazone and ceftazidime possess anti-Pseudomonas activity. Ceftazidime was found to be more active in vitro against Pseudomonas than cefoperazone or piperacillin. New antibiotics for gram-negative bacteria resistant to other agents are carbapenems, aztreonam, quinolones and isepamicin. Enterococci can be treated with a cell wall-active agent (e.g. penicillin, ampicillin, or vancomycin) and an aminoglycoside. Staphylococci are susceptible to penicillinase-resistant penicillins (e.g. oxacillin, nafcillin and methicillin). Resistant strains are uniformly sensitive to vancomycin. A penicillin or vancomycin and an aminoglycoside combination result in a more rapid bacteriocidal effect than is produced by either drug alone. *Key words: newborn infant, sepsis, antibiotic therapy.*

Despite the much more sophisticated diagnosis and management of neonatal sepsis in recent years, it is still a major cause of neonatal morbidity and mortality. It is estimated that the incidence of neonatal sepsis varies from less than one to eight cases per 1000 live births. The incidence of sepsis will be influenced markedly by the quality of intrauterine life, host factors, and environmental factors. Therefore, the incidence of neonatal sepsis in preterm infants is one in 40 (or higher) newborns.

In the preantibiotic era mortality from neonatal sepsis exceeded 90 percent, but with the availability of antibiotics it has fallen to a range of 10 to 50 percent. The incidence of neonatal sepsis and rate of mortality have not decreased during the past decade and may even have increased because of the development of life support techniques that have permitted the survival of the extremely premature or otherwise high-risk neonate[1-9].

Two patterns of disease, early-onset and late-onset, have been associated with systemic bacterial infections during the first month of life.

Early-Onset Disease

Early-onset disease presents as a fulminant, multisystemic illness during the first few days of life. The mortality is high, varying in some series between 15 and 50 percent. These infants have a history of one or more significant obstetric complications. Among these risk factors are premature delivery or low birth weight, premature rupture of membranes, chorioamnionitis, maternal peripartum infection, abnormal vaginal flora (e.g., group B streptococci carrier, sexually transmitted disease, bacterial vaginosis), obstetric manipulations (e.g., vaginal exams, internal fetal monitoring) in the presence of ruptured membranes, septic or traumatic delivery and fetal hypoxia. It is unusual for a full-term infant to develop early-onset sepsis after an uneventful pregnancy and delivery[10].

Most of the cases are due to group B streptococci (GBS), gram-negative enteric bacteria and Listeria monocytogenes. These pathogens are usually acquired from the birth canal during delivery. The source of bacteriemia is frequently unapparent, but careful inspection may reveal a focus, such as infection of the

umbilical stump. Bacteria can be inoculated through the skin by use of obstetric forceps, and organisms may infect the skin and soft tissues if abrasions or congenital defects are present. Transient bacteriemia may accompany procedures, such as endotracheal suctioning, that traumatize mucosal membranes.

In cases with prolonged rupture of membranes, initial colonization of the neonate usually takes place after rupture of the maternal membranes. If delivery is delayed, however, vaginal bacteria may ascend and in some cases produce inflammation of the fetal membranes, umbilical cord and placenta. Fetal infection may then result from aspiration of infected amniotic fluid. Infection of the mother at the time of birth, particularly genital infections, may play a significant role in the development of infection in the neonate. Transplacental hematogenous infection during or shortly before delivery is also possible.

Late-Onset Disease

Late-onset disease may occur as early as five days of age, but is more commonly recognized after the first week of life. The mortality rate is lower than in early-onset sepsis-approximately 10 to 20 percent. Infants may have a history of obstetric complications, but these are less characteristic than in early-onset disease. Bacteria responsible for late-onset sepsis include those acquired from the maternal genital canal and organisms acquired after birth from human contacts or from contaminated equipment or materials. Some organisms, such as E. coli, GBS and L. monocytogenes, may be responsible for both early-onset and late-onset diseases, whereas others, such as S. aureus and Pseudomonas aeruginosa, are usually associated with late-onset disease.

Initial Empiric Therapy

The signs of neonatal sepsis are very subtle, particularly in the early stages, and may not be clinically distinguishable from those caused by other common neonatal problems. Frequently it is the mother or nurse who first notices that the baby is not quite as well as he has been, he is quieter and stiller than usual, perhaps a little pale, and either feeds poorly or vomits. Some time later "harder" signs develop.

Neonatal sepsis is still a life-threatening emergency. Any delay of diagnosis and treatment may have devastating consequences. Isolation of a pathogenic microorganism from the blood is the most specific method of diagnosing neonatal sepsis. Bacterial growth is evident in the majority of cultures of blood within 48-72 hours. However, antimicrobial treatment of neonates with suspected sepsis should begin immediately after appropriate cultures have been obtained. Waiting for the results of the cultures may cause delay in the beginning of therapy which may adversely affect the prognosis of sepsis. Even a four-hour delay may increase mortality rate.

The empirical therapy for presumed sepsis is benign as compared to the consequences of not treating the truly infected infant. The adage that "three days of ampicillin and gentamicin never killed anybody" has some merit in this context.

After the two or three-day empirical therapy with antibiotics, the choice of antibiotics should be reevaluated when results of cultures and susceptibility tests become available. If the cultures are negative and the clinical findings of the patient are well, antimicrobial therapy should be stopped. Otherwise resistant gram-negative colonization is quite high. Possible reasons why antibiotics are not stopped include the nonspecific nuture of signs of sepsis in neonates, physicians' reluctance to discontinue antibiotics once started, and the logistical difficulty of obtaining routine culture results at weekends. However, if the baby has pneumonia, or what looks like sepsis, antibiotic therapy should not be stopped, even if blood culture is negative.

Decreasing gestational age is associated with increased rates of infection. The ruling out of sepsis in the immature neonate is very difficult. Therefore, antibiotic therapy for suspected sepsis is frequently initiated at birth in small preterm infants and continued for five or more days, despite a negative blood culture[11].

Infants born to women who have received intrapartum antibiotics represent a difficult treatment dilemma for the clinician because culture growth may be inhibited by exposure to intrapartum treatment. Therefore, all symptomatic infants should be treated for at least 10 days, even if cultures show no growth. For asymptomatic newborns, decisions can be made according to cultures and laboratory data (white blood cell count < 5000/mm^3 or > 30.000/mm^3, immature/total leukocytes > 0.2, C-reactive protein > 0.8 mg/dl, microerythrocyte sedimentation rate > 15 mm/hr). When the sepsis screening tests are negative in an asymptomatic infant, the likelihood of infection is very low, and the treatment can safely be discontinued. In general, full course antibiotic treatment should be given in an asymptomatic preterm infant who has a positive screen. In asymptomatic full-term infants, closer follow up is needed before the beginning of antibiotic therapy[1, 12, 13].

Selection of an empirical antibiotic regimen should be based on:

– Postnatal age at the onset of disease: Because different microorganisms are responsible for early- or late-onset disease, the choice of antimicrobial agents also differs.

– Patient-specific factors: the patient's clinical conditions (including invasive procedures) and previous antibiotic therapy.

– Bacterial prevalence: the bacterial species most likely to cause infection.

– Bacterial susceptibility: antibiotic resistance pattern in one's own hospital. Antimicrobial agents play a major role in the ecology of the microbial flora in the nursery. Extensive use of these drugs helps to eliminate sensitive strains

and allows proliferation of resistant strains. Thus, there is a selective pressure toward colonization by microorganisms that are resistant not only to the antimicrobial agents used in the hospital but also to other similar drugs, because of cross-resistance patterns.

– Pharmacokinetical properties of the antibiotic.

A combination of two antibiotics should be initiated in suspected neonatal sepsis.

– Empirical therapy must cover most of the pathogens which cause sepsis.

– Synergistic effects of antibiotics (e.g. penicillin + aminoglycoside for GBS).

– Some infecting organisms are likely to develop resistant mutants during therapy (e.g. Pseudomonas species).

– Higher bactericidal serum activity is required than can usually be achieved with a single agent (e.g. enterococci, Listeria).

Early-Onset Sepsis

In infants who developed sepsis during the first week of life, empiric therapy must cover GBS, Enterobacteriaceae (especially E. coli) and Listeria monocytogenes. The bacteriology of neonatal sepsis in Europe is, in general, similar to that in the United States. In tropical areas, a different pattern is seen: E. coli, Klebsiella and Serratia species are the dominant causes of neonatal sepsis; GBS are infrequent causes. In this part of the world, the majority of early-neonatal infections are probably caused by gram-negative bacteria, rather than by GBS as in the United States. The difference in the incidence of GBS may reflect a genetic factor or differences in sexual practices. In developing countries, multiple-resistant hospital acquired bacteria, which are transmitted by lack of hygiene, may cause early-onset infections.

Penicillin or ampicillin plus an aminoglycoside combination is generally effective against all these organisms. Ampicillin and an aminoglycoside combination provides broader antimicrobial activity. Compared with penicillin, ampicillin has increased efficiency against L. monocytogenes, as well as against some gram-negative pathogens, E. coli and Proteus mirabilis.

Most GBS are highly sensitive to penicillin and can be treated with penicillin or ampicillin alone. But infections due to GBS can be treated with a combination of penicillin or ampicillin and an aminoglycoside. Although aminoglycosides are relatively ineffective against GBS in vitro, when added to penicillin or ampicillin, they enhance the antibacterial activity[1].

Listeria monocytogenes are also susceptible to penicillin or ampicillin and can be treated with either of these drugs. But based on in vitro synergy studies, combination therapy with either penicillin or ampicillin and an aminoglycoside has been recommended[1].

Late-Onset Sepsis

Initial empirical antimicrobial treatment for infants who developed sepsis beyond the first few days of life must cover the organisms associated with early-onset sepsis as well as hospital-acquired pathogens such as Staphylococci, Enterococci and Pseudomonas aeruginosa.

Penicillin or ampicillin and an aminoglycoside combination may also be used in the initial therapy of late-onset suspected sepsis as in cases with early-onset sepsis. In nosocomial infections, netilmicin or amikacin should be preferred. In some hospitals, strains which cause nosocomial infections have undergone considerable alterations during the past 20 years, with a gradual increase in resistance to kanamycin, gentamicin and tobramycin. Fortunately, amikacin, and in some instances netilmicin, have retained their activity in this setting. Amikacin is resistant to degradation by most of the plasmid-mediated bacterial enzymes that inactivate other aminoglycosides. Therefore, it is held in reserve for treatment of hospital-acquired gram-negative infections that are suspected or proven to be multiple-resistant.

If there is an increased risk of staphylococcal infection (e.g. presence of vascular catheter), antistaphylococcal penicillin or vancomycin plus an aminoglycoside may be used in the initial antibiotic therapy. A ceftriaxone and vancomycin combination has also been used in the empirical therapy of late-onset sepsis[14]. In cases where there is increased risk of Pseudomonas infection (e.g. presence of typical mucocutaneous skin lesions), anti-Pseudomonas agents may be preferred in the initial empirical therapy. But we recommend using these antibiotics according to the results of the culture rather than routinely.

In some centers third-generation cephalosporins in combination with penicillin or ampicillin have been used in the initial therapy of early-onset and late-onset neonatal sepsis. Third-generation cephalosporin may also be combined with an aminoglycoside in some centers in places where aminoglycoside-resistance to this antibiotic is high[14-17]. The main advantages in using third-generation agents are excellent activity against the major pathogens of newborns, including aminoglycoside-resistant gram-negative bacilli, and excellent CSF penetration, as well as their safety and tolerability.

However, third-generation cephalosporins should not be used in the initial therapy of suspected sepsis because these antibiotics are not active against L. monocytogenes[1, 3]. Extensive use of cephalosporins for initial therapy of neonatal sepsis may lead to the more rapid emergence of drug-resistant microorganisms among gram-negative bacilli than has occurred with the aminoglycosides[18, 19].

Gram-negative Enteric Bacilli

Infections due to E. coli and K. pneumonia can be treated with the combination of a penicillin-derivative (ampicillin or extended-spectrum penicillins depending

on the isolate) and an aminoglycoside. Third-generation cephalosporins alone or together with an aminoglycoside may also be used in the treatment of such infections, although occasionally these organisms are resistant to cephalosporins[20]. In a study, ceftriaxone/gentamicin and azlocillin/gentamicin combinations have been found to have equal efficiency and reliability in the treatment of neonatal sepsis[21].

The treatment of Enterobacter species, Serratia species, Citrobacter species, indol-positive Proteus species and P. aeruginosa is more controversial. All these organisms carry a chromosomally encoded inducible beta-lactamase. Normally, this enzyme is under repressor control, and many isolates appear sensitive to penicillins, cephalosporins and monobactams. However, exposure to a beta-lactam antibiotic results in induction of expression of the enzyme which persists as long as the inducer is present. When mutation occurs in the beta-lactamase repressor gene, production of beta-lactamase is permanently induced and the organism becomes resistant to beta-lactam antibiotics. Even organisms initially susceptible to a beta-lactam antibiotic may become highly resistant during therapy.

Third-generation cephalosporins are poor inducers of beta-lactamase expresion, but are sensitive to these enzymes and are significantly associated with the development of repressor mutations. Like the third-generation cephalosporins, the extended-spectrum penicillins are poor inducers of beta-lactamase expression. On the other hand, these antibiotics are seldomly associated with repressor mutation and therefore may have therapeutic advantages[1,21,22]. Therefore, infections due to these gram-negative bacilli should be treated with a combination of an extended-spectrum penicillin and an aminoglycoside.

Nevertheless, third-generation cephalosporins in combination with an aminoglycoside have been used in the treatment of sepsis due to these organisms. Among the third-generation cephalosporins, cefoperazone and ceftazidime (and cefsulodin) possess anti-Pseudomonas activity. Ceftazidime was found to be more active in vitro against Pseudomonas than cefoperazone or piperacillin.

Both synergistic and antagonistic interactions have been demonstrated when the other beta-lactam antibiotics (e.g. penicillins) were combined with cephalosporins. Antagonism may be related to the ability of cephalosporins to induce beta-lactamase production which inactivates penicillins. Therefore, the use of third-generation cephalosporins in combination with penicillins should be avoided. However, it has been reported that early diagnosis and treatment with piperacillin plus cefotaxime reduced the mortality rate of sepsis[23].

Extended-spectrum penicillins are carboxypenicillins and acylampicillins. Most pathogens incriminated in neonatal sepsis are susceptible to these antibiotics, but their most important feature is activity against P. aeruginosa and certain

Proteus species that are resistant to ampicillin. Extended-spectrum penicillins are susceptible to staphylococcal beta-lactamases and are not reliable for treating staphylococcal disease.

Carboxypenicillins are carbenicillin and ticarcillin. Antimicrobial activity of ticarcillin is similar to that of carbenicillin with the exception that ticarcillin is more active against P. aeruginosa. The co-administration of clavulanic acid (a potent beta-lactamase inhibitor) with ticarcillin significantly enhances the antibacterial activity of the drug against several organisms, including many ticarcillin-resistant strains.

Acylampicillins include the ureidopenicillins (mezlocillin and azlocillin) and piperacillin. Piperacillin and azlocillin are the most active of extended-spectrum penicillins against P. aeruginosa. Mezlocillin, the least active of the three, is at least as effective as ticarcillin against this organism[24].

Although aminoglycosides exhibit somewhat similar activity against most gram-negative bacilli, tobramicin has the greatest anti-Pseudomonas activity. Amikacin is the only drug of this class that provides activity against Serratia species.

Alternative for Resistant Strains

Carbapenems: Imipenem is the first of new beta-lactam antibiotics, the carbapenems. It is combined with cilastin. Cilastin has no antibacterial activity, but is a potent inhibitor of dehydropeptidase-1, the renal tubular brush border enzyme that metabolizes imipenem. Its spectrum of activity includes most aerobic and anaerobic gram-positive and gram-negative bacteria[25]. There are synergistic interactions between imipenem and aminoglycosides[26]. Antagonistic interactions are usually observed when imipenem is combined with other beta-lactams, probably as a result of chromosomal beta-lactamase induction by imipenem. Both imipenem and cilastin penetrate well into the CSF in the presence of meningeal inflammation. However, neurotoxicity associated with imipenem has limited its usefulness in cases with meningitis. Emergence of imipenem-resistant strains during therapy with this drug is rare except for P. aeruginosa. In a high percentage of cases of P. aeruginosa infection treated with imipenem, resistance has emerged during the course of therapy[27]. Meropenem is another carbapenem which under investigations seems to have somewhat broader gram-negative activity than imipenem[28].

Aztreonam: Aztreonam is a synthetic monocyclic beta-lactam (monobactam) antibiotic[25]. But this drug is stable to hydrolysis by beta-lactamases and does not induce chromosomal beta-lactamase production. The antimicrobial activity of aztreonam differs from those of other beta-lactam antibiotics and more closely resembles that of an aminoglycoside. Its aminoglycoside-like activity, good CSF penetration and absence of nephrotoxic or ototoxic side effects make aztreonam

potentially useful when combined with ampicillin for the treatment of neonatal sepsis. When combined with aminoglycosides, aztreonam interacts synergically against P. aeruginosa and many gram-negative enteric bacilli[29, 30].

Isepamicin: Isepamicin is a new aminoglycoside that has activity against many bacteria that are resistant to other aminoglycosides[31, 32].

Quinolones: The quinolones, or floroquinolones, are bactericidal by inhibiting bacterial DNA replication[25]. Ciprofloxacin alone, or in combination with other antibiotics, has been used in some newborn centers in the treatment of gram-negative infections due to organisms (including P. aeruginosa) resistant to all other agents. However, the quinolones have not yet been approved for use in children, because of a concern for a possible effect of the quinolones on cartilage development in young children. To date, studies in older children seem to show no cartilage damage after treatment with quinolones. Magnetic resonance imaging and histopathological monitoring of ciprofloxacin use suggest that the quinolones do not cause arthropathy in humans as in experimental animals. Ultimately the quinolones will likely be approved for use in children[33-35]. However, the quinolones do not penetrate the blood-brain barrier well and are not, therefore, used to treat meningitis.

Enterococci

In general, enterococci are resistant to many antibiotics including cephalosporins, penicillinase-resistant penicillins and aminoglycosides. Furthermore, vancomycin inhibits but fails to kill these organisms. However, the cell wall-active antibiotics facilitate bacterial uptake of the aminoglycosides. Therefore, enterococci can be treated with a cell wall-active agent (such as penicillin, ampicillin, or vancomycin) and an aminoglycoside. In recent years high-level resistance to aminoglycosides and penicillin and vancomycin has prevalence among enterococci. Therefore management of infection caused by multiple resistant enterococci is a therapeutic dilemma[36-38].

Staphylococci

Because S. epidermidis is present on the skin, isolation of the organism from cultures of blood may represent skin contamination but may also be an important episode of bloodstream invasion. A repeat culture of blood may assist in differentiating contamination from bloodstream invasion.

The apparent increased incidence of S. epidermidis sepsis has been associated with increased survival of very small premature infants with immature immune systems and with the introduction of invasive procedures for maintenance and monitoring of the infants, including long-term vascular access devices.

Coagulase-negative staphylococci are the predominant cause of vascular-catheter-related infections. Staphylococcus aureus is more aggressive and associated with more complications than coagulase-negative staphylococci[39].

Most hospital-acquired strains of staphylococci are usually resistant to penicillin, ampicillin and cephalosporins. Staphylococci susceptible to penicillinase-resistant penicillins such as oxacillin, nafcillin and methicillin. Oxacillin may be preferred to nafcillin and methicillin because of their side effects. Some strains of staphylococci have become resistant to penicillinase-resistant penicillins. However, such strains are uniformly sensitive to vancomycin[40].

Although the activity of aminoglycosides against gram-positive bacteria is limited and resistant strains of staphylococci emerge rapidly during exposure to aminoglycosides, a penicillin or vancomycin and aminoglycoside combination results in a more rapid bacteriocidal effect than is produced by either drug alone[41].

Various studies suggest that teicoplanin is highly effective and safe in neonatal staphylococcal infections[42]. However emergence of teicoplanin-resistant coagulase-negative staphylococci is not rare[43, 44].

Duration of Therapy

The duration of therapy depends on the initial response to the appropriate antibiotics but should be 10 to 14 days in most infants with sepsis and minimal or absent focal infection. The minimal duration of therapy is 21 days for infants with meningitis due to gram-negative bacteria. Meningitis caused by GBS and L. monocytogenes should be treated for a minimum of 14 days[1-4, 45].

Side Effects of Anitibiotics

There are some side effects of antibiotics used in the treatment of neonatal sepsis[46].

1. Nephro- and ototoxicity due to aminoglycosides: Aminoglycoside clearance is dependent on renal glomerular filtration which is markedly decreased in neonates, especially those preterm. These drugs appear to be less nephrotoxic and ototoxic in neonates than in older patients, and the role of serum concentration monitoring should be limited to specific neonatal patients.

Numerous factors intervene in bringing about aminoglycoside-induced kidney damage, such as factors related to the antibiotic itself (intrinsic toxicity, administration route, type of monitoring of blood concentrations), those related to the subject treated (neonatal age, constitutional sensitivity), and other related to associated pathology (neonatal anoxia, renal hypoperfusion, respiratory distress-mechanical ventilation, hyperbilirubinemia, electrolyte disorders, and even the acute sepsis calling for antibiotic therapy), as well as pharmacological factors (concomitant therapies such as diuretics, indomethacin and other antibiotics, particularly glycopeptides and cephalosporins)[47].

2. Bleeding disorders due to third-generation cephalosporins: Bleeding disorders associated with the use of third-generation cephalosporins have been documented. Hemostatic abnormalities can be mediated by several mechanisms. The most important mechanism is interference with the production of vitamin K-dependent clotting factors. This is most commonly observed with moxalactam and cefamandole therapy, and is rare with cefotaxime and ceftriaxone. This side effect is usually avoidable or reversible by the administration of supplemental vitamin K[48].

3. Kernicterus risk and antibiotics: Hyperbilirubinemia is frequently observed in neonates, and serious neurological complications such as kernicterus can be precipitated when the concentration of unconjugated bilirubin is abnormally increased. The administration of drugs which bind to albumin and compete with bilirubin can increase the possibility of such a complication. Antibiotics could be classified into four groups: high-level displacers (sulfisoxazole, sulfamethoxazole, dicloxacillin, cefoperazone, ceftriaxone), intermediate-level displacers (moxalactam, nafcillin), low-level displacers (aztreonam, carbenicillin) and nondisplacers (mezlocillin, cefuroxime, kanamycin). Antibiotics with a tendency to displace bilirubin should be avoided in jaundiced newborns whenever appropriate alternatives are available[49].

4. High sodium contents of extended-spectrum penicllins: Sodium contents of extended-spectrum penicillins are important in the treatment of neonatal infections (5 mEq/g in carbenicillin and ticarcillin; 2 mEq/g in azlocillin, mezlocillin and piperacillin)[24].

Prophylaxis

1. Group B Streptococcal infection: In places where GBS carrier rate is high, the ideal approach toward preventing GBS neonatal disease involves intrapartum administration of antibiotics to colonized women because 30 to 70 percent of infants born to women colonized with GBS become colonized themselves during the delivery. Among colonized newborns, disease occurs in one to two percent[50].

The American Academy of Pediatrics (AAP) recommended universal screening of pregnant women at 26 to 28 weeks of gestation for vaginal or anorectal colonization with GBS[51]. This strategy prevents more cases but at greater cost. Screening all women with risk factors (e.g. preterm labor, premature rupture of members, fever during pregnancy, chorioamnionitis, multiple gestation) is simple, effective, inexpensive and avoids unnecessary antibiotic use[52-58].

If the cultures are positive, antibiotic therapy should be given to the mother. Treatment should include intravenous ampicillin or penicillin until delivery. When maternal cultures are negative for GB, the occurrence of neonatal GBS infection is very low. However negative cultures do not exclude the possibility of neonatal infection caused by other bacteria.

Vaginal disinfection with a chlorhexidine gel during labor modestly reduces group B streptococcal vertical transmission. Because the method is cheap, simple and safe, it should be considered for routine use[59].

2. Premature rupture of membranes: PROM and chorioamnionitis occur in approximately 10 and one percent of all pregnancies, respectively. Neonatal infections can be documented in one percent of infants delivered to women with PROM alone, and in 10 percent of infants born to women with PROM and clinical amnionitis. The risk for neonatal sepsis is much higher in preterm infants. An intrauterine infection was found in two thirds of women presenting with preterm PROM[60, 61].

Therefore intrapartum broad-spectrum antibiotics that provide anaerobic coverage (e.g. ampicillin with or without sulbactam) should be administered to any woman with premature rupture of membranes or clinical chorioamnionitis[62-64]. However, antibiotics should not be routinely administered to women in preterm labor with intact membranes[65].

In infants born to mothers with PROM, neonatal signs of infection including leukopenia, leukocytosis, thromboytopenia, and positive gastric aspirate cultures are not good predictors of sepsis. Thus the administration of prophylactic antibiotic therapy (same as early-onset sepsis) in these cases may be warranted in preterm infants[60]. However, it may be unnecessary to administer prophylactic antibiotics to term, appropriate-for-gestational-age infants born after PROM, except in cases with a low Apgar score and maternal chorioamnionitis[66].

3. Meconium aspiration: Antibiotic prophylaxis is usually done for newborn babies intubated at birth for aspirating meconium from the trachea to prevent pneumonia and sepsis. However, a recent study indicates that well-term babies who are intubated for aspirating meconium need not be put on routine antibiotic cover. But this prophylaxis may be needed in preterm infants[67].

4. Staphylococcal infection: Hexachlorophene bathing after birth decreases staphylococcal colonization, but this chemical is ineffective against gram-negative enteric bacilli.

5. Antibiotic use during invasive procedures: (e.g. endotracheal intubation, vascular catheterization) has no effect on the prevention of nosocomial infections. Attempts to prevent nosocomial bacteriemias by routinely administering prophylactic antibiotics should be avoided because of the possibility of development of resistant organisms[68].

Although staphylococcal infections are high in patients who have vascular catheterization, duration of catheterization is not found to be a significant predictor of risk for catheter-related sepsis[69], and prophylactics with an antibiotic are not recommended[70].

Topical mupirocin is routinely applied to insersion sites of vascular catheters of neonates. However, mupirocin resistance in coagulase-negative staphylococci, has been reported after topical prophylaxis for the reduction of colonization of central venous catheters[71].

Nosocomial Infection Control Measures

Several measures have been instituted to control epidemics of antibiotic-resistant gram-negative bacilli[72]. The most common measures include:

1. Closing the unit to new admissions until control of the outbreak is underway.

2. Cultures from the health personnel: The nose, throat, anus and hands of health personnel potentially harbor gram-negative pathogens. However, these cultures usually never yield significant levels of carriage even in the midst of an outbreak.

3. Reinforcing hand-washing practices. Gram-negative contaminants can be resistant to simple washing with nonmedicated soap and water. Repeated hand-washing in the hospital reduces the colonized bacteria, but they are able to replicate during nonworking hours.

4. Establishing a barrier between infected or colonized patients and those who do not harbor the resistant organism. However, most resistant organisms arise from the patient's endogenous flora rather than outside sources. Sophisticated genotyping of multiple hospital isolates confirms that a marked majority of gram-negative organisms colonizing or infecting hospitalized patients are distinct from one another, even among patients occupying the same unit at the same time. Only 10 to 20 percent of gram-neative bacillary infections seem to be caused by cross-contamination from one patient to another, and in those instances it is unusual for more than two patients to be affected by a single isolate.

5. Restriction of the use of the antibiotic to which the offending strain is resistant.

6. Modifying routine regimens to include newer antibiotics. This strategy only delays the problem because of developing resistance to new antibiotics.

7. Limiting the use of third-generation cephalosporins since these agents seen particularly prone to rapidly induce resistance to themselves and other beta-lactam agents.

8. Rotation of antibiotics to decrease emergence of resistance.

9. Use of multiple antibiotic regimens rather than monotherapy.

Colonization rates with resistant gram-negative bacteria have been known to fluctuate widely without any change in antibiotic practice. Even with strict antibiotic control, colonization and infection with resistant organisms rarely disappeared entirely. Consequently antibiotic-resistant gram-negative pathogens will remain in the hospital environment for years.

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