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Treatment Options for the Pharmacological Therapy of Neonatal Meningitis

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Contents

Summary

Neonatal bacterial meningitis has a relatively low incidence in developed countries, but continues to cause morbidity and mortality despite advances in antimicrobial therapy. Bacterial pathogens commonly associated with neonatal meningitis include Group B streptococci, *Escherichia coli* K1 and other coliforms, *Listeria monocytogenes* and staphylococci. As it can be difficult to differentiate meningitis from septicaemia in neonates, empirical antibiotic therapy should be effective for both. Selection of an empirical antibiotic regimen should be based on: (a) bacterial prevalence and susceptibility; (b) drug characteristics; (c) postnatal age at the onset of disease; and (d) patient-specific factors. A penicillin in combination with an aminoglycoside or cefotaxime is commonly used in empirical therapies. The increased risk of staphylococcal infection in older neonates requires consideration of an antistaphylococcal antibiotic in the empirical therapy regimen. Once a causative organism has been identified, antimicrobial therapy should be directed towards that pathogen. Duration of therapy remains empirical, but should be at least 7 days for documented bacterial meningitis. Viral meningitis continues to have a high mortality despite the availability of antiviral agents.

Adjunctive therapies may further reduce the morbidity and mortality of meningitis. While most of these therapeutic options have not been investigated in neonates, they may prove to be of benefit in the future. Anti-inflammatory agents, such as glucocorticoids, nonsteroidal anti-

inflammatory agents and immunoglobulin, may modulate the inflammatory response of a meningeal infection. Other possible therapies in neonatal meningitis include cerebral blood flow modulators and disease prevention with maternal vaccines and perinatal antibiotics. Practical aspects of drug therapy such as route of administration and serum drug concentration monitoring can improve both drug therapy and patient outcome. While antibiotics have greatly improved the treatment outcome of neonatal meningitis, it is clear that additional intervention will be required to increase cure rates and reduce sequelae.

Although the incidence of neonatal meningitis is low in developed countries (e.g. 2 to 10 cases/10 000 live births in the United States), its associated morbidity and mortality are high. Mortality is 20% or higher in many studies and long term sequelae of the disease vary from 30 to 50% (Schlech et al. 1985). Thus, despite the availability of a number of potent and effective antimicrobial agents, this condition continues to exact a high death toll in newborn infants.

1. Aetiology and Presentation of Neonatal Meningitis

Most cases of neonatal bacterial meningitis in developed countries are caused by Group B streptococci and coliforms. Group B streptococci is a common coloniser of the vagina and/or rectum in pregnant women; 40 to 70% of infants, of mothers colonised at birth, will acquire the mother's organisms within the first few days of life. However, the organism can also be acquired from nursery personnel due to poor handwashing. Invasive disease with Group B streptococci usually occurs within the first week of life. *Escherichia coli* K1 accounts for most coliform meningitis in neonates, but other coliforms, such as *Enterobacter* spp., *Citrobacter diversus, Klebsiella pneumoniae* and *Salmonella enteritidis,* are also observed. Similar to the case with Group B streptococci, about one-half of pregnant women are colonised with *E. coli* and 75% of infants from these colonised mothers will also become colonised (McCracken et al. 1974). As with streptococci, *E. coli* may also be acquired via horizontal spread from nursery staff. It is estimated that < 0.5% of colonised infants will develop meningitis.

Listeria monocytogenes, a Gram-positive rod, also causes a significant number of cases of meningitis, although colonisation of pregnant women and healthy newborns is unusual. *Listeria* may account for as many as 10% of cases of neonatal meningitis with the disease usually occurring within the first week of life (Schlech et al. 1985). Other bacterial causes include enterococci, staphylococci and non-typable *Haemophilus influenzae.*

Meningitis in neonates can also be caused by viruses; herpes simplex virus (HSV) and enteroviruses account for most cases. Fungal meningitis is rare in neonates and is not discussed in this article.

Meningitis in neonates is usually associated with septicaemia – about 25% of newborns with septicaemia will develop meningitis (Klein et al. 1983). After pathogens gain entry to the central nervous systems (CNS) through capillary endothelial cells (the so-called blood-brain barrier), they rapidly multiply and liberate a number of substances which apparently contribute to the inflammatory reponse and resultant pathology (e.g. cell wall components, endotoxin); antimicrobial therapy may also contribute to the release of such products into the cerebrospinal fluid (CSF). Such substances stimulate macrophage-equivalent brain cells and cerebral capillary endothelium to produce cytokines, such as tumor necrosis factor and interleukin-1, which contribute to the attraction of leucocytes to the site of the infection. Leucocytes, in turn, release proteolytic substances. The result of this cascade of events is damage to the vascular endothelium and resultant increase in permeability allowing an influx of protein to the CSF and thus oedema. The release of toxic substances by the leucocytes that are attracted to the subarachnoid space also con-

tributes to this process by causing cytotoxic oedema. The presence of cerebral oedema, often accompanied by intracranial hypertension, alterations of cerebral metabolism and decreased cerebral blood flow are all thought to contribute to focal or diffuse damage which may be permanent (Sande et al. 1989).

The clinical manifestations of meningitis in the neonate are quite subtle and nonspecific. The classic signs of meningeal irritation commonly observed in older infants, children and adults are present in < 20% of neonates with meningitis (Klein et al. 1986). Instead, nonspecific signs and symptoms, such as irritability, poor feeding, respiratory compromise including apnoea and temperature instability, are observed. Because these symptoms are only suggestive rather than pathognomonic of CNS infection, antimicrobial therapy is typically started on an empirical basis. Neonates with a working diagnosis of septicaemia are regularly screened for meningitis as well, but, as is the case with clinical findings, examination of the CSF often does not reveal the typical leucocytosis, low glucose and high protein expected in older individuals. Thus, a Gram stain of the CSF and cultures of blood, urine and CSF, as well as antigen detection tests are often critical to the definitive diagnosis (St Gene et al. 1988). Clinical features suggestive of HSV infection include vesicular rash, keratitis and conjunctivitis while diarrhoea and abdominal distention may suggest enteroviral infection. However, the latter signs are nonspecific and may occur with bacterial infections as well.

Antimicrobial selection is crucial in the treatment of meningitis. While the choice of therapy for meningitis is certainly vital for patients of any age, the neonate represents an immunocompromised host of sorts and, thus, the use of cidal agents is important to outcome. Newborn infants not only lack the usual physical barriers to infection (fully keratinised epidermis and fully developed mucosa), but also have inadequate numbers of white cells. Further, those white cells that are present exhibit impaired chemotactic responses and decreased opsonising abilities. Decreased complement, reticuloendothelial function and lower levels of serum immunoglobulins also contribute to an increased susceptibility of the neonate to serious infections including sepsis and meningitis.

2. Pharmacological Therapy of Neonatal Meningitis

Conventional pharmacological therapy for neonatal meningitis includes appropriate empirical and directed anti-infective therapy. Pharmacological therapy can usually be achieved with several available drugs or combinations thereof. However, the previously discussed factors are important in the selection of an appropriate therapy on an individual basis. Many options available to the clinician are based on the pharmacological properties of the specific agents and may not have adequate clinical data to warrant their routine use in neonates. The complicated cases of neonatal meningitis often require the use of therapeutic options which may not have been proven to be effective and safe. The clinician must weigh the benefits versus the risks of these therapeutic options, as with any pharmacological therapy.

Anti-infective therapy is the major component of pharmacological therapy for neonatal meningitis; however, several other adjunctive therapies may be appropriate in particular cases. Recently, the use of corticosteroids, intravenous immunoglobulin and monoclonal antibodies (section 2.1) have gained attention as immunomodulators in the treatment of pediatric infections, but their role in neonatal meningitis remains unclear. While there are limited or no data available on these agents in the neonatal population specifically, these options are available for use. Altered cerebral blood flow (CBF), increased intracranial pressure (ICP) and cerebral oedema perhaps also play a role in the neurological sequelae from meningitis. There have been several pharmacological agents studied which may modulate CBF, ICP and cerebral oedema. Examples include corticosteroids, diuretics and barbiturates.

Finally, there are several practical aspects of pharmacological treatment that provide options to the clinician. Factors such as route of drug admin-

istration, developmental pharmacokinetics and serum drug concentration monitoring are important considerations available to the clinician during treatment. The clinician that considers all of the factors and has an appreciation for their appropriate application can optimise the pharmacological treatment of neonatal meningitis.

2.1 Bacterial Meningitis

2.1.1 Empirical Treatment

The identification of the bacterial causes of neonatal meningitis is aggressively pursued because of the availability of antibacterial agents to treat this form of the disease. However, it is often not obvious whether the disease is a bacterial meningitis, although empirical therapy is begun until the diagnosis can be ruled out. Selection of empirical therapy varies depending on several factors: (a) bacterial prevalence and resistance; (b) drug characteristics (efficacy, toxicity, pharmacokinetics and cost); (c) postnatal age at onset of disease; and (d) patient-specific considerations. Table I summarises several commonly used empirical regimens and their advantages and disadvantages.

The factors for determining which empirical regimen is most appropriate should be addressed on an individual basis. While Group B streptococci, *Listeria* spp. and coliforms are the most common pathogens in the United States, staphylococcal and Group A streptococcal infections are still common in many parts of the world. It is also important to be aware of the resistance patterns within the community, particularly with Group B streptococci, *Enterobacteriaceae* and coagulase-negative staphylococci. Selected drugs should have activity against suspected pathogens, low toxicity, adequate CNS penetration and low cost. Patient specific factors such as renal and hepatic function, postconception age, clinical status, vascular access and immunocompetency must also be assessed.

Drug selection should be based on the most important factors affecting outcome, efficacy and safety. The efficacy and/or toxicity of a particular regimen may depend on patient-specific factors. The clinical status of the neonate may dictate which regimen is best. For example, a neonate with underlying renal disease may not be a candidate for aminoglycosides as initial empiric therapy. The intramuscular (IM) route of drug administration may be inappropriate in a septic, hypotensive neonate and chloramphenicol should never be administered by the IM route, thus requiring intravascular access (intravenous therapy) for initial empirical therapy in these circumstances. Older neonates (> 14 days postnatal age) have a lower risk of *Listeria* and Group B streptococcal infections and an increased risk of staphylococcal infection. These age-related changes are important considerations in the empiric selection of antibiotics. Each regimen in table I may be useful in a particular clinical presentation and the clinician must determine the important factors present and select the most appropriate regimen for the neonate.

A 1989 study surveyed 80 paediatric infectious disease programme directors in the United States and Canada to determine the most commonly employed empirical regimen for neonatal meningitis (Word & Klein 1989). Of the 64 respondents, 38 (59%) were using a combination of either ampicillin or benzylpenicillin (penicillin G), and an aminoglycoside as empirical therapy for suspected neonatal meningitis. Nearly all (24/26) of the remaining respondents (38% of the total respondents) indicated that the combination of cefotaxime and ampicillin was used. One institution was using the combination of ceftriaxone and ampicillin in neonates. Ampicillin offers increased Gram-negative activity, retains activity against *Listeria* and enterococci, and is not markedly more expensive than benzylpenicillin. It is thus the preferred agent in combination with an aminoglycoside, cefotaxime or ceftriaxone. Gentamicin offers significant cost savings over other available aminoglycosides and is recommended for the empiric treatment of neonatal meningitis unless specific resistance patterns within the community or hospital necessitate the use of tobramycin or amikacin.

Cefotaxime has a wide therapeutic margin, has increased penetration into the CNS and has been used extensively in neonates. Ceftriaxone has been

implicated as a cause of biliary sludging and increased diarrhoea due to its biliary excretion, and has been avoided in neonates (Lee et al. 1990; Nahata & Miller 1989). The development of bacterial resistance to cefotaxime in a neonatal intensive care unit has been reported (Bryan et al. 1985). Resistance patterns should be carefully monitored and cefotaxime use in neonatal intensive care units (NICU) in which resistance has emerged should be limited to neonates in whom aminoglycosides may not be desirable (e.g. renal failure). Cefotaxime in combination with ampicillin is the preferred empirical regimen for suspected neonatal meningitis in these patients (McCracken et al. 1987).

2.1.2 Specific Therapy for Bacterial Meningitis

Once positive identification of a causative organism has been determined, antibacterial therapy should be directed towards eradication of the organism. While coliforms, Group B streptococci, *Listeria* spp. and staphylococci are most common, there are many other bacteria that can cause neonatal meningitis. Table II includes a summary of the preferred and alternative antibiotic regimens for specific causative organisms. Recommended doses for both the empiric and specific treatment of neonatal meningitis are provided in tables III and IV, and are based on neonatal maturity and drug disposition. However, these dosage recommendations are based on the pharmacokinetic characteristics of the agents; there are very limited data to substantiate the efficacy and safety of most of these antibiotics in neonates. An extensive summary of the pharmacokinetics of antibacterial agents in neonates has recently been published, although it is beyond the scope of this review (Paap & Nahata 1990).

Group B streptococci are common neonatal pathogens that constitute a significant fraction of documented cases of neonatal meningitis. The treatment of Group B streptococcal meningitis may be complicated by the presence of tolerant strains

Table I. Common empirical antibiotic regimens for neonatal meningitis

Drugs	Advantages	Disadvantages
Maternal- or community-acquired		
Ampicillin + aminoglycoside	*Listeria* and enterococci coverage, low cost	Poor staphylococcal coverage, poor aminoglycoside CNS penetration
Ampicillin + chloramphenicol	Good CNS penetration of both drugs, *Listeria* and enterococci coverage, low cost	Increased toxicity of chloramphenicol
Ampicillin + cefotaxime	Good CNS penetration of both drugs, *Listeria* and enterococci coverage, decreased toxicity	Cefotaxime resistance, decreased staphylococci coverage
Penicillin + aminoglycoside	*Listeria* coverage, low cost	Decreased staphylococci coverage, resistance to penicillin, poor aminoglycoside CNS penetration
Nosocomial-acquired		
Methicillin + aminoglycoside	Low cost, increased staphylococci coverage	Decreased *Listeria* and enterococci coverage, moderate CNS penetration
Vancomycin + aminoglycoside	Low resistance, increased staphylococci and enterococci coverage	Poor CNS penetration of both drugs, possible increased nephrotoxicity, high cost
Vancomycin + cefotaxime	Increased CNS penetration of cefotaxime, increased staphylococci and enterococci coverage	Poor CNS penetration of vancomycin, high cost

Abbreviation: CNS = central nervous system.

Table II. Specific antimicrobial therapy, duration of treatment and alternatives for neonatal meningitis pathogens

Pathogen	Drug(s) of choice	Duration (days)	Alternatives
Bacteroides fragilis	Metronidazole	14-21	Clindamycin; imipenem/cilastatin; mezlocillin
Campylobacter fetus	Chloramphenicol	14	Imipenem/cilastatin; clindamycin
Citrobacter freundii	Cefotaxime ± aminoglycoside	14	Ceftriaxone or mezlocillin ± aminoglycoside; cotrimoxazole (trimethoprim/sulfamethoxazole)
Enterobacter spp. *Serratia* spp.	Cefotaxime + aminoglycoside	14-21	Ampicillin, chloramphenicol, or ceftriaxone and aminoglycoside; aztreonam
Escherichia coli *Klebsiella* spp. and other coliforms	Cefotaxime	14-21	Ampicillin or chloramphenicol and aminoglycoside; aztreonam; ceftriaxone
Flavobacterium meningosepticum	Vancomycin	14	Cotrimoxazole; clindamycin; imipenem/cilastatin
Group A streptococci	Benzylpenicillin	14	Ampicillin; cefotaxime; ceftriaxone; clindamycin
Group B streptococci	Benzylpenicillin ± aminoglycoside	10-14	Ampicillin, cefotaxime, ceftriaxone, methicillin, nafcillin ± aminoglycoside
Group D streptococci (enterococcal)	Ampicillin + aminoglycoside	14	Vancomycin ± aminoglycoside; mezlocillin and aminoglycoside
Group D streptococci (nonenterococcal)	Benzylpenicillin	14	Vancomycin; ampicillin
Haemophilus influenzae	Ampicillin (if sensitive)	14	Cefotaxime; ceftriaxone; chloramphenicol
Listeria monocytogenes	Ampicillin ± aminoglycoside	14	Mezlocillin; imipenem/cilastatin
Neisseria meningitidis	Benzylpenicillin	7-10	Ampicillin; chloramphenicol; cefotaxime; ceftriaxone; cotrimoxazole
Pseudomonas aeruginosa	Ceftazidime + aminoglycoside	14-21	Mezlocillin + aminoglycoside
Staphylococcus epidermidis or *S. aureus* (methicillin-sensitive)	Methicillin or nafcillin	10	Vancomycin; clindamycin
Staphylococcus epidermidis or *S. aureus* (methicillin-resistant)	Vancomycin	14	Imipenem/cilastatin; cotrimoxazole
Streptococcus pneumoniae	Benzylpenicillin	10	Chloramphenicol; cefotaxime; ceftriaxone; vancomycin
Treponema pallidum	Benzylpenicillin	10	Cefotaxime; ceftriaxone

which increase the minimum inhibitory concentrations (MIC) of penicillin (> 1 mg/L) and cause > 10-fold difference between the MIC and the minimum bacteriocidal concentrations (MBC) of penicillin. Meningitis caused by a penicillin-tolerant strain should be treated with an alternative agent such as ampicillin, cefotaxime or chloramphenicol with or without a concurrent aminoglycoside. Treatment with an aminoglycoside combination may only be necessary until the CSF has been sterilised. However, repeat lumbar puncture is not routinely performed and combination therapy may be continued for the complete course of antibiotics.

Infections of the CNS due to staphylococci are relatively uncommon in the full term neonate, but have become frequent pathogens in preterm neonates (Hall 1991). Gruskay et al. (1989) reported that 10 premature neonates with presumed *Staphylococcus epidermidis* meningitis had minimal signs of CNS inflammation and a low morbidity

Table III. Meningitis dosing guidelines for antimicrobial agents

Drug	Route	PNA (days)	Weight (g)	Total daily dose (mg/kg/day)	Interval
Benzylpenicillin	IV/IM	0-7	<2000	100 000U	q12h
			>2000	150 000U	q8h
		>7	<2000	150 000U	q8h
			>2000	200 000U	q6h
Ampicillin	IV/IM	0-7	<2000	100	q12h
Methicillin			>2000	150	q8h
Nafcillin		>7	<2000	150	q8h
Oxacillin			>2000	200	q6h
Carbenicillin	IV/IM	0-7	<2000	150	q12h
Ticarcillin			>2000	225	q8h
		>7	<2000	225	q8h
			>2000	300	q6h
Azlocillin	IV/IM	0-7	<2000	100	q12h
Mezlocillin			>2000	150	q8h
Piperacillin		>7	<2000	150	q8h
			>2000	200	q6h
Aztreonam	IV/IM	0-7	All	60	q12h
		>7	<2000	90	q8h
			>2000	120	q6h
Cefoperazone	IV/IM	0-7	All	60	q12h
Cefuroxime		>7	<2000	60	q12h
Latamoxef			>2000	90	q8h
Cefotaxime	IV/IM	0-7	All	100	q12h
Ceftazidime		>7	<2000	100	q12h
			>2000	150	q8h
Ceftriaxone	IV/IM	0-7	All	50	q12h
		>7	<2000	50	q12h
			>2000	75	q12h
Imipenem (cilastatin)	IV	0-7	All	60	q8h
		>7	<2000	60	q8h
			>2000	80	q6h

Abbreviations: IV = intravenous; IM = intramuscular; PNA = postnatal age; q12h = every 12 hours; q8h = every 8 hours; q6h = every 6 hours.

and mortality from the CNS infections. Affected preterm neonates often have indwelling central venous catheters, are receiving intravenous hyperalimentation and have extended hospital stays which contribute to their increased risk of these Gram-positive infections. Coagulase-negative staphylococci such as *Staphylococcus epidermidis* are commonly resistant to β-lactam antibiotics and require treatment with vancomycin. Presumed nephrotoxicity and ototoxicity necessitates close therapeutic monitoring of vancomycin therapy. Monitoring of serum drug concentrations are recommended and are outlined in section 3.2.

The optimal duration of therapy remains a difficult clinical decision. There is a lack of data to support a specific duration of therapy and the pe-

riods listed in table II have been empirically determined. In a recent historical review by Radetsky (1990), duration of therapy varied widely for the common causes of bacterial meningitis; parameters such as defervescence, CSF sterilisation and clinical improvement were cited as criteria for determing the length of treatment. It is important to assess the patient's clinical status and response to treatment before considering discontinuation of therapy. However, we agree that treatment should be administered for at least 7 days or longer for documented bacterial meningitis.

2.2 Viral Meningitis/Encephalitis

Viruses are also known to cause significant numbers of CNS infections in neonates. For example HSV infection affects 1500 to 2200 newborns per year in the US (Stone et al. 1989), often in the form of CNS infections. While most neonatal viral infections are caused by HSV and enterovirus, other pathogens such as cytomegalovirus have been implicated.

Unlike the case with antibacterial agents, little is known about the use of antiviral agents in neonatal CNS infections and treatment is largely supportive in nature. Because HSV infections have been the most extensively studied (for review see Whitley 1991), it is known that there is a significantly higher mortality rate associated with disseminated disease than with localised infections such as encephalitis (Whitley et al. 1991a). Vidarabine (adenine arabinoside) has been shown to reduce morbidity and mortality in neonates with HSV infections, including CNS infection (Ch'ien et al. 1975; Whitley et al. 1980, 1983). It is obvious, however, that the morbidity and mortality rates remain quite high even with this specific form of antiviral therapy. In a recent report by Whitley et al. (1991b) on 202 neonates with HSV infections including 71 with encephalitis, intravenous aciclovir (30 mg/kg/day) was found to be therapeutically equivalent to vidarabine (30 mg/kg/day). The mortality rate in neonates with encephalitis (14%) was the same for both treatment groups.

As mentioned above, cytomegalovirus also accounts for cases of neonatal infection. While no proven drug therapy has been established, a trial of ganciclovir is currently underway.

Table IV. Empirical dosing guidelines for aminoglycosides and vancomycin in neonates (see text section 3.2 for general guidelines on serum concentration monitoring) [adapted from Paap & Nahata 1990]

	Amikacin Kanamycin (mg)	Gentamicin Tobramycin Netilmicin (mg)	Vancomycin
≤ 7 days PNA (based on bodyweight in g)			
	IM/IV	IM/IV	IV
<800	10 q36h	3.5 q36h	20 q36h
800-1500	10 q24h	3.0 q24h	20 q24h
1500-2000	7.5 q18h	2.5 q18h	20 q18h
>2000	7.5 q12h	2.5 q12h	15 q12h
>7 days PNA (based on PCA in weeks)			
	IM/IV	IM/IV	IV
< 27	7.5 q36h	3.0 q36h	20 q36h
27-30	7.5 q24h	2.5 q24h	20 q24h
30-34	7.5 q18h	2.5 q18h	20 q18h
34-38	7.5 q12h	2.5 q12h	15 q12h
> 38	7.5 q8h	2.5 q8h	15 q8h

Abbreviations: PNA = postnatal age; PCA = post-conception age; IM = intramuscular; IV = intravenous; q36h = every 36 hours; q24h = every 24 hours; q18h = every 18 hours; q12h = every 12 hours; q8h = every 8 hours.

3. Adjunctive Therapies

Despite the availability of rapidly effective antimicrobial agents, morbidity and mortality from neonatal CNS infections remain unacceptably high. This has caused an increased interest and research in other areas including immune modulation, blood flow modulation and disease prevention.

3.1 Anti-Inflammatory Agents

Animal and human research has provided significant insight into the contribution of Gram-positive cell wall and Gram-negative endotoxin-mediated inflammation. The inflammatory response has been shown to contibute to the alterations in cerebral blood flow, intracranial pressure

and oedema, and pleocytosis (Mustafa et al. 1989). Neurological sequelae of meningeal infection have been linked to the occurrence of these changes and has been an area of extensive research.

The inflammatory cascade has been targeted for pharmacological treatment in an effort to reduce the sequelae associated with acute meningeal infection. Several important cytokines have been isolated during acute infection and have been used as markers of the degree of inflammation present. Components such as the complement system, prostaglandins and interleukins have been the subjects of intense investigation. Bacteriolysis with antibiotics has been shown to increase the inflammatory response and may contribute to the morbidity and mortality of the disease. Treatment strategies that have been proposed to minimise the inflammatory response include the use of antibodies and modulators of the inflammatory cascade such as corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs).

Intravenous immunoglobulin gamma (IVIG) has been advocated for the treatment of neonatal sepsis based on the primary immunodeficiency of premature neonates. There are limited data evaluating the efficacy of IVIG in neonatal meningitis. Preliminary studies suggest that IVIG may be beneficial in reducing the severity of disease in neonates infected with Group B streptococci (Freidman et al. 1990). In the published trials, it is difficult to separate the patients with meningitis from those with neonatal sepsis for analysis. The use of IVIG in neonatal meningitis should be considered only when a primary immunoglobulin deficiency has been documented and the neonate is not responding to conventional antibiotic therapy. Further studies with IVIG in neonatal meningitis need to be completed before its exact role can be assessed.

Recent studies have suggested that there has been a significant improvement in the neurological outcome with the use of dexamethasone during the treatment of bacterial meningitis (Girgis et al. 1989; Lebel et al. 1988; McCracken & Lebel 1989; Odio et al. 1991). However, these studies included a few neonates (< 2 months of age) and it is difficult to extrapolate the results to this population. Since neonates have significantly less developed brain structure and are infected by different pathogens than older infants, the benefit of corticosteroids remains unknown in neonates. However, corticosteroids are used in neonates for pulmonary disease with relatively few adverse effects (Ng et al. 1989). The results of ongoing trials of corticosteroids in neonatal meningitis need to be evaluated before routine use can be recommended.

While the role of immunomodulators such as NSAIDs, pentoxifylline and monoclonal antibodies appears to hold great promise in the future treatment of infectious diseases, there are no data evaluating their place in the treatment of human neonatal meningitis. Treatment with monoclonal antibodies against endotoxin may also find a role in Gram-negative meningitis, as has been suggested for patients with Gram-negative bacteraemia (Ziegler et al. 1991; see also Rozenberg-Arska & Visser, this issue).

3.2 Cerebral Blood Flow Modulators

Altered cerebral blood flow has been implicated as an important factor in the outcome of neonates with meningitis. Several pharmacological agents have been used to stabilise cerebral blood flow, decrease intracranial pressure and reduce neurological complications of neonatal meningitis. Diuretic agents, such as mannitol and furosemide (frusemide) have been used to reduce mean arterial pressure, intracranial pressure and cerebral blood flow (Cottrell et al. 1977). Other agents such as phenobarbital and thiopental sodium have also been used to decrease cerebral metabolic demand, cerebral blood flow and intracranial pressure. The validity of these approaches have come under scrutiny recently with the development of sophisticated tests of regional cerebral blood flow, suggesting that the manipulation of cerebral blood flow may induce regions of cerebral ischaemia (Ashwal et al. 1990).

3.3 Maternal/Perinatal Antibiotics and Vaccinations

The administration of antibiotics and vaccines to the mother prior to delivery has been used to decrease the neonate's exposure to pathogens in the

birth canal and to stimulate maternal antibody response to common neonatal pathogens that can be placentally transferred to the neonate. A current focus of research is in the prevention of Group B streptococcal disease via maternal vaccination. Maternal immunisation with a polysaccharide vaccine of Group B streptococcus induced protective levels of antibody in approximately 50% of the infants born to mothers enrolled in one study (Baker et al. 1988); the low response was partially attributed to the low immunogenicity of the polysaccharide vaccine. A conjugate vaccine is currently being studied for this purpose. Maternally administered IVIG may also have a prophylactic role in the prevention of these serious infections (Baker & Noya 1990). However, for prophylactic effect for specific pathogens, a hyperimmune IVIG preparation may be required for optimal efficacy (Baker et al. 1990).

4. Practical Aspects of Drug Treatment in Neonatal Meningitis

The effectiveness of a selected drug therapy can be optimised if the clinician has an understanding of the technological and physiological factors that affect the drug disposition in neonates. Assuring that the neonate receives the prescribed treatment, using, if available, a serum drug concentration monitoring laboratory and understanding the ontogeny of drug biodisposition are all important when treating neonatal meningitis. Drug administration and serum drug concentration monitoring are important technical aspects to treatment which should be appreciated. However, a comprehensive review of neonatal drug disposition is beyond the scope of this review, although several have been recently published (Besunder et al. 1988; Koren 1988; Stewart & Hampton 1987).

4.1 Drug Administration

Drug administration to neonates has been an area of controversy. Results from studies examining patient outcome after direct CSF administration of antibiotics for CNS infections have been conflicting. In an effort to increase the concentration of antibiotics in the CNS, a trial of intrathecally administered gentamicin was compared with systemic antibiotics (McCracken & Mize 1976); the use of intrathecal gentamicin did not improve morbidity or mortality associated with the CNS infection. In another study, intraventricular gentamicin increased mortality compared with conventional systemic therapy for neonatal meningitis (McCracken et al. 1980). Although Wright et al. (1981) in a smaller subsequent study evaluating intraventricular amikacin for neonatal meningitis reported favourable results, intraventricular administration of antibiotics is not considered beneficial in the treatment of neonatal meningitis.

Table V. Effect of site of injection and IV flow rate on the time to deliver 95% of an IV administered dose (adapted from Fould & Roberts 1979)

IV flow rate (ml/min)	Approximate time to deliver 95% of an administered dose (min)			
	distance of injection site from patient (ml)[a]			
	0.15	8.15	12.15	17.75
3	<10	190	200	-
10	<10	90	80	-
25	<10	70	70	130
100	<5	15	30	70

a Distance in ml of volume in IV tubing.
Abbreviations: IV = intravenous.

Research characterising intravenous (IV) drug delivery has shown the complexity of IV drug administration in neonates and infants. The IV delivery of drugs to paediatric patients requires an appreciation for flow dynamics and IV drug delivery systems. Several important variables have been identified which affect the time required to administer an IV drug. The IV flow rate and site of injection have a major impact on the time to deliver 95% of a given dose (table V) [Gould & Roberts 1979]. Clearly, the extended delivery time associated with distal drug administration sites and low flow rates are unacceptable. Based on the findings of this research, recommendations regarding the administration of drugs to neonates have been

established in many NICU and paediatric hospitals. We recommend IV drug delivery as proximal to the patient as possible by rapid bolus or via syringe pump to assure complete drug delivery to the neonate. This is also an important factor to consider when evaluating drug studies in neonates that were completed before the problems of IV drug delivery were appreciated at low IV flow rates.

4.2 Drug Concentration Monitoring

Serum concentrations of antibiotics are monitored during therapy to assure optimal outcome by either improving efficacy or preventing the toxicity associated with drugs. This topic has been reviewed in detail by Paap and Nahata (1990), but merits some discussion in relation to neonatal meningitis.

Before routine serum concentration monitoring can be justified, it is imperative to define the relationship between serum concentrations of a drug and its efficacy and/or adverse effect(s). This has been accomplished for a number of commonly used antimicrobial agents. The aminoglycosides are perhaps the most frequently monitored drugs in infected patients. The basis for monitoring their serum concentrations stems from data in adult patients suggesting that the therapeutic efficacy and toxicity correlate well with the serum concentrations (Moore et al. 1984); these drugs also have a narrow therapeutic index and there is large interpatient variability in pharmacokinetics. It is unclear whether such conclusions can be extrapolated to infants for several reasons: (a) the therapeutic range has not been clearly defined in neonates; (b) although it can be readily understood that the maximum concentration (C_{max}) must exceed the MIC against the infecting organism, it is not known by how much; (c) when the recommended dosage regimens are used, adequate serum concentrations are usually achieved; and (d) the incidence of nephrotoxicity and ototoxicity is extremely low in neonates (Adelman et al. 1989; Buchanan et al. 1985; Kalenga et al. 1984; McCracken 1986). Moreover, neonates often receive aminoglycosides for empirical treatment lasting only 2 to 3 days. Thus, routine monitoring of their serum concentrations is not justified in these patients. It is our practice to monitor the peak and trough serum concentrations of aminoglycosides in very premature and/or very seriously ill neonates, neonates receiving > 3 days of therapy, and patients with underlying renal dysfunction or fluctuating fluid status. Serum concentrations and renal function should be carefully followed in patients receiving other potentially nephrotoxic agents concomitantly with aminoglycosides.

Vancomycin has become the drug of choice for presumed or proven infections caused by methicillin-resistant staphylococci. Much of the discussion regarding aminoglycosides is also applicable to vancomycin. Again, it is difficult to justify routine monitoring of vancomycin concentrations, especially in neonates. Even in adults, the logic for routine monitoring of vancomycin serum concentrations has been questioned (Edwards & Pancorbo 1987; Rodvold et al. 1987). Since many neonates receive an aminoglycoside concomitantly with vancomycin for coverage of both Gram-negative and Gram-positive pathogens, additive nephrotoxicity should be considered. Although controversial, some investigators suggest that this is not a major problem unless the neonates are receiving amphotericin B or have other factors adversely affecting renal function (Nahata 1987a).

The frequency of chloramphenicol use in neonates has decreased due to both the availability of safer alternatives and the fear of potential toxicity. However, if this drug is used, C_{max} should be monitored 2 hours after an IV dose to ensure therapeutic, nontoxic concentrations. This is particularly important due to the variable hydrolysis of chloramphenicol succinate to active chloramphenicol in neonates (Nahata 1987b).

Accurate analytical methods and a well coordinated, interprofessional effort are needed to make a serum concentration monitoring programme successful. Analytical methods such as fluorescence polarisation immunoassays, enzyme immunoassay (EMIT) and high performance liquid chromatography (HPLC) methods are obviously preferred over bioassays. Physicians, pharmacists, nurses,

phlebotomists and laboratory personnel should work collaboratively such that interpretable data are generated and guidelines for monitoring are closely followed.

5. Conclusions

Although data regarding the pharmacological treatment of neonatal meningitis are limited, it is clear that antimicrobial therapy alone is associated with a marked, albeit reduced, rate of morbidity and mortality compared to no antimicrobial therapy. Currently marketed antibiotics are remarkable for their ready penetration into the CNS and rapid bactericidal action. However, it is obvious that these strengths will not ensure the higher cure rates and decreased sequelae desired. Hopefully, current advances in immune modulation, cerebral blood flow modulation and, most importantly, prevention, will allow us to achieve these ends.

References

Adelman C, Linder N, Levi H. Auditory nerve and brain stem evoked response thresholds in infants treated with gentamicin as neonates. Annals of Otology, Rhinology and Laryngology 98: 283-286, 1989

Ashwal S, Stringer W, Tomasi L, Schneider S, Thompson J, et al. Cerebral blood flow and carbon dioxide reactivity in children with bacterial meningitis. Journal of Pediatris 117: 523-530, 1990

Baker CJ, Noya FJD. Potential use of intravenous immune globulin for group B streptococcal infection. Reviews of Infectious Diseases 12 (Suppl. 4): S476-S482, 1990

Baker CJ, Rench MA, Edwards MS, Carpenter RJ, Hays BM, et al. Immunization of pregnant women with a polysaccharide vaccine of Group B streptococcus. New England Journal of Medicine 319: 1180-1185, 1988

Baker CJ, Rench MA, Noya FJD, Garcia-Prats JA, et al. Role of intravenous immunoglobulin in prevention of late-onset infection in low-birth-weight neonates. Reviews of Infectious Diseases 12 (Suppl. 4): S463-S469, 1990

Band JD, Clegg HW, Hayes PS, Facklam RR, Stringer J, Dixon RE. Transmission of group B streptococci: Traced by multiple epidemiologic markers. American Journal of Diseases of Childhood 135: 355-358, 1981

Besunder JB, Reed MD, Blumer JL. Principles of drug biodisposition in the neonate: a critical review of the pharmacokinetic-pharmacodynamic interface (Part 1). Clinical Pharmacokinetics 14: 189-216, 1988

Bryan CS, John Jr JF, Pai MS, Austin TL. Gentamicin vs cefotaxime for therapy of neonatal sepsis. American Journal of Diseases of Children 139: 1086-1089, 1985

Buchanan N. Aminoglycoside monitoring in neonates - a reappraisal. Australian and New Zealand Journal of Medicine 5: 457-459, 1985

Ch'ien LT, Whitley RJ, Nahmias AJ, Lewin EB, Linnemann CC, et al. Antiviral chemotherapy and neonatal herpes simplex virus infection: a pilot study - experience with adenine arabinoside (ARA-A). Pediatrics 55: 678-685, 1975

Cottrell JE, Robustelli A, Post K, Turndorf H. Furosemide and mannitol induced changes in intracranial pressure and serum osmolality and electrolytes. Anesthesiology 47: 28-30, 1977

Edwards DJ, Pancorbo S. Routine monitoring of serum vancomycin concentrations: waiting for proof of its value. Clinical Pharmacy 6: 652-654, 1987

Freidman CA, Wender DF, Temple DM, Rawson JE. Intravenous gamma globulin as adjunct therapy for severe group B streptococcal disease in the newborn. American Journal of Perinatology 7: 1-4, 1990

Girgis NL, Farid Z, Mikhail IA, Farrag I, Sultan Y, et al. Dexamethasone treatment for bacterial meningitis in children and adults. Pediatric Infectious Disease Journal 8: 848-851, 1989

Gould T, Roberts RJ. Therapeutic problems arising from the use of the intravenous route of drug administration. Journal of Pediatrics 95: 465-471, 1979

Gruskay J, Harris MC, Costarino AT. Neonatal Staphylococcus epidermidis meningitis with unremarkable CSF examination results. American Journal of Diseases of Children 143: 580-582, 1989

Hall SL. Coagulase-negative staphylococcal infections in neonates. Pediatric Infectious Disease Journal 10: 57-67, 1991

Kalenga M, Devos D, Moulin D, Verellen G, Bertrand JM. The need for pharmacokinetic monitoring of gentamicin in critically ill neonates. Developmental Pharmacology and Therapeutics 7 (Suppl. 1): 130-133, 1984

Klein JO, Feigin RD, McCracken GH. Report of the task force on the diagnosis and management of meningitis. Pediatrics 78 (Suppl.): 959-979, 1986

Klein JO, Marcy SM. Bacterial sepsis and meningitis. In Remington JS, Klein JO (Eds) Infectious Diseases of the Fetus and Newborn, 2nd ed. pp 679-735, WB Saunders Co., Philadelphia, 1983

Koren G. Clinical pharmacology of antimicrobial drugs during development: are infants and children different? In Koren G et al. (Eds) Antimicrobial therapy in infants and children, pp. 47-53, Marcel Dekker Inc., New York, 1988

Lebel MH, Freij BJ, Syrogiannopoulos G, Chrane DF, Hoyt MJ, et al. Dexamethasone therapy for bacterial meningitis. New England Journal of Medicine 319: 964, 1988

Lee SP, Lipsky BA, Teefey SA. Gallbladder sludge and antibiotics. Pediatric Infectious Disease Journal 9: 422-423, 1990

McCracken Jr GH. Aminoglycoside toxicity in infants and children. American Journal of Medicine 80 (Suppl. 6B): 172-178, 1986

McCracken Jr GH, Lebel MH. Dexamethasone therapy for bacterial meningitis in infants and children. American Journal of Diseases of Children 143: 287-289, 1989

McCracken Jr GH, Mize SG. A controlled study of intrathecal antibiotic therapy in Gram-negative enteric meningitis in infancy. Report of the neonatal meningitis cooperative study group. Journal of Pediatrics 89: 66, 1976

McCracken Jr GH, Mize SG, Threlkeld N. Intraventricular gentamicin therapy in Gram-negative bacillary meningitis of infancy. Lancet 1: 787, 1980

McCracken Jr GH, Nelson JD, Kaplan SL, Overturf GD, Rodriguez WJ, et al. Consensus report: antimicrobial therapy for bacterial meningitis in infants and children. Pediatric Infectious Disease Journal 6: 501-505, 1987

McCracken Jr GH, Sarff LD, Glode MP, Mize SG, Schiffer MS, Robbins JB. Relation between Escherichia coli K1 capsular polysaccharide antigen and clinical outcome in neonatal meningitis. Lancet 2: 246-250, 1974

Moore RD, Smith CR, Lietman PC. The association of aminoglycoside plasma level with therapeutic outcome in Gram-ne-

gative pneumonia. American Journal of Medicine 77: 657-662, 1984

Mustafa MM, Lebel MH, Ramilo O, Olsen KD, Reisch JS, et al. Correlation of interleukin-1B and cachectin concentrations in cerebrospinal fluid and outcome from bacterial meningitis. Journal of Pediatrics 115: 208-213, 1989

Nahata MC. Lack of nephrotoxicity in pediatric patients receiving concurrent vancomycin and aminoglycoside therapy. Chemotherapy 33: 302-304, 1987a

Nahata MC. Serum concentrations and adverse effects of chloramphenicol in pediatric patients. Chemotherapy 33: 322-327, 1987b

Nahata MC, Miller MA. Diarrhoea associated with ceftriaxone and its implications in paediatric patients. Journal of Clinical Pharmacy and Therapeutics 14: 305-307, 1989

Ng PC, Thompson MA, Dear PRF. Dexamethasone and infection in preterm babies: a controlled study. Lancet 2: 54-56, 1989

Odio CM, Faingezicht I, Paris M, Nassar M, Baltodano A, et al. The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis. New England Journal of Medicine 324: 1525-1531, 1991

Paap CM, Nahata MC. Clinical pharmacokinetics of antibacterial drugs in neonates. Clinical Pharmacokinentics 19: 280-316, 1990

Radetsky M. Duration of treatment in bacterial meningitis: a historical inquiry. Pediatric Infectious Disease Journal 9: 2-9, 1990

Rodvold KA, Zokufa H, Rotschafer JC. Routine monitoring of serum vancomycin concentrations: can waiting be justified? Clinical Pharmacy 6: 655-658, 1987

St Geme III JW, Polin RA. Neonatal sepsis. Progress in diagnosis and management. Drugs 36: 784-800, 1988

Sande MA, Tauber MG, Scheld WM, McCracken Jr GH. Report of a second workshop: Pathophysiology of bacterial meningitis. Pediatric Infectious Disease Journal 8: 901-918, 1989

Schlech III WF, Ward JI, Band JD, Hightower A, Fraser DW, Broome C. Bacterial meningitis in the United States, 1978 through 1981: The national bacterial meningitis surveillance study. Journal of The American Medical Association 253: 1749-1754, 1985

Stewart CF, Hampton EM. Effect of maturation of drug disposition in pediatric patients. Clinical Pharmacy 6: 548-564, 1987

Stone KM, Brooks CA, Guinan ME, Alexander ER. National Surveillance for neonatal herpes simplex virus infection. Sexually Transmitted Diseases 16: 152-156, 1989

Word BM, Klein JO. Therapy of bacterial sepsis and meningitis in infants and children: 1989 poll of directors of programs in pediatric infectious diseases. Pediatric Infectious Disease Journal 8: 635-637, 1989

Whitley RJ. Herpes simplex virus infections of the central nervous system: encephalitis and neonatal herpes. Drugs 42: 405-427, 1991

Whitley R, Arvin A, Prober C, Burchett S, Corey L, et al. A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection. New England Journal of Medicine 324: 444-449, 1991b

Whitley R, Arvin A, Prober C, Corey L, Burchett S, et al. Predictors of morbidity and mortality in neonates with herpes simplex virus infections. New England Journal of Medicine 324: 450-454, 1991a

Whitley RJ, Nahmias AJ, Soong SJ, Galasso GG, Fleming CL, et al. Vidarabine therapy of neonatal herpes simplex virus infection. Pediatrics 66: 495-501, 1980

Whitley RJ, Yeager A, Kartus P, Bryson Y, Connor JD, et al. Neonatal herpes simplex virus infection: follow-up evaluation of vidarabine therapy. Pediatrics 72: 778-785, 1983

Wright PF, Kaiser AB, Bowman CM, McKee KT, Trujillo H, et al. The pharmacokinetics and efficacy of an aminoglycoside administered into the cerebral ventricles in neonates: implications for further evaluation of this route of therapy in meningitis. Journal of Infectious Diseases 143: 141-147, 1981

Ziegler EJ, Fisher CJ, Sprung CL, Straube RC, Sadoff JC, et al. Treatment of gram-negative and septic shock with HA-1A human monoclonal antibody against endotoxin. New England Journal of Medicine 324: 429-436, 1991

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