Meningitis and Sepsis in an Infant

Case objectives:

Medical Expert:

1) Demonstrate a comprehensive understanding of the risk factors for sepsis/meningitis in neonates and young infants, common causative organisms, and initial empiric antibiotic therapy.
2) Demonstrate an appreciation of the implications of fever in a neonate and young infant.
3) Describe the recommended methods of temperature measurement in infants and children and define normal values.
4) Demonstrate knowledge of the possible presenting symptoms of serious infections such as sepsis/meningitis in young infants, and the indications for septic workup/ spinal tap.
5) Demonstrate the ability to interpret CSF results, understand the typical findings in viral vs. bacterial meningitis, and how to interpret results in the context of a bloody tap.
6) Understand the possible short term complications of sepsis/meningitis in young infants, including hypotension/shock, SIADH/hyponatremia, seizures.
7) Know how to prevent and/or manage these complications, including appropriate fluid management, prevention/ correction of hyponatremia, control of seizures.
8) Be familiar with research in regard to the use of steroids in the treatment of meningitis.
9) Understand the indications for doing a repeat LP in cases of meningitis, and how to interpret the results
10) Describe the different patterns of presentation of GBS disease in the neonate and young infant.
11) Understand the possible long-term health implications of meningitis, and appropriate screening/follow-up measures.
12) Be familiar with the role of MRI/EEG in the assessment of an infant/child with meningitis and their prognostic value in terms of future development and learning potential.

Communicator:

1) Discuss strategies for effective communication with parents of a seriously ill infant.

Part One

You arrive at the hospital on a Tuesday morning in November. You are covering on the wards for the week. Pulling into the parking lot, you step out of your car and brace yourself against the late autumn wind.

Prior to leaving home for the hospital, you had received handover from Dr. Grant the pediatrician who had been on call the night before. Among the patients for whom you will be responsible today is a seven-week-old infant named Tyler Morgan.

Dr. Grant had admitted him at approximately 4 AM for a reported problem with ongoing gastroesophageal reflux. He had shared with you his opinion that it was mainly a "social admission" as he found the parents to be quite unnecessarily distressed by Tyler's spitting up problem.

You pick up your day sheet from the ward clerk, speak to the nursing staff and begin your rounds. About one hour later, Tyler's nurse asks you when you will be coming to see him. She indicates to you that she is a bit concerned that he is not looking as well as he had when her shift began and that he seemed somewhat lethargic. You ask how his vital signs are and she indicates that they are stable and that it is no hurry. You tell her that you will see him next. You then receive a series of pages from the emergency department. As a result, it takes another half hour before you are able to assess Tyler.

Prior to entering the room, you familiarize yourself with the history in his chart. It reveals that he was born at term following an uneventful pregnancy, weighing 6 lbs. 12 oz. He is the first infant of a young couple. Mom was known to be GBS positive and had received antibiotics more than four hours prior to delivery. He went home after 48 hours. He had been re-admitted at three days of life for jaundice requiring phototherapy. He responded well to this treatment and was discharged uneventfully. He developed some problems with gastroesophageal reflux and was put on ranitidine by his family doctor. He was then admitted at 29 days of age for the same problem. At that point, he was experiencing significant but non-bilious vomiting after every feeding. He was investigated for pyloric stenosis and this diagnosis was ruled out. His ranitidine was changed to omeprazole.

Yesterday, Tyler's parents had again brought him to the hospital because of similar problems with vomiting. They had not noted any fever and there had been no known infectious contacts. The vomiting was described as rather forceful and his overall intake of formula was reduced. He was getting a standard cow milk-based product. Again, the vomiting was non-bilious and non-bloody but he didn't seem to

be keeping anything down. His urine output had been maintained throughout the day and night. There had been no blood in the stool or diarrhea.

His admission note documents normal growth since birth and normal developmental milestones.
In the emergency department last night, his heart rate had been 166, blood pressure 92/62, RR 52 and axillary temperature of 37.9°C. Dr. Grants note documents no abnormal physical findings. He did order a CBC which demonstrated a total white blood cell count of 2.9, HB 106 and platelets 372. The differential was still pending.

You go in to see Tyler and note that his parents are not present. You can tell from across the room that something is significantly amiss. You can hear Tyler moaning from across the room. As you approach, you notice significant pallor and mottled appearance. He is moving very little but his head is rotating from left to right and back again. His heart rate is 140, respiratory rate is 55 and oxygen saturations are 94% in room air. He is afebrile. His fontanelle and sutures are unremarkable. He is hypotonic and only minimally responsive to your handling. Brief abdominal exam is unremarkable. As you manipulate him, he emits a weak cry.

You are confident that his airway and breathing are sufficient. You take steps to address his other apparent difficulties. You quickly run a differential diagnosis for this significant problem through your mind and share your concerns and plan with Tyler's nurse.

Pause to discuss next steps

An intravenous is started on Tyler and he receives 20 ml per kilogram of normal saline as a bolus. His bedside blood glucose is 5.8. He remains pale but his perfusion improves significantly with the fluid.

A panel of bloodwork is ordered and drawn.

His parents arrive during the fluid bolus and you describe for them the concerns that you have and the possible conditions that Tyler may be experiencing. You tell them that a lumbar puncture will need to be performed. You describe for them the possible complications of the procedure. They consent but are clearly and understandably distraught.

You consider the contraindications to a lumbar puncture in this situation and are confident that none are present.

You go on to perform the procedure uneventfully. Tyler’s pathetic cry during the procedure does not bode well.

You order appropriate doses of the appropriate antibiotics considering the possible pathogens which may be responsible for this baby's illness. You order maintenance intravenous therapy, frequent vital signs and continuous electronic monitoring.

You tell his parents that the lumbar puncture was completed successfully and attempt to gather further history but nothing of relevance is reported.

Approximately one hour later, the initial report from his spinal fluid becomes available. The sample contained 1256 white blood cells, mainly neutrophils, 134 red blood cells. Glucose was zero and protein was 2.9. Numerous gram-positive diplococci were seen on Gram stain.

You convey these results to the parents and indicate that close monitoring and intravenous antibiotic therapy will be required.

As you return to the desk, you consider the possible complications that could occur in this baby and ensure that your current therapies and interventions are optimized. You note that the differential from last night's white count is now available. Tyler's absolute neutrophil count was 0.68 with an absolute band count of 0.08. The few granulocytes present demonstrate toxic vacuolation. The blood work that you ordered starts to come back as well. His sodium is 129 with a potassium of 5.0 Urea and creatinine are normal. Blood sugar is 6.3. All other chemistries are unremarkable.

You are disappointed to note that these results indicate that he may already be demonstrating one concerning complication of meningitis. You revise your IV fluid orders for Tyler to ensure that this problem is addressed.

Your disappointment deepens when you think back on how the baby's temperature was measured in the middle of the night and how the trajectory of his illness may have been altered had it been done differently.

Tyler's parents maintain vigil at his bedside throughout the afternoon. He remains lethargic and pale but vital signs are acceptable. You order out for some pizza as you have a feeling that this is going to be a long night. As you sit down to have your first bite of food since breakfast, a nurse enters the lounge to ask you to come see Tyler immediately because he may be having a seizure.

End of Part One

Part Two

As you stride quickly down the hall, she tells you that she had gone in to do her routine assessment and found him to be even more pale and lethargic. His heart rate was 205. Tyler then began to demonstrate tonic extensor arm and leg posturing, his

eyes deviated to the left and then there was clonic twitching of his right arm and leg. As you enter the room, his bedside nurse is repeating his vital signs which are unchanged. He continues to demonstrate increased tone with some clonic jerks of the left arm and leg. He is saturating 86% in room air. You think quickly through the acute management of a seizure, convey some brief orders to his nurse and quickly examine him. You are told that this episode has been now going on for probably five minutes.

Pause to discuss what should be done next.

You assess his airway, breathing and circulation and are satisfied, at least for now. His blood sugar is eight. You decide to order an anticonvulsant appropriate to his age. Oxygen is administered as is 20 mg per kilogram of phenobarbital. You ask to have him moved into the resuscitation room because of the possible complications of the medication you are administering.

You order more blood work considering these developments.

The seizure stops with the phenobarbital but his respiratory drive following the seizure he is unpredictable and he begins to gasp. His circulation is poor and he remains quite tachycardic, so a bolus of saline is given.

You consider the indications for endotracheal intubation, and are quite certain that the time has come. He receives appropriate pre-medication to facilitate this procedure and it is successfully completed on the first attempt.

Blood work done at the time of the seizure becomes available to you. Sodium is now 127. PH 7.43, pCO 21.6 ,P02 122, HCO3 10.6 base excess 11.1. You revise your IV fluid orders again.

Since this result was from blood taken during the seizure, you decide to wait to settle him on the ventilator before repeating it.

You work with the respiratory therapist to decide upon appropriate initial ventilation settings, including PEEP, Inspiratory pressure and I:E ratio. You note that he is requiring 40% FiO2 to keep acceptable saturations.

The blood gas is repeated. His arterial pH is now 7.28, pCO2 35 and pO2 105. Bicarb is 11.3.

You are fairly certain of the cause of this blood gas abnormality, but, as always, you wisely force yourself to ponder the full differential diagnosis of this finding. You are unsatisfied with his circulatory status and give another bolus of saline, hoping that this will help correct his acid-base abnormality. His circulatory status improves slightly but not enough and you give another 20cc/kg of saline, for a total of 60cc/kg overall this evening. You consider the possible risks and benefits of giving

bicarbonate in this case, and decide to go ahead with an appropriate dose for the situation.

In the meantime, you receive the microbiology report from the blood and spinal fluid, noting that they are both growing gram-positive, beta hemolytic diplococci.

Tyler's vital signs, urine output and overall status stabilize with your interventions. You decide to continue maintenance Phenobarbital for him.
Bloodwork in the morning demonstrates normal electrolytes and blood gases. Microbiology reports that the positive CSF and blood cultures are streptococcus agalactiae, sensitive to Ampicillin.

You discuss the case with infectious diseases and PICU colleagues at a regional children's hospital. You are advised that the baby can be switched to Ampicillin alone at high meningitic doses and that given the degree of illness, a repeat LP is recommended prior to discontinuing the antibiotics. The PICU physician has no further suggestions beyond getting an EEG and head imaging, considering the baby's rocky course and the known complications of the disease.

The MRI shows bilateral, frontal watershed ischemic changes.

EEG shos multiple epileptiform discharges despite the Phenobarbital.

He is extubated after 48 hours on the ventilator.

On day 6 of the hospitalization, he has a repeat LP. It shows 792 WBC w/76% neutrophils, 13 RBC, protein 2.5 and glucose 1.5. Gram stain shows scant gram positive cocci. He stays on high dose Ampicillin until criteria are met to discontinue it.

You have been meeting with Tyler's parents regularly throughout the illness and as he is being readied for transfer back to the ward, you prepare yourself to have a discussion with them about Tyler's prognosis and the important aspects of his medical follow-up.

You review what you learned during your wonderful residency academic sessions about breaking bad news to parents, but it doesn't make you any less trepidatious about meeting with them.

Part Three

He is transferred back to the ward and has some difficulties re-establishing feedings. He is gradually weaned from gavage support and is ready to go home, having been successfully taken off of the Phenobarbital.

His hearing assessment 3 months after discharge is fortunately normal. During his developmental follow-up, he does surprisingly well but does demonstrate some subtle asymmetries of tone, with increased reflexes in the legs and a tendency toward thumb adduction and radial grasp in the right hand. Despite this, he walks at 14 months and his ambulation progresses nicely.

You arrange for assessment and follow-up with physiotherapy and occupational therapy.

At 24 months, he is speaking in two word combinations and has an expressive vocabulary of 50-60 words. His tone abnormalities persist and require ongoing therapy and follow-up.

As you reflect upon your experiences with Tyler you are struck by the incredible capacity of babies to get very sick very quickly, and how amazingly well they can recover from such dire circumstances. You are further reminded of the importance of collecting reliable clinical information when assessing potentially ill infants.

You decide to raise the issue of temperature measurement in infants and children at your next department meeting, using Tyler's experiences as an illustrative case.

End of Case

Resources:

1. Bacterial Meningitis, Lancet Infect Dis 2010; 10: 32–42 attached
2. Management of the infant at increased risk for sepsis, Paediatr Child Health Vol 12 No 10 December 2007 attached
3. Fever without source, Pediatr Clin N Am 53 (2006) 167– 194
4. Cochrane Review, Corticosteroids for acute bacterial meningitis attached, optional

Acute bacterial meningitis in infants and children

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Bacterial meningitis continues to be an important cause of mortality and morbidity in neonates and children throughout the world. The introduction of the protein conjugate vaccines against *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis* has changed the epidemiology of bacterial meningitis. Suspected bacterial meningitis is a medical emergency and needs empirical antimicrobial treatment without delay, but recognition of pathogens with increasing resistance to antimicrobial drugs is an important factor in the selection of empirical antimicrobial regimens. At present, strategies to prevent and treat bacterial meningitis are compromised by incomplete understanding of the pathogenesis. Further research on meningitis pathogenesis is thus needed. This Review summarises information on the epidemiology, pathogenesis, new diagnostic methods, empirical antimicrobial regimens, and adjunctive treatment of acute bacterial meningitis in infants and children.

Introduction

Bacterial meningitis, an inflammation of the meninges affecting the pia, arachnoid, and subarachnoid space that happens in response to bacteria and bacterial products, continues to be an important cause of mortality and morbidity in neonates and children.[1–4] However, mortality and morbidity vary by age and geographical location of the patient and the causative organism. Patients at risk for high mortality and morbidity include newborns, those living in low-income countries, and those infected with Gram-negative bacilli and *Streptococcus pneumoniae*.[1–4] Severity of illness on presentation (eg, low score on Glasgow coma scale), infection with antimicrobial-resistant organisms, and incomplete knowledge of the pathogenesis of meningitis are additional factors contributing to mortality and morbidity associated with bacterial meningitis.[1–7]

Suspected bacterial meningitis is a medical emergency; thus, immediate steps must be taken to establish the specific diagnosis, and empirical antimicrobial treatment must be started rapidly. The mortality of untreated bacterial meningitis approaches 100% and, even with optimum treatment, mortality and morbidity might happen. Neurological sequelae are relatively common in survivors of meningitis, particularly after pneumococcal meningitis.[1–6]

Epidemiology

Almost all microbes that are pathogenic to human beings have the potential to cause meningitis, but a relatively small number of pathogens (ie, group B streptococcus, *Escherichia coli*, *Listeria monocytogenes*, *Haemophilus influenzae* type b [Hib], *S pneumoniae*, and *Neisseria meningitidis*) account for most cases of acute bacterial meningitis in neonates and children, although the reasons for this association remain incompletely understood.

The absence of an opsonic or bactericidal antibody is a major risk factor in most cases of meningitis caused by group B streptococcus, *E coli*, Hib, *S pneumoniae*, and *N meningitidis*.[8–12] Age-related incidence of Hib and *N meningitidis* disease is inversely related to prevalence of serum bactericidal activity,[8,10] and the lack of type-specific antibody is a major risk factor for neonatal group B streptococcal disease.[11] Determinations of microbial targets capable of inducing opsonic or bactericidal antibodies and successful vaccination programmes with such targets in infants and children have changed the epidemiology of bacterial meningitis.[13–18] However, microbial targets for opsonic or bactericidal antibodies have not been determined against all pathogens that commonly cause meningitis.

The advancement of vaccine design in enhancing immunogenicity has been shown to be important in preventing meningitis caused by Hib, *S pneumoniae*, and *N meningitidis*. Protein-conjugated capsular polysaccharide vaccines have almost completely eliminated meningitis caused by vaccine serotypes. Routine immunisation in young infants and children with Hib conjugate vaccines has virtually eradicated meningitis due to these organisms in many high-income countries;[13] in the USA, Hib meningitis happens primarily in children that are not immunised and among infants too young to have completed the primary immunisation series.[14] Additionally, introduction of the seven-valent pneumococcal conjugate vaccine (PCV7) has led to a substantial reduction in the incidence of pneumococcal meningitis in infants and children younger than 5 years.[15–17] Use of these protein-conjugated vaccines has also reduced Hib and pneumococcal meningitis among unvaccinated populations through herd immunity. At present, limitations with PCV7 and meningococcal conjugate vaccines include an apparent increase in the incidence of invasive pneumococcal disease, including meningitis caused by non-PCV7 serotypes, such as serotype 19A (a penicillin and third-generation cephalosporin-resistant non-PCV7 serotype), and an apparent decline in bactericidal antibody against *N meningitidis* in infants, requiring a booster immunisation in the second year of life.[17,18]

Pathogenesis

A relatively small number of microbial pathogens has been shown to account for most cases of meningitis in infants and children, but how those pathogens cross the blood–brain barrier and cause meningitis is incompletely

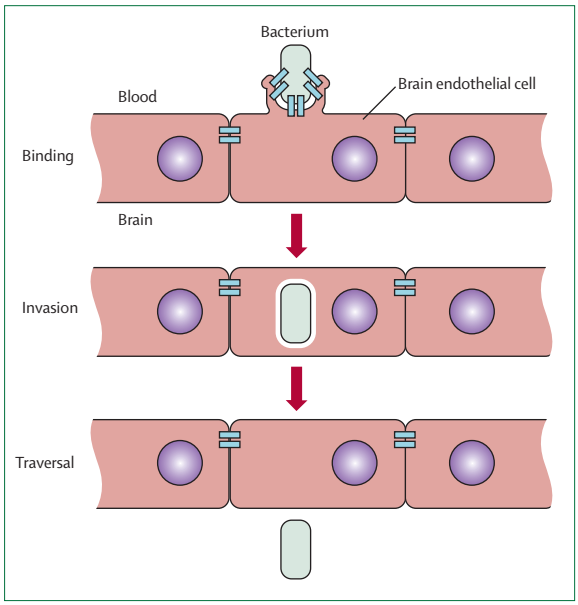

Figure: **Bacterial interaction with the blood–brain barrier, contributing to penetration into the brain**

understood.[7,19] Experimental animal models and human cases of meningitis suggest that *E coli* and group B streptococcus penetrate the brain initially through the cerebral vasculature.[20–23] The blood–brain barrier is a structural and functional barrier that is formed by brain microvascular endothelial cells,[24] which protects the brain from any microbes and toxins circulating in the blood. However, meningitis-causing pathogens, including *E coli*, group B streptococcus, *S pneumoniae*, and *N meningitidis*, have been shown to cross the blood–brain barrier as live bacteria.[7,19,25–29]

Meningitis-causing pathogens cross the blood–brain barrier transcellularly, paracellularly, or by means of infected phagocytes (so-called Trojan horse mechanism).[19] Transcellular traversal of the blood–brain barrier has been shown for most meningitis-causing pathogens in infants and children, including *E coli*, group B streptococcus, and *S pneumoniae* (figure).[7,19,25–28]

Recent studies have shown that microbial traversal of the blood–brain barrier happens via microbial interactions with host receptors (table 1).[7,19,25–29] For example, *E coli* penetration into the brain involves its binding to and invasion of the human brain microvascular endothelial cells (HBMEC) that constitute the blood–brain barrier.[7,19] The *E coli* proteins that contribute to HBMEC binding (ie, FimH and OmpA) do so through interactions with their respective HBMEC receptors, CD48 and endoplasmin (formerly gp96).[30,47–49] Endoplasmin is an endoplasmic reticulum paralogue of heat shock protein 90 that is also present on the surface of HBMEC.[30] In addition, it acts as a cellular receptor for *L monocytogenes* Vip, which is involved in infection of the spleen, liver, and brain of mice.[31] However, endoplasmin also interacts with OmpA, affecting different host signalling molecules.[30,31]

E coli invasion of HBMEC has also been shown to happen through other interactions with host receptors.[7,19,25,50–52] For example, cytotoxic necrotising factor 1 (CNF1) interacts with 40S ribosomal protein subunit A (RPSA) on HBMEC.[32,53] The monomer of RPSA (37 kDa laminin receptor protein) is a ribosome-associated cytoplasmic protein and a precursor of the 67 kDa laminin receptor. It is unclear how the laminin receptor is matured and synthesised from the laminin receptor protein, but the mature monomer is shown to be present on the cell surface and functions as a membrane receptor for the adhesive basement membrane protein laminin.[54] RPSA has also been shown to be a cellular target for various CNS-infecting microorganisms (table 1), including *S pneumoniae*, *N meningitidis*, Hib, dengue virus, adeno-associated virus, Venezuelan equine encephalitis virus, and prion protein.[33–37] The mechanism by which the same receptor is involved in CNS penetration by different organisms remains to be established.

Other meningitis-causing pathogens, such as group B streptococcus and *L monocytogenes*, possess several microbial structures that allow their binding to and invasion of HBMEC. Group B streptococcal binding to HBMEC happens via Lmb (laminin-binding protein), FbsA (fibrinogen-binding protein), pili, and IagA (via lipoteichoic acid anchoring),[22,38,55,56] but whether these structures are unique to meningitis isolates of group B streptococcus is unclear. *L monocytogenes* invasion of HBMEC is mediated by internalin B (InlB).[42] Several HBMEC receptors for InlB have been identified, which include the receptor for the globular head of complement component C1q (gC1q-R) and Met tyrosine kinase,[57,58] but their contributions to *L monocytogenes* invasion of HBMEC remain incompletely understood. For example, InlB does not compete for the same interaction site on Met tyrosine kinase as the natural ligand, hepatocyte growth factor.[59] gC1q-R is also the HBMEC receptor for *Plasmodium falciparum*-infected erythrocytes (table 1).[41] *L monocytogenes* penetration into the CNS has been attributed to transmigration of *L monocytogenes*-infected monocytes and myeloid cells across the blood–brain barrier,[60,61] although the main route of *L monocytogenes* penetration into the CNS still needs to be determined.

S pneumoniae crosses the blood–brain barrier partly through interaction between cell-wall phosphorylcholine and the platelet-activating factor receptor (PAFR), as shown by partial inhibition of pneumococcal invasion of HBMEC by a PAFR antagonist,[28,39] and delayed translocation of pneumococci from the lung to the blood and from the blood to the cerebrospinal fluid (CSF) in PAFR-knockout mice.[62] PAFR has also been shown to interact with Hib (table 1),[40] but its contribution to Hib traversal of the blood–brain barrier is unclear.

N meningitidis invasion of HBMEC is mediated by the outer membrane protein Opc binding to fibronectin,

	Ligands	References
Endoplasmin		
Escherichia coli	OmpA	30
Listeria monocytogenes	Vip	31
37 kDa laminin receptor protein		
Escherichia coli	CNF1	32
Neisseria meningitidis	PilQ/PorA	33
Streptococcus pneumoniae	CbpA	33
Hib	Omp2	33
Prion protein	..	34
Viruses (sindbis, dengue, tick-borne encephalitis, Venezuelan equine encephalitis, adeno-associated)	..	35–38
Platelet-activating factor receptor		
Streptococcus pneumoniae	Phosphorylcholine	39
Hib	Phosphorylcholine	40
gC1q-R		
Plasmodium falciparum	Infected erythrocytes	41
Listeria monocytogenes	InlB	42
CD46		
Neisseria meningitidis	Pili	43
Measles	Haemagglutinin	44
Adenovirus	Ad35 knob	45
Human herpesvirus 6	Glycoprotein H	46

CNF1=cytotoxic necrotising factor 1. gC1q-R=receptor for the globular head of complement component C1q. Hib=*Haemophilus influenzae* type b.

Table 1: **Blood–brain barrier receptors used by CNS-infecting microorganisms**

thereby anchoring the bacteria to the integrin $\alpha_5\beta_1$ receptor on the cell surface.[29] In addition, *N meningitidis* pili bind to CD46 on HBMEC,[43] and lipo-oligosaccharides have been shown to contribute to a high-degree of bacteraemia and subsequent penetration into the CNS.[63] CD46 has also shown to be a receptor for measles, adenovirus, and human herpesvirus 6 (table 1).[44–46]

The involvement of host receptors and signal-transduction pathways in the microbial invasion of the blood–brain barrier might provide a new way to prevent and treat meningitis by the targeting of such host receptors or signalling molecules.[7,19,64–69] A proof-of-concept study has shown that down-modulation of the HBMEC receptor for CNF1 (RPSA) and blockade or inhibition of host molecules involved in *E coli* invasion of HBMEC (eg, cytosolic phospholipase A2α) were efficient in preventing *E coli* penetration into the brain.[19,32,53,64] Recent studies suggest that this concept is also relevant to other meningitis-causing pathogens,[19,33,64] and could indeed be used to prevent or treat meningitis.

Of note, the mechanisms involved in microbial invasion of the blood–brain barrier differ from those involved in the release of cytokines and chemokines in response to meningitis-causing pathogens. For example, interleukin-8 secretion in response to *E coli* strain K1 happens in HBMEC, but not in non-brain endothelial cells (eg, human umbilical vein endothelial cells). However, *E coli* proteins involved in binding to and invasion of HBMEC did not affect the release of interleukin 8 from HBMEC.[70] Similar findings were seen for a group B streptococcus Lmb mutant, which was defective for the invasion of HBMEC, but induced equal concentrations of interleukin 8 compared with the parent strain.[38] In addition, *N meningitidis* invasion of HBMEC has been shown to involve c-Jun kinases 1 and 2, although the release of interleukins 6 and 8 from HBMEC in response to bacterial invasion involves the p38 mitogen-activated protein kinase pathway.[68] These findings suggest that targets for prevention of bacterial penetration into the brain differ from those involved in CNS inflammation associated with meningitis.

Diagnosis

Clinical findings

Bacterial meningitis requires early diagnosis and empirical antimicrobial treatment. However, the symptoms and signs depend on the age of the child, the duration of illness, and the host response to infection. The clinical features of bacterial meningitis in infants and children can be subtle, variable, non-specific, or even absent. In infants, they might include fever, hypothermia, lethargy, irritability, poor feeding, vomiting, diarrhoea, respiratory distress, seizures, or bulging fontanelles. In a study of neonatal meningitis, fever or hypothermia was noted in 62% of cases.[71] In older children, clinical features might include fever, headaches, photophobia, nausea, vomiting, confusion, lethargy, or irritability.

Other signs of bacterial meningitis on physical examination include Kernig's sign (flexing the hip and extending the knee to elicit pain in the back and legs), Brudzinski's sign (passive flexion of the neck elicits flexion of the hips), focal neurological findings, and increased intracranial pressure. Signs of meningeal irritation are present in 75% of children with bacterial meningitis at the time of presentation.[72] By contrast, in a retrospective review of 326 children presenting to a paediatric emergency department in the Netherlands between 1988 and 1998 with signs of meningeal irritation, 30% had bacterial meningitis.[73] Absence of meningeal irritation in children with bacterial meningitis was substantially more common in those younger than 12 months.[74] The constellation of systemic hypertension, bradycardia, and respiratory depression (Cushing's triad) is a late sign of increased intracranial pressure.

Laboratory findings

CSF examination is of paramount importance for the diagnosis of all forms of meningitis (table 2). Patients with suspected meningitis should receive a lumbar puncture after a mass lesion has been ruled out on clinical grounds or by CT scan of the head, and if there is no cardiopulmonary compromise. Evidence for mass

lesions will include focal neurological signs and evidence of increased intracranial pressure, and CSF pressure should be recorded during the lumbar puncture.

A Gram stain of CSF will show whether bacteria are present, and a positive Gram stain shows bacterial counts higher than 1×10³ cells per mL in CSF.[75–78] Gram stain is positive in about 90% of children with pneumococcal meningitis, about 80% of children with meningococcal meningitis, half of patients with Gram-negative bacillary meningitis, and a third of patients with listeria meningitis.[75–78] Cytospin centrifugation increases the chances of detecting organisms in Gram-stained CSF.[79] CSF cell count and differential, and concentrations of protein and glucose are helpful in the differential diagnosis of various forms of meningitis (table 2). A low CSF white blood cell count with positive Gram stain is a risk factor for an unfavourable outcome.[6]

CSF culture can be negative in children who receive antibiotic treatment before CSF examination. For example, complete sterilisation of *N meningitidis* from CSF happened within 2 h of giving a parenteral third-generation cephalosporin and the beginning of sterilisation of *S pneumoniae* from CSF by 4 h into treatment.[80] In such children, increased CSF white blood cell counts and increased CSF protein concentration are usually sufficient to establish the diagnosis of bacterial meningitis. Blood cultures or non-culture diagnostic tests might help in identifying the infecting pathogen.

	Opening pressure (cm H_2O)	White blood cells ($\times10^6$ cells per L)	Glucose (mg/dL)	Protein (mg/dL)
Bacteria*				
Common	>20	>1000	<10	>100
Less common	<20	5–1000	10–45	50–100
Mycobacterium tuberculosis				
Common	>20	100–500	10–45	>100
Less common	<20	5–100	<10	50–100
Borrelia burgdorferi				
Common	<20	100–500	10–45	50–150
Less common	<20	5–100	<10	>150
Treponema pallidum				
Common	<20	5–500	10–45	50–150
Less common	<20	>500	<10	>150
Fungi				
Common	Variable	5–500	10–45	>100
Less common	Variable	>500	<10	50–100
Viruses				
Common	<20	5–500	Normal	50–100
Less common	<20	>500	10–45	>100

*Group B streptococci, *Escherichia coli, Listeria monocytogenes, Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae* type b.

Table 2: **Likely pathogens for CNS infections on the basis of cerebrospinal fluid analysis**

Non-culture methods

Non-culture tests should be considered for patients who need earlier identification of pathogens or have previously received antibiotics, or whose initial CSF Gram stain is negative with negative culture at 72 h incubation. Such tests include latex agglutination, PCR, loop-mediated isothermal amplification method, microarray or biochip, and immunochromatography (table 3).

Latex agglutination uses latex beads adsorbed with microbe-specific antibodies. In the presence of homologous antigen there is visible agglutination of the antibody-coated latex beads. Latex agglutination assays have been sensitive towards Hib antigen, but less sensitive with *N meningitidis* antigen.[78,81] In the multicentre pneumococcal meningitis surveillance study, latex agglutination was positive in 49 (66%) of 74 CSF samples that grew *S pneumoniae*, and in four of 14 CSF samples that were culture-negative.[6]

The use of standard or sequential-multiplex PCR has been shown to be useful in identification of infecting pathogens in patients who have previously received antibiotics or in resource-poor settings.[82–87] Multiplex real-time PCR or broad-range PCR aimed at the 16S ribosomal RNA gene of eubacteria is promising for the detection of pathogens from CSF. The detection rate was substantially higher with PCR than with cultures in patients who had previously received antibiotics.[82] However, the limit of detection differs between assays. Real-time PCR has been shown to detect as few as two copies of *E coli*, *N meningitidis*, and *S pneumoniae*, 16 copies of *L monocytogenes*, and 28 copies of group B streptococcus,[82] whereas the sensitivity for broad-range 16S ribosomal DNA PCR was about 10–200 organisms per mL CSF.[84,85] The time needed for the whole process from DNA extraction to the end of real-time PCR was 1·5 h,[82] an attractive timeframe for its application in clinical practice.

A Gram-stain-specific probe-based real-time PCR using 16S ribosomal RNA has been shown to allow simultaneous detection and discrimination of clinically relevant Gram-positive and Gram-negative bacteria directly from blood samples,[86] which might provide more rapid and accurate diagnosis of bacterial infection in infants and children. In addition, sequential PCR-based serotyping of *S pneumoniae* using serotype-specific primers could improve ascertainment of pneumococcal serotype distribution in settings in which prior use of antibiotics is high.[87]

A recently developed nucleic-acid amplification technique, loop-mediated isothermal amplification, which amplifies DNA under isothermal conditions (63°C), is a promising tool, particularly in resource-poor settings, because it does not need thermocycling apparatus and the results can be read with the naked eye (based on turbidity or colour development by SYBR Green dye for

	Clinical application	Comments
Latex agglutination[78,81]	Yes	Sensitive with *Haemophilus influenzae* type b, but less sensitive with *Neisseria meningitidis*
PCR[82-87]	Not yet	Need to develop specific and broad targets or primers
Loop-mediated isothermal amplification[88,89]	Not yet	Does not require thermocycling apparatus; potentially useful in resource-poor settings
Microarray or biochip[90–92]	Not yet	Requires a suitable biochip
Immunochromatography[93]	Not yet	Highly sensitive for *Streptococcus pneumoniae*

Table 3: **Non-culture diagnostic tests for identification of pathogens for meningitis**

staining nucleic acids).[88,89] The assay detected ten or more copies of *S pneumoniae* in oral mucosa swab samples,[88] but its use in the diagnosis of bacterial meningitis has not been tested.

Identification of pathogens by use of a microarray or biochip involves extraction of genomic DNA from CSF, amplification of targeted DNA, and hybridisation of labelled DNA with oligonucleotide probes (pathogen-specific or virulence genes) immobilised on a microarray.[90–92] However, its usefulness in clinical practice has not been shown.

A rapid immunochromatographic test for *S pneumoniae* was evaluated in 122 children with pneumococcal meningitis.[93] Compared with CSF culture (sensitivity of 71%) and latex agglutination (86%), immunochromatography was 100% sensitive for the diagnosis of pneumococcal meningitis, suggesting that immunochromatography might be useful in the diagnosis of pneumococcal meningitis.

Bacterial meningitis score

The ability to distinguish between bacterial and non-bacterial aseptic meningitis in infants and children in the emergency department could contribute to limiting hospital admissions or unnecessary use of antibiotics. The bacterial meningitis score has been developed for assessing infants and children with meningitis, and outpatient management might be considered for children who had pleocytosis (7×10^6 cells per L or more) and none of the following five criteria on presentation: history of a seizure with the illness, blood neutrophil count of at least 10×10^9 cells per L, positive CSF Gram stain, CSF protein of at least 80 mg/dL, or CSF neutrophil count of at least 1×10^9 cells per L. However, this proposed diagnostic tool only achieved 95% sensitivity.[94,95] For example, five patients with bacterial meningitis who had pleocytosis were found to have a bacterial meningitis score that indicated low risk, and 5·5% of meningitis cases happened without pleocytosis.[95] Because bacterial meningitis is defined as inflammation that happens in response to bacteria and bacterial products, patients with CSF culture positivity without pleocytosis or increased CSF protein concentrations are presumably representative of the early stages of bacterial meningitis.[7]

Antimicrobial treatment

Eradication of the infecting organism from the CSF is entirely dependent on antibiotics, and bactericidal antibiotics should be administered intravenously at the highest clinically validated doses to patients with suspected bacterial meningitis.[96,97] Several retrospective and prospective studies showed that delay in antibiotic treatment was associated with adverse outcomes.[98–101] In patients with suspected bacterial meningitis for whom immediate lumbar puncture is delayed due to pending brain imaging study or the presence of disseminated intravascular coagulation, blood cultures must be obtained and antimicrobial treatment should be initiated immediately. Selection of empirical antimicrobial regimens is designed to cover the likely pathogens, based on age of the patient and specific risk factors (table 4), with modifications if CSF Gram stain is positive.

The ability of an antimicrobial agent to penetrate the blood–brain barrier is the most important factor that determines whether efficient bacterial killing happens in the CSF. Blood–brain-barrier penetration is affected by lipophilic property, molecular weight, and protein-binding ability of drugs, inflammation of the meninges, and efflux transporters.[102,103] Lipophilic agents (ie, fluoroquinolones and rifampicin) penetrate relatively well into the CSF even if the meninges are not inflamed, whereas hydrophilic agents (ie, β-lactams and vancomycin) have decreased penetration into CSF in the absence of meningeal inflammation.[102–104]

An important factor in the choice of empirical antimicrobial agents is the emergence of antimicrobial-resistant organisms, including *S pneumoniae* that is resistant to penicillin or third-generation cephalosporins, and Gram-negative bacilli that are resistant to many β-lactam drugs. For example, the prevalence of *S pneumoniae* strains that are relatively resistant to penicillin (minimum inhibitory concentration [MIC] 0·1–1·0 μg/mL) or highly resistant to penicillin (MIC greater than 1·0 μg/mL) is increasing, and many of the penicillin-resistant pneumococci have reduced susceptibility to third-generation cephalosporins (ie, cefotaxime and ceftriaxone).[96,97] Treatment failures in bacterial meningitis as a result of multiresistant organisms have been reported.[105] Therefore, empirical treatment for patients with bacterial meningitis in areas where resistant *S pneumoniae* strains are prevalent must include the addition of vancomycin (panel). However, penetration of vancomycin into the CSF can be reduced in the absence of meningeal inflammation and also in patients who receive adjunctive dexamethasone treatment.

Treatment of patients at risk of infection with *L monocytogenes* must include a synergistic regimen containing ampicillin and an aminoglycoside (eg, gentamicin), whereas a regimen for Gram-negative bacilli with a high likelihood of resistance (eg, nosocomial meningitis) should include an aminoglycoside (eg,

amikacin) plus a third-generation or fourth-generation cephalosporin, or meropenem. The penetration of intravenously given aminoglycosides into the CSF remains variable or poor even in the presence of meningeal inflammation, and thus cannot be used as monotherapy for bacterial meningitis.[106]

Antibacterial killing activity in CSF also depends on the bacterial burden at the start of treatment. The MIC and minimum bactericidal concentration are established in laboratories by use of bacterial inoculum size of 10^4–10^5 organisms per mL. However, some patients with bacterial meningitis (eg, caused by group B streptococcus and *S pneumoniae*) who have many organisms on CSF Gram stain are likely to yield 10^7–10^8 organisms per mL,[6,76] and MIC values can be 100–1000-times higher than would normally be expected. For example, MICs of β-lactam antibiotics, including penicillin against group B streptococcus, were increased 1000 times when the inoculum size increased from 10^4 to 10^8 organisms per mL.[107] Careful monitoring of the response to antimicrobial treatment is therefore warranted for patients with bacterial meningitis who have high bacterial burden on the basis of initial CSF Gram stain.

Antimicrobial susceptibility patterns must be established for all organisms isolated from the CSF. For example, group B streptococcus is commonly responsible for neonatal bacterial meningitis, and has been shown to be uniformly susceptible to β-lactam antibiotics (eg, penicillin MIC 0·1 μg/mL or less), and thus penicillin is at present the drug of choice for invasive group B streptococcal infection including meningitis.[108] However, studies have reported isolates of group B streptococcus with penicillin MICs of 0·12–1·0 μg/mL that had mutations in the target penicillin-binding proteins similar to the mechanisms involved in penicillin-resistant *S pneumoniae*.[109,110] The optimum empirical regimen for meningitis caused by penicillin non-susceptible group B streptococci that includes third-generation cephalosporins has not been established.

Similarly, penicillin has been the standard treatment for meningococcal meningitis, but penicillin resistance has evolved, with an implication of treatment failures.[111,112] A recent study in Spain reported an increased incidence in penicillin non-susceptible strains of *N meningitidis* (eg, MICs 0·1–0·5 μg/mL) from 9·1% in 1986 to 71·4% in 1997.[113] By contrast, relative resistance to penicillin (MIC 0·1 μg/mL) has been shown to occur in 3–4% of the meningococcal isolates in the USA and in 2% of the 137 isolates recovered between 2000 and 2006 from equatorial sub-Saharan Africa (the so-called meningitis belt).[114,115] These findings support the use of a third-generation cephalosporin for meningococcal meningitis in areas where penicillin resistance is prevalent, at least until penicillin susceptibility is known.

The potential roles of newer β-lactam antibiotics (meropenem, cefepime, ertapenem), recently developed quinolones (moxifloxacin, gatifloxacin, gemifloxacin, garenoxacin), and lipopeptides (daptomycin) in the treatment of meningitis caused by resistant bacteria have been shown in animal models of experimental meningitis.[102,106,116–124] For example, gatifloxacin was as effective as the combination of ceftriaxone and vancomycin against a highly cephalosporin-resistant pneumococcal strain in an experimental meningitis model.[120] Moxifloxacin and garenoxacin had CSF bacterial killing rates that exceeded those found with the combination of ceftriaxone and vancomycin against experimental meningitis caused by vancomycin-tolerant *S pneumoniae*.[124] However, clinical effectiveness of these newer antimicrobial drugs as monotherapy in the treatment of meningitis caused by penicillin non-susceptible isolates of *S pneumoniae* has not been established, but they might be useful if other drugs cannot be used, and continued monitoring of antimicrobial susceptibility patterns, including newer agents, is thus important. Of interest, dexamethasone did not substantially affect the penetration of gemifloxacin and moxifloxacin into the CSF.[119,121] Fluoroquinolones are not recommended for use in children younger than 18 years because of concerns about their effects on growing cartilage in experimental animals.[125]

	Likely pathogens
<1 month	Group B streptococci, *Escherichia coli*, *Listeria monocytogenes* (neonatal pathogens)
1–3 months	
No immunisation or one dose of primary immunisation	*Neonatal pathogens*, *S pneumoniae*, *N meningitidis*, Hib
3–6 months	
No immunisation	*S pneumoniae*, *N meningitidis*, Hib
At least two doses of primary immunisation (with Hib-Omp vaccine)	*S pneumoniae*, *N meningitidis*
>7 months to 5 years	
No immunisation	*S pneumoniae*, *N meningitidis*, Hib
Primary immunisation completed	*S pneumoniae* (non-PCV serotypes), *N meningitidis*
6–21 years	*S pneumoniae*, *N meningitidis*

Risk factors for specific pathogens are as follows: cerebrospinal fluid leak, cochlear implant, nephrotic syndrome (*Streptococcus pneumoniae*); terminal complement deficiencies, freshmen living in dormitories, outbreaks (*Neisseria meningitidis*); asplenia, sickle-cell disease, HIV infection, otitis, sinusitis (*S pneumoniae, Haemophilus influenzae* type b [Hib]); immunodeficiency, diabetes mellitus (*S pneumoniae, Listeria monocytogenes*). PCV=pneumococcal conjugate vaccine.

Table 4: **Likely pathogens for meningitis based on age and immunisation status**

Adjunctive treatment

Neurological sequelae are common in survivors of meningitis, and include hearing loss, cognitive impairment, and developmental delay. For example, the Metropolitan Atlanta Developmental Disabilities Surveillance Program in 1991 identified bacterial meningitis as the leading postnatal cause of developmental disabilities, including cerebral palsy and mental retardation.[126] Hearing loss happens in 22–30% of survivors of pneumococcal meningitis compared to 1–8% after meningococcal meningitis.[6,96,97,127]

Panel: **Empirical antimicrobial regimen for treatment of bacterial meningitis, by age**

Less than 1 month
Ampicillin (50–100 mg/kg every 6 h) plus gentamicin (2·5 mg/kg every 8 h), or cefotaxime (50 mg/kg every 6–8 h) can be used in the setting of suspected Gram-negative bacilli

1–3 months
Ampicillin (50–100 mg/kg every 6 h) plus cefotaxime (75 mg/kg every 6–8 h) or ceftriaxone (50 mg/kg every 12 h), or vancomycin (15 mg/kg every 6 h) can be added in the setting of suspected pneumococcal meningitis (eg, positive Gram stain)

3 months to 21 years
Cefotaxime (75 mg/kg every 6–8 h, up to a maximum of 12 g daily) or ceftriaxone (50 mg/kg every 12 h, up to a maximum of 4 g daily) plus vancomycin (15 mg/kg every 6 h, up to a maximum 1 g per dose), or rifampicin (10 mg/kg every 12 h, up to a maximum of 600 mg daily) can be added in the setting of administration of dexamethasone

In a 2007 Cochrane review, adjunctive treatment with dexamethasone was associated with lower case mortality, and lower rates of severe hearing loss and long-term neurological sequelae.[128] The beneficial effect of adjunctive dexamethasone treatment was evident in adults with bacterial meningitis. Dexamethasone given shortly before or when antibiotics were first given has been shown to reduce the rate of hearing loss in children with Hib meningitis, but its beneficial effects on hearing and other neurological sequelae are not as clear against meningitis caused by other organisms.[6,129] The American Academy of Pediatrics Committee on Infectious Diseases suggests that dexamethasone treatment might be considered for infants and children older than 6 weeks with pneumococcal meningitis after considering the potential benefits and possible risks.[130]

The widespread use of dexamethasone in children with bacterial meningitis needs careful monitoring of clinical (eg, fever curve, resolution of symptoms and signs) and bacteriological responses to antimicrobial treatment, particularly for patients with meningitis caused by pneumococci that are resistant to third-generation antibiotics, in whom bacteriological killing in the CSF depends on vancomycin. Monitoring of the clinical response (eg, fever curve) can be complicated by the use of dexamethasone. For example, secondary fever (recurrence of fever after at least 24 h without fever) happens more commonly in patients treated with dexamethasone than in those who are not (52% *vs* 24%, p=0·0009).[6] In addition, concomitant giving dexamethasone and vancomycin can reduce penetration of vancomycin into the CSF by virtue of the anti-inflammatory activity of dexamethasone, resulting in treatment failure.[131] However, CSF bactericidal activity has been shown in children who have meningitis due to cephalosporin-resistant pneumococci, and such cases should be treated with dexamethasone as well as vancomycin and ceftriaxone.[132]

Another issue with adjunctive dexamethasone treatment is the possibility of neuronal injury, including hippocampal apoptosis in experimental animals with pneumococcal and *E coli* meningitis who received dexamethasone.[133,134] Long-term follow-up studies are thus needed to address the effect of dexamethasone treatment on any cognitive and neuropsychological outcomes in patients with bacterial meningitis.

A recent multicentre, double-blind randomised study in six Latin American countries showed that adjunctive treatment with oral glycerol (1·5 g/kg every 6 h for 48 h) prevents severe neurological sequelae in childhood meningitis (odds ratio 0·31; 95% CI 0·31–0·76) compared with placebo.[135] Glycerol is a hyperosmolar agent, and because of its safety, wide availability, low cost, and oral administration, its use as adjunctive treatment in children with bacterial meningitis, particularly in resource-limited settings, is promising.

Future challenges

Bacterial meningitis continues to be an important cause of mortality and morbidity throughout the world, particularly for those infections in newborns, individuals living in low-income countries, and infections caused by antimicrobial-resistant pathogens (eg, cephalosporin-resistant pneumococcus) or organisms that are difficult to treat (eg, multi-resistant Gram-negative bacilli). Success with the protein-conjugate Hib and *S pneumococcus* PCV vaccines in the prevention of meningitis shows that identification of conserved targets for opsonic or bactericidal antibodies is likely to enhance the development of effective vaccination programmes for the prevention of meningitis caused by *N meningitidis* and other meningitis-causing bacteria. Advances in microbial genome sequencing and functional genomic approaches are likely to be beneficial in the identification of such microbial targets.

Emergence of antimicrobial-resistant bacteria presents a constant challenge to the development of new bactericidal antibiotics for the treatment of bacterial meningitis. Another important consideration for the treatment of bacterial meningitis is the substantial morbidity in survivors of meningitis; effective strategies to prevent morbidity are lacking at present, partly because of our incomplete knowledge on the pathogenesis of neurological sequelae associated with bacterial meningitis.

New information available on the pathogenesis of meningitis is likely to be useful for the prevention and treatment of bacterial meningitis. Most meningitis-causing pathogens cross the blood–brain barrier, involving specific interactions of microbial structures

Search strategy and selection criteria

The information for this Review was identified by searches of Medline in June, 2009 (date limits January, 2000, to June, 2009), with the following search terms (alone and in combination): "neonatal bacterial meningitis", "bacterial meningitis in infants and children", "pathogenesis of bacterial meningitis", "microbial invasion and/or traversal of the blood–brain barrier", "diagnosis of bacterial meningitis", "treatment of bacterial meningitis", and "adjunct therapy of bacterial meningitis", with the emphasis on new information reported since 2000. Earlier original articles were also included, which formed the foundation for subsequent studies. Only papers published in English were considered.

with the host receptors, and eliciting host signalling molecules. Blockade or inhibition of such host receptors or signalling molecules is efficient in preventing microbial traversal of the blood–brain barrier, and this host-based approach presents a new approach in our strategies to prevent and treat bacterial meningitis.

Conflicts of interest

I declare that I have no conflicts of interest.

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Management of the infant at increased risk for sepsis

Canadian Paediatric Society

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Neonatal sepsis continues to cause a significant proportion of perinatal mortality and long-term morbidity in the term and preterm infant population. The most common single organism that causes early-onset neonatal sepsis is the group B streptococcus (GBS or *Streptococcus agalactiae*) (1). Invasive early-onset GBS disease has an incidence of approximately two per 1000 live-born infants in the absence of intrapartum antibiotic prophylaxis (IAP) (2,3), with a case-fatality rate of between 2% and 13% in recent studies (4-6). Therefore, preventive strategies have been promoted and recently endorsed by the Society of Obstetricians and Gynaecologists of Canada (7). It has been demonstrated that the administration of intravenous penicillin at least 4 h before delivery to mothers colonized with GBS is highly effective in preventing perinatal transmission and early-onset invasive infection in the newborn (8). The recommendations are to screen all mothers with rectovaginal cultures at 35 to 37 weeks, and treat those with positive cultures for GBS at the time they present in labour. This strategy leads to as many as 22% of all mothers in labour at term being treated with IAP to prevent disease in 0.2% of infants and prevent mortality in 0.01% of infants (9). In the United Kingdom, it was calculated that it would require 24,000 antepartum cultures and 7000 women in labour treated with antibiotics to prevent one neonatal death (10). As a consequence, other authorities have developed different recommendations, questioning whether routine IAP is an appropriate use of resources (10,11), and whether the pressure exerted for the development of bacterial resistance is justified. In Canada, the current incidence of invasive neonatal GBS disease is uncertain because there is no centralized or mandatory reporting system.

PURPOSE OF THE STATEMENT

The aim of the present statement is to develop evidence-based practice guidelines answering the following question: How should an infant be monitored, investigated and treated given the presence of clinical signs of sepsis, the GBS culture status of the mother (positive, negative or unknown), the treatment status of the mother (completed, incomplete or no IAP), and the presence or absence of maternal risk factors for neonatal sepsis?

METHODS OF STATEMENT DEVELOPMENT

A search was carried out in MEDLINE and the Cochrane library, and last updated in January 2006. The MEDLINE search terms were '*Streptococcus agalactiae*' and 'newborn'. The hierarchy of evidence from the Centre for Evidence-Based Medicine (United Kingdom) was applied and, for this statement, the levels of evidence for treatment, prognosis and diagnosis were used (www.cebm.net, click on the EBM Tools tab or www.cebm.net/levels_of_evidence.asp#levels).

DEFINITIONS

Limited diagnostic evaluation

Limited diagnostic evaluation consists of a complete blood count (CBC), and observation of vital signs every 4 h for a period of 24 h. The newborn can be cared for and observed in the mother's postpartum room. If the CBC shows a low total white blood cell (WBC) count of less than 5.0×10^9/L, then the risk of sepsis is substantially increased and a full diagnostic evaluation and initiation of therapy would usually be indicated.

Full diagnostic evaluation

Full diagnostic evaluation consists of a CBC, blood culture and lumbar puncture (LP); a chest x-ray should be obtained if respiratory difficulties are present. LP can be deferred in unstable infants, and performed later to ascertain the presence of hypoglycorrhachia or pleocytosis. Infants whose only sign of sepsis is respiratory distress may also be considered for deferment of LP if close follow-up can be ensured.

THE UNWELL INFANT

The initial signs of sepsis may be subtle, and may include temperature instability, tachycardia, poor peripheral perfusion and respiratory distress. Because the progression of invasive disease is very rapid, any infant with clinical signs suggestive of infection should be treated immediately following a prompt full diagnostic evaluation; delay between presentation and therapy increases the risk of a poor outcome (12) (evidence level 2b). There is no clear distinction in the clinical signs present when the infant has GBS sepsis compared with any other invasive organism.

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Table 1
Empirical therapy for infants with positive cerebrospinal fluid (CSF) evaluation

CSF findings	Most common organisms	Suggested expectant antimicrobials for early-onset meningitis
Gram-positive cocci	Group B streptococci, less commonly: *Staphylococcus* species or enterococci	Ampicillin or penicillin plus gentamicin
Gram-positive rods	*Listeria monocytogenes*	Ampicillin plus gentamicin
Gram-negative rods	*Escherichia coli,* less commonly: *Klebsiella*, *Pseudomonas* and *Citrobacter*	Cefotaxime plus gentamicin
Gram-negative cocci	Uncommon	Cefotaxime
Pleocytosis, or other findings strongly suggestive of meningitis, but Gram stain-negative, or too unstable to have an LP	Any of the above are possible	Ampicillin plus gentamicin

LP Lumbar puncture. Source: Canadian Paediatric Society, 2007

Although IAP with a penicillin dramatically reduces the frequency of early-onset invasive GBS disease, it does not affect the frequency of sepsis caused by other organisms (1,13) (evidence level 2b). Of note, invasive GBS can still occur in infants of mothers who have had a negative screening culture at 35 to 37 weeks; now that IAP is widespread and effective, the majority of the remaining infants with invasive GBS are those whose maternal cultures were negative (14), but who became colonized between screening and delivery (evidence level 2b). Also, invasive GBS disease is still possible, even if very rare, in mothers who received adequate IAP (15) (evidence level 4). Thus, neither the maternal screening history nor intrapartum exposure to antibiotics should affect the approach to the management of the infant with clinical signs of sepsis (recommendation category B). Therefore, prospective therapy, while awaiting culture results, should cover the most common bacteria: GBS, other streptococci, *Escherichia coli*, other Gram-negative organisms and *Listeria monocytogenes*.

An infant with signs of sepsis does not require confirmatory tests other than obtaining cultures before commencing therapy, because no other tests have an adequately high negative predictive value to avoid therapy (evidence level 2a). In particular, a normal WBC count or differential should not prevent treatment in such an infant because the negative likelihood ratio of a normal CBC is approximately 0.7 (recommendation grade B) (16).

Empirical therapy

There are no good prospective studies to indicate optimal choice of therapy in the newborn infant with possible sepsis (17), but ampicillin and gentamicin are usually appropriate based on the usual susceptibilities of the predominant organisms causing early-onset sepsis (evidence level 4). Infants with a positive cerebrospinal fluid (CSF) evaluation or with clinical signs of meningitis if the LP has been deferred, should be treated with antibiotics which both penetrate the CSF and are active against the likely organisms (Table 1). If there is information from the maternal history suggesting an organism that is unlikely to respond to these antibiotics, empirical therapy should be adjusted appropriately. Blood cultures using modern automated systems are almost always positive by 48 h (18). Therefore, if the laboratory results and clinical course do not indicate bacterial infection, therapy may be discontinued after 48 h. The majority of antibiotic courses are given to infants who eventually prove not to have had sepsis; strategies for further reduction of the duration of antibiotic therapy in such infants should be considered. For example, because gentamicin is usually now given once per day in the full-term infant, and ampicillin is given every 12 h, the initial antibiotic order could be to give ampicillin for four doses every 12 h and gentamicin for two doses every 24 h, followed by reassessment after verification of culture results at 48 h, and reordering the antibiotics in case of positive cultures (or ongoing signs of sepsis).

WELL-APPEARING INFANT OF A GBS-POSITIVE MOTHER, WHO RECEIVED IAP MORE THAN 4 H BEFORE DELIVERY

IAP with a penicillin for least 4 h is highly effective at eradicating GBS transmission (19), and thus preventing the majority of invasive neonatal GBS disease (evidence level 1b) (20). Therefore, if a GBS-positive woman receives intrapartum antibiotics for at least 4 h before delivery and if the newborn appears healthy and is more than 35 weeks gestational age, the newborn requires no therapy for prevention of early-onset GBS (recommendation grade A).

If the baby remains well at 24 h of age and is otherwise eligible for discharge at this time, early discharge can be contemplated provided the caregiver knows the appropriate resources in the community for accessing health care and is able to transport the baby immediately to a health care facility if clinical signs of sepsis develop.

There is insufficient information regarding the efficacy of alternative antibiotics (used when the mother is at risk of anaphylaxis from penicillin). Such infants should be managed as if the mother received incomplete IAP (next heading) until further data are available.

WELL-APPEARING INFANT OF A GBS-POSITIVE MOTHER WHO RECEIVED IAP LESS THAN 4 H BEFORE DELIVERY OR NOT AT ALL

The risk of invasive early-onset GBS disease in an infant whose mother is GBS-positive and does not receive IAP is approximately 1% (21). Only one-quarter of these babies are asymptomatic at birth. This risk of significant disease probably does not justify routine empirical treatment in these circumstances, and careful observation with treatment at the first clinical sign of infection appears to be reasonable. Ninety-five per cent of infants with early-onset GBS infection present with clinical signs within 24 h (22) (either temperature instability, tachycardia, poor peripheral perfusion, respiratory distress or abnormal CBC). Four per cent of infected infants present between 24 h and 48 h of age, with only 1% developing signs after 48 h of age. Thus, prolonging hospitalization from 24 h to 48 h would require the observation of more than 2000 infants to detect each case of invasive infection. Therefore, if careful assessment of the infant at 24 h confirms that they remain well, discharge at that time may well be appropriate as long as adequate patient education and follow-up are ensured.

The use of the CBC is sometimes promoted for determining risk, both for GBS and for other organisms, among infants who are at elevated risk but appear well. However, the positive predictive value of an abnormal CBC is low in the newborn and it is, therefore, uncertain how to proceed when an infant is clinically well but has an abnormal CBC; unfortunately, most studies investigating the usefulness of the CBC have not been confined to well-appearing infants and, therefore, their usefulness in this specific situation is somewhat conjectural. One study (23) confined to well-appearing term infants showed a positive predictive value of 1.5% of an 'abnormal' CBC (total WBC of 5.0×10^9/L or lower, or 30×10^9/L or greater, or an absolute polymorphonuclear cell count of less than 1.5×10^9/L or an immature to mature polymorphonuclear cell ratio greater than 0.2) in identifying the development of 'clinical sepsis' in 1665 healthy term infants who were at risk; of note, none of these infants developed a positive blood culture (evidence level 2b).

Several scoring systems have been developed for analyzing CBC results (24), and all involve analysis of the count of immature neutrophils, but there is very wide interobserver variability in the identification of immature or 'band' neutrophils (25). Even the best scoring system only achieves a likelihood ratio of between four and eight (24) (evidence level 2a). Finding a 'left-shift' or an elevated total WBC count is not sufficiently predictive to alter management. The individual finding on a CBC with the highest positive predictive value is a low total WBC count of less than 5.0×10^9/L; if this finding is present, the likelihood ratio is between 10 and 20 (16), leading to a post-test probability of sepsis of approximately 10% to 20% (evidence level 2b) and, therefore, probably justifying treatment even in a well-appearing infant after a full diagnostic workup. However, only between 22% and 44% of infants with sepsis will have such a low total WBC count (16).

WELL-APPEARING INFANT OF A GBS-NEGATIVE MOTHER WHO HAD RISK FACTORS AT DELIVERY

Before the recommendation for universal culture-based screening, IAP was recommended for mothers with any one of the following five risk factors: over 18 h rupture of membranes, pyrexia higher than 38°C, premature labour at less than 36 weeks, GBS bacteriuria at anytime during pregnancy or previous child with invasive GBS disease. These risk factors were present in as many as 22% of mothers, and only identified approximately 50% of infants who eventually developed invasive GBS disease (26,27) (evidence level 2b).

Although invasive GBS disease does occur in infants whose mothers have negative screening cultures at 35 to 37 weeks, the risk is very low even in those with prolonged rupture of membranes or intrapartum pyrexia (28) (evidence level 2b). It is suggested that a limited diagnostic evaluation be performed in this newborn population (recommendation grade B).

WELL-APPEARING INFANT OF A MOTHER WITH UNKNOWN GBS STATUS AND NO RISK FACTORS

A mother who has not had an antenatal GBS culture or whose results are not readily available, and her newborn baby, should be managed according to the risk factors listed in the previous section. In the absence of these risk factors, and if the baby remains well, no specific intervention is required (recommendation grade B).

WELL-APPEARING INFANT OF A MOTHER WITH UNKNOWN GBS STATUS WITH RISK FACTORS

The five risk factors mentioned above occur in approximately 20% of deliveries at term, and are present in approximately 50% of infants with invasive GBS disease (26,27). This fourfold increase in risk to the infant in a mother with unknown GBS status has led to the recommendation that she should receive IAP (7). In this circumstance, the infant should be treated in the same way as he or she would be treated if the mother were GBS-positive (ie, IAP more than 4 h before delivery and routine neonatal care; IAP less than 4 h or no IAP, limited diagnostic evaluation and minimum 24 h observation) (recommendation grade B).

THE LATE PRETERM INFANT

The mother who delivers at less than 37 weeks will often not have results of antenatal GBS screening available. In such a case, the infant has a 'risk factor' (prematurity) for invasive GBS disease and, if he or she appear well, should have a limited diagnostic evaluation. Infants of this gestational age should not be discharged before 48 h at the earliest (Figure 1).

CHORIOAMNIONITIS

Chorioamnionitis is a difficult condition to diagnose because the prevalence of pyrexia during labour is high

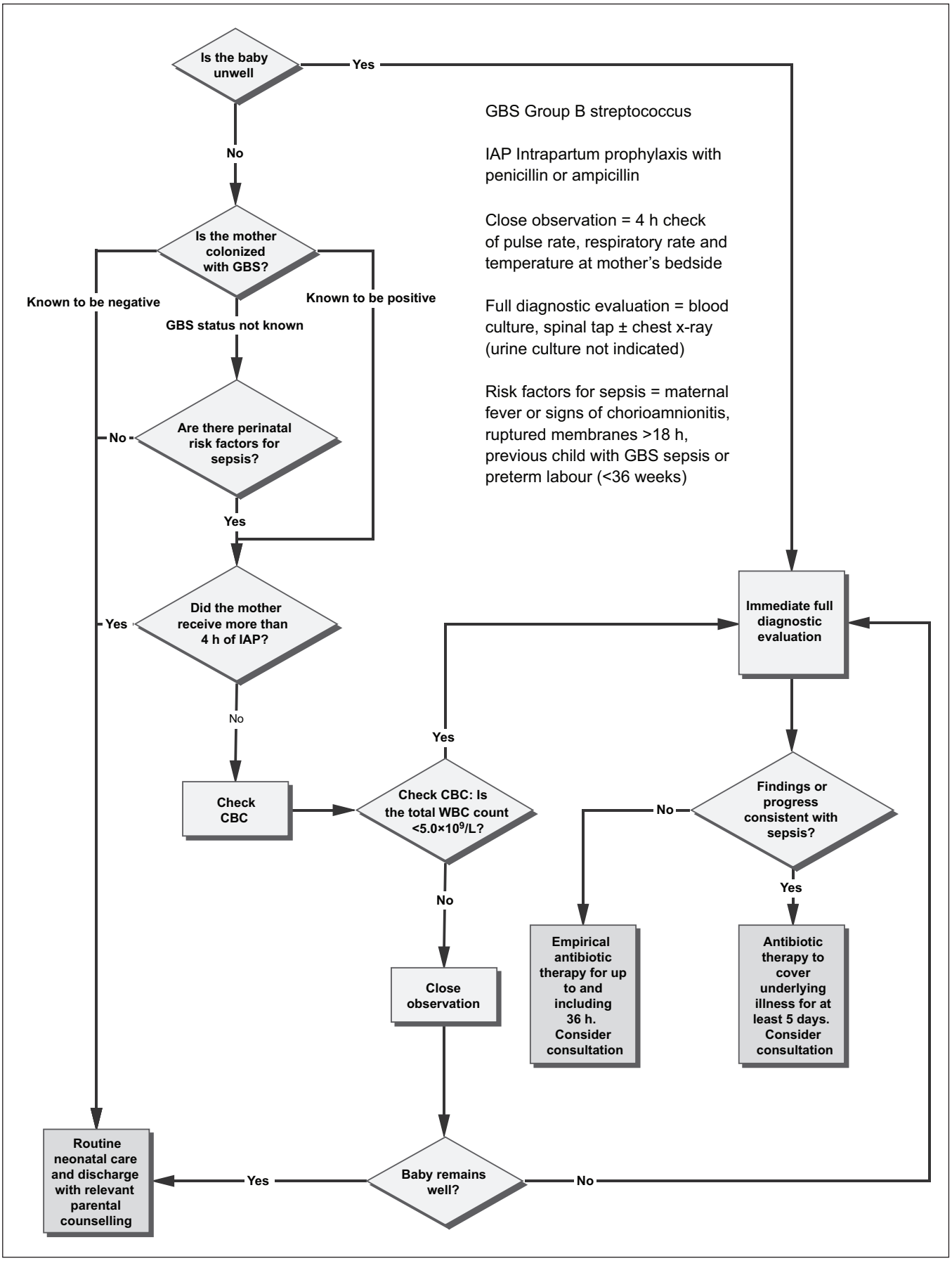

Figure 1) *Algorithm for the management of newborn babies who may be at risk for neonatal sepsis. Source: Canadian Paediatric Society, 2007*

(29), especially if the mother has had epidural analgesia (30). Other signs of chorioamnionitis are less frequent; there is poor correlation between clinical signs of chorioamnionitis and histology (29). Therefore, chorioamnionitis is frequently classified as 'possible', when the main sign is fever, and 'definite', when the classical triad of fever, left-shift in the WBC and lower uterine tenderness is present.

The risk of sepsis (which may be due to a variety of different organisms, including GBS, *E coli* and other Gram-negative organisms) in an infant whose mother had definite chorioamnionitis is approximately 8%, and is approximately 3% to 4% if 'possible' and 'definite' chorioamnionitis are considered together (31,32) (evidence level 2b); among all mothers with fever, the incidence is 2% to 6% depending on the height of the fever (31) (evidence level 2b). Infants who do not have signs at birth are unlikely to develop sepsis, the odds ratio for sepsis among infants who are well at birth is 0.26 (95% CI 0.11 to 0.63) (31). The incidence of invasive infection in the present study in an initially well-appearing infant with a maternal history of fever or chorioamnionitis was less than 2%, and this is confirmed by other data (33) (evidence level 2b). Therefore, it seems reasonable to perform a CBC and closely observe such an infant, and to only perform a full diagnostic evaluation and treat with antibiotics if the CBC is strongly suggestive of infection (low total WBC count) or if clinical signs develop. A requirement for extensive resuscitation at birth should be considered a sign of possible infection in such infants (32,33).

RECOMMENDATIONS

- Any newborn infant with clinical signs suggestive of sepsis should have an immediate full diagnostic evaluation followed by the institution of empirical antibiotic therapy without delay (recommendation category B).
- If a mother who is GBS-positive receives IAP with a penicillin more than 4 h before delivery, no further evaluation or observation for invasive GBS disease in a well-appearing infant is required (recommendation category A).
- If a GBS-positive woman receives IAP less than 4 h before delivery (or receives no antibiotics or a nonpenicillin regimen), then a limited diagnostic evaluation is required, and the infant should not be discharged before 24 h of age. At the time of discharge, the infant should be evaluated and the parents should be educated regarding signs of sepsis in the newborn. Discharge at 24 h to 48 h is conditional on the parents' ability to immediately transport the baby to a health care facility if clinical signs of sepsis develop (recommendation grade B).
- If the CBC reveals a total WBC count less than 5.0×10^9/L, full diagnostic evaluation and empirical antibiotic therapy should be considered (recommendation grade B).
- If a GBS-negative woman with risk factors delivers a baby who remains well, the infant does not require evaluation for GBS (recommendation grade B).
- If a woman with unknown GBS status and with risk factors at the time of delivery receives IAP more than 4 h before delivery, the infant requires no specific intervention (recommendation grade B).
- If a woman with unknown GBS status and with risk factors at the time of delivery receives IAP less than 4 h before delivery, limited diagnostic evaluation is required and the infant is not discharged before 24 h of life (recommendation grade B).
- The well-appearing infant born at less than 36 weeks gestation with an unknown maternal GBS status should have a limited diagnostic evaluation and is not a candidate for early discharge.
- The well-appearing infant of a mother with possible chorioamnionitis requires a limited diagnostic evaluation for sepsis (recommendation grade B).

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FETUS AND NEWBORN COMMITTEE

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Fever Without Source in Children 0 to 36 Months of Age

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Fever, one of the most common chief complaints of children seeking medical attention [1,2], prompted over 5 million emergency department (ED) visits in 2002 [3]. Most of these children have identifiable causes of their fevers, but many will have fever without an apparent source (FWS) after conclusion of the history and physical examination. Despite the frequency of fever as a chief complaint, there is considerable controversy in the management of the young child who has FWS [4–8]. The challenge in the evaluation of the febrile young child lies in balancing the minimization of risk to the patient with the costs of testing and treatment.

Definition of fever

A variety of temperatures have been used to define fever, but the most commonly accepted definition of fever is a temperature of $\geq$38.0°C (100.4°F), a value derived from studies by Wunderlich, who took 1 million measurements on 25,000 patients and determined that this temperature was the upper limit of normal [9]. Although less invasive means of measuring temperature exist, such as axillary and aural thermometry, the variability of measurements at these sites [10–12] warrants using the current outpatient reference standard, rectal thermometry, when measuring temperatures in young children. An accurate temperature measurement is especially important if a practitioner chooses to use fever guidelines because the implementation of these guidelines is initiated once a patient meets a certain temperature threshold.

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Once it is determined that a child has a fever, measured in the emergency department or in the practitioner's office, further evaluation can then proceed. However, a child who presents with a reported fever at home but who is afebrile in the ED or in the office poses more of a challenge. Parents may not be able to accurately define fever [13], and subjective assessment by parents has been shown to have generally good but variable sensitivity in the detection of fever [14–16]. Parental assessment is often colored by "fever phobia," inaccurate concerns and misconceptions about the potential danger of fever [17,18]. Additionally, bundling of infant creates confusion for both providers and parents because bundling of infants may raise the skin temperature but not rectal temperature [19]. However, a fever measured at home with rectal thermometry generally warrants the same concern as a fever measured in the ED or in the office. Six of 63 patients with bacteremia or bacterial meningitis in a large office-based study of young febrile infants were found to be afebrile in physicians' offices but were febrile at home [20].

Epidemiology

The management of the febrile young child continues to evolve. Contributing to this confusion is the changing epidemiology of bacterial infection in young children. *Haemophilus influenzae* previously presented a significant burden of disease, resulting in substantial morbidity and mortality in young children. *H influenzae* represented 19% of all positive cultures in febrile children who presented to a pediatric walk-in clinic in 1972 [21], but after widespread use of the *H influenzae* type b vaccine starting in 1991, the epidemiology of invasive bacterial disease changed dramatically. *H influenzae* type b has been nearly eliminated [22,23], with a 94% decline in *H influenzae* meningitis shortly after the introduction of the Hib vaccine [24]. Combining the results of two large studies of occult bacteremia in patients seen in the mid 1990s in Boston and Philadelphia, there were no blood cultures that grew *H influenzae* from 15,366 patients seen in these pediatric emergency departments [25,26].

Corresponding to the decrease in invasive disease caused by *H influenzae*, there has been an increase in the percentage of invasive diseases caused by *Streptococcus pneumoniae*. The burden of disease caused by *S pneumoniae* has been significant. *S pneumoniae* represented 83% to 92% of positive blood cultures taken from young febrile children presenting to EDs in the mid 1990s, and the overall prevalence of occult bacteremia was 1.6% to 1.9% [25,26]. In 1998, there were an estimated 12,560 cases of invasive pneumococcal disease (bacteremia, meningitis, and pneumonia) and 110 deaths in children younger than 2 years of age, with a case fatality rate of 1.4% [27]. This low overall case fatality rate likely reflects the generally good outcomes in patients with bacteremia, which represented 75% of the invasive disease in this population [27]. However, the case fatality rate resulting from *S pneumoniae* meningitis is higher than

meningitis caused by *Neisseria meningitidis*, *Streptococcus* group B, *Listeria monocytogenes*, or *H influenzae* [24]. Additionally, there has been an increasing prevalence of multidrug resistant *S pneumoniae*, and the proportion of isolates with multidrug resistance is highest in children under 5 years of age [28,29]. Although an effective, 23-valent polysaccharide pneumococcal vaccine has been licensed since 1983, this vaccine is insufficiently immunogenic in young children and is, therefore, ineffective and not recommended for children younger than 2 years of age, which is the age group most at risk for invasive pneumococcal infection.

The introduction of the heptavalent pneumococcal conjugate vaccine (PCV7), covering the seven most common pneumococcal serotypes, has changed the landscape of invasive bacterial disease in young children. There are over 90 pneumococcal serotypes that have been identified, but the seven serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F) cause approximately 82% of the cases of invasive pneumococcal disease [27]. This vaccine, licensed in 2000, is recommended for universal administration to children younger than 2 years old in a 4-dose regimen (doses are given at 2, 4, 6, and 12–15 months), as well as to high-risk older children (eg, children with sickle cell disease, chronic cardiac and pulmonary diseases, and other immunocompromising conditions) [30].

This vaccine has been shown to be both safe [31] and highly effective in preventing invasive pneumococcal disease, with a prelicensure study demonstrating an efficacy of 97% [32]. In a postlicensure surveillance of the Northern California Kaiser Permanente [32] study cohort, the cohort that served as the largest prelicensure study group of the PCV7 vaccine, the incidence of invasive pneumococcal disease caused by vaccine and cross-reactive vaccine serotypes declined from 51.5 to 98.2 cases of invasive disease per 100,000 person-years in children less than 1 year old to 0 cases per 100,000 person-years 4 years after licensure [33]. There was also a reduction of invasive pneumococcal disease in children less than 2 years old, declining from 81.7 to 113.8 cases of invasive disease per 100,000 person-years to 0 cases per 100,000 person-years 4 years after the vaccine was licensed [33]. There was a decline in invasive pneumococcal disease for all serotypes, not just the seven covered by PCV7, with a decline of 94% and 91% in children less than 1 year of age and 2 years of age, respectively. There was also a significant decline in drug-resistant pneumococci and a 25% decrease in invasive pneumococcal disease in people older than 5 years old, suggesting herd immunity because these patients were not themselves immunized. These declines occurred despite the fact that only 24% of children less than 2 years old received all four recommended doses because of a vaccine shortage [33].

These findings have been replicated in other settings. In Massachusetts, there was a 69% decline in the incidence of total invasive pneumococcal disease as well as an 88% decline in non-meningitis vaccine-serotype disease [34]. Similarly, there was a 69% decline in the total incidence of invasive pneumococcal disease and a 78% decline in the incidence of disease caused by vaccine serotypes, seen in a national network of regional surveillance centers administered

by the Centers for Disease Control and Prevention, accompanied by a decline in penicillin-resistant pneumococcal isolates [35]. There was a 66% decline in the incidence of invasive pneumococcal infections (77% decline in vaccine-covered serotypes) noted from a network study of children's hospitals [36]. Three likely mechanisms are involved in the PCV7-associated decrease in disease: individual risk decline, decline in antibiotic-resistant bacteria, and herd immunity.

Caveats

Although the differential diagnosis of fever is quite broad and includes both infectious and noninfectious causes [37], the majority of febrile children have underlying infectious causes of fever. For the purposes of this article, patients are presumed to be febrile from infectious sources. Additionally, diagnostic strategies emphasize the detection of bacterial disease because bacterial diseases are more likely to be associated with worse outcomes, but viral infections can also be associated with significant morbidity and mortality, especially in younger children.

Most large studies addressing serious bacterial illness use children from large, urban, tertiary care children's hospital emergency departments. Physicians in primary care settings are less compliant with ED-derived recommendations for the evaluation and treatment of febrile children, but compared with ED patients, outcomes for these patients are similar [20,38]. This similarity in outcome may be the result of several causes: the sickest patients may preferentially present to the ED, patients may get closer follow-up by their primary care providers, the judgment of primary care providers may be more sensitive than criteria put forth in various guidelines, or because the likelihood of serious disease in these children is low [39].

Finally, most studies of febrile young children exclude patients who have potentially complicating risk factors. These studies typically have excluded children who are immunocompromised (eg, sickle cell disease, cancer, or long-term steroid use), have indwelling medical devices (eg, ventriculoperitoneal shunts and indwelling venous access catheters), are currently taking antibiotics, or have prolonged fevers (≥ 5 days).

Approach to the young febrile child

History and physical examination

The history and physical examination are invaluable in the assessment of the febrile child. The level and duration of a child's fever as well as the mode of temperature measurement are important to note. There is an increase in the prevalence of pneumococcal bacteremia with an increase in temperature [40], and this is more pronounced in young children. In children less than 3 months of age

who have temperatures $\geq 40.0^{\circ}C$, 38% have serious bacterial infection [41]. The duration of the fever itself at the time of ED presentation does not predict whether a child has occult bacteremia [42]. The use of antipyretics should be noted. Parents often give inaccurate doses of antipyretics [43,44], and paradoxically, in one study, patients treated with antipyretics presented to the ED with higher temperatures than those patients who were untreated at home [45]. A response (or lack thereof) to antipyretic medications does not predict whether the underlying cause is bacterial or viral [45–49]. Additional important data include associated signs and symptoms, underlying medical conditions, exposure to ill contacts, and immunization status.

An assessment of the child's overall appearance is critical. If a child appears to be toxic, this mandates an aggressive work-up, antibiotic treatment, and hospitalization, regardless of age or risk factors. The physical examination may reveal obvious sources of infection, and the identification of a focal infection may decrease the need for additional testing. For example, febrile patients with recognizable viral conditions (eg, croup, chickenpox, and stomatitis) have lower rates of bacteremia than patients with no obvious source of infection [50]. Similarly, febrile children with influenzavirus A have lower rates of serious bacterial infections compared with febrile children without influenzavirus A [51]. Febrile patients with otitis media appear to have the same rate of bacteremia as febrile children without otitis media [52,53].

With the exception of neonates and young infants, if a child has a nontoxic appearance, a more selective approach can be undertaken. When a child who has a febrile illness has an obviously identifiable cause, the treatment and disposition should generally be tailored to this specific infection. The approach to the young child who has FWS is discussed below.

Age-specific considerations

The approach to the young child who has a fever without a source varies depending on the age of the child. Traditionally, young children have been categorized in into three distinct age groups for the purposes of fever evaluation: the neonate (0–28 days old), the young infant (commonly defined as infants between 1 and 3 months of age, although some authors define this group to include children only between 1 and 2 months of age), and the older infant or toddler (commonly defined as 3 to 36 months of age, although some studies include patients only up to 24 months old in this group). Although the use of chronologic age distinctions are somewhat artificial (for example, the difference in the risk of serious bacterial illness is likely to be inconsequentially different between a 28-day-old child and a 29-day-old child), there is some rationale behind these seemingly arbitrary age distinctions. Younger children have decreased immunologic function and are more commonly infected with virulent organisms. Additionally, the physical examination is more difficult because young children have a limited behavioral repertoire.

Young infants: 0 to 3 months old

The traditional approach to young infants has included aggressive investigation, antibiotic administration, and hospital admission [54]. However, the hospitalization of young infants can result in iatrogenic complications, financial ramifications, and parental stress [55,56]. Recently, this approach has been challenged, and the current recommendations are not as strict regarding mandatory admission in well-appearing infants over 28 days old.

Neonates: birth to 28 days old

Neonates are at a particularly high risk for SBI. The majority of febrile neonates presenting to the ED are diagnosed ultimately as having a nonspecific viral illness, but approximately 12% of all febrile neonates presenting to a pediatric emergency department have serious bacterial illness [57,58]. When they are infected, neonates are infected typically by more virulent bacteria (eg, *Streptococci* group B, *Escherichia coli*, and *L monocytogenes*) and are more likely to develop serious sequelae from viral infections (eg, herpes simplex virus meningitis). *Streptococci* group B, a common bacteria pathogen in this age group, is associated with high rates of meningitis (39%), non-meningeal foci of infection (10%), and sepsis (7%) [59]. This age group is the least likely to be affected by the use of the pneumococcal vaccine because only a small percentage of neonates are infected by this pathogen. Although infection is uncommon, those neonates who are infected with *S pneumonia* have a mortality rate of 14% [60]. The most common bacterial infections in this are group are urinary tract infections (UTIs) and occult bacteremia [57,58].

Evaluation of the febrile neonate

Traditional risk-stratification strategies have used ancillary testing to supplement the limited information available from the history and physical examination. Unfortunately, it is difficult to predict accurately which neonates have invasive disease, even when laboratory testing is used. Initial studies by Dagan and colleagues [61,62] appeared promising. These ''Rochester criteria'' (Rochester, Boston, and Philadelphia criteria are discussed below) were applied to infants less than 90 days old, and neonates were included. Using the Rochester criteria, Jaskiewicz and colleagues [63] found that 2 of 227 children younger than 30 days old who met low-risk criteria had SBI. However, Ferrera and colleagues [64] found that 6% of neonates who were retrospectively classified as low risk by the Rochester criteria had SBI.

Baker and colleagues [65] retrospectively stratified neonates into high- and low-risk patients based on the ''Philadelphia criteria'' they had derived for older infants. The neonates who were placed in the high-risk category had a higher incidence of bacterial disease (18.6%), but 4.6% of neonates who were classified as low-risk patients had a serious bacterial infection. Additionally, 11 different

bacterial pathogens were identified in 32 patients with SBI, and only one of these 32 patients was infected with *S pneumoniae*. Kadish and colleagues [58] found a similar rate of SBI in neonates whom they categorized as low risk when they retrospectively applied both the Philadelphia criteria and similar criteria created by Baskin and colleagues (the "Boston criteria"). They also found a wide range of bacterial pathogens, but only two cultures in 55 patients with SBI were positive from *S pneumoniae.*

Because of the inability to accurately predict serious infections in this age group, the recommendations for these patients include obtaining blood cultures, urine for rapid urine testing, urine cultures, and cerebrospinal fluid (CSF) [66,67]. A peripheral white blood cell (WBC) count is often ordered in the evaluation of febrile neonates, but the discriminatory value of the WBC count is insufficient to differentiate between patients with SBI versus nonbacterial infection [68–70]. Because of the inability of the white blood cell count to predict SBI, blood cultures should be ordered on all patients. Although various options for rapidly testing for urinary tract infection exist (eg, urine dipstick, standard urinalysis, and enhanced urinalysis), no rapid test detects all cases of UTI, so urine cultures must be ordered in all of these patients [71,72]. Urine should be collected by bladder catheterization or suprapubic aspiration because bag urine specimens are associated with unacceptably high rates of contamination [73,74]. A lumbar puncture should be performed in all febrile neonates. Chest radiographs are indicated only in the presence of respiratory symptoms, and stool analyses are indicated only in the presence of diarrhea. In neonates, the presence of signs suggestive of viral illness does not negate the need for a full diagnostic evaluation. Unlike older children, in whom documented respiratory syncytial virus (RSV) infections decrease the likelihood of serious bacterial illness, RSV-infected neonates have the same rate of SBI compared with RSV-negative neonates [75].

Treatment and disposition of the febrile neonate

Because of the high rates of serious bacterial infections, all febrile neonates should receive antibiotics. Typically, these patients are treated with a third-generation cephalosporin or gentamicin. Ceftriaxone is not recommended for neonates who have jaundice because of the concern for inducing unconjugated hyperbilirubinemia [76–78]. Other third-generation cephalosporins, such as cefotaxime, 50 mg/kg intravenously (IV) (100 mg/kg if there is a concern for meningitis based on CSF results), or gentamicin, 2.5 mg/kg IV, are used in this age group. Additionally, although the incidence of *L monocytogenes* is quite low [79], ampicillin, 50 mg/kg IV (100 mg/kg IV if there is a concern for meningitis) is still recommended in the empiric treatment of these patients [80].

Neonatal herpes simplex virus (HSV) infections occur in approximately 1 per 3200 deliveries in the United States [81]. Neonates with HSV infections usually present within the first 2 weeks of life, and only a minority of infected children have fever [82]. Rates of morbidity and mortality are high with neonatal HSV, but

treatment with high-dose acyclovir improves outcomes in patients [83]. Acyclovir is not recommended routinely for empiric treatment in addition to standard antibiotics in febrile neonates [82] but should be considered in febrile neonates with risk factors for neonatal HSV (20 mg/kg IV). Risk factors include primary maternal infection, especially those neonates delivered vaginally, prolonged rupture of membranes at delivery, the use of fetal scalp electrodes, skin, eye or mouth lesions, seizures, and CSF pleocytosis [81,84,85].

Febrile neonates should be hospitalized, regardless of the results of laboratory studies. Outpatient management of these patients has been suggested [86] and occurs frequently when patients present to pediatricians' offices [20]. However, given the lack of prospective studies addressing this approach as well as the limitations inherent in the screening evaluation in the emergency department and frequent difficulties in arranging follow-up evaluation, hospitalization is strongly recommended [66,67].

Young infants: 1 to 3 months old

The approach to febrile young infants, defined most commonly as children less than either 2 or 3 months old (in this discussion, age less than 3 months will be used), changed dramatically in the 1980s and early 1990s. Before this time, most febrile young infants presenting to academic medical centers were hospitalized and frequently started on antibiotic therapy. The aggressive approach was based in part on the relatively limited amount of information obtainable from examination of young infants [65,87], the high morbidity rate observed with *H influenzae* type b infection, and the efficacy of antibiotics in the treatment of serious bacterial infection.

The "Rochester criteria" put forth by Dagan and colleagues [61,62] stratified children less than 60 days old into high- and low-risk groups. The children who met these criteria appeared well, had been previously healthy, and had no evidence of skin, soft tissue, bone, joint, or ear infection. Additionally, the children had normal peripheral WBC count (5000–15,000/mm^3), normal absolute band counts ($\leq$ 1500/mm^3), $\leq$ 10 WBC/high-power field (hpf) of centrifuged urine sediment, and for those patients with diarrhea, $\leq$ 5 WBC/hpf on stool smear [61,62]. The low-risk group identified children who were unlikely to have serious bacterial infection, with a negative predictive value of 98.9% [63].

In 1992, Baskin and colleagues [88] described the "Boston criteria" for febrile children between 1 and 3 months of age who presented to the emergency department with temperatures $\geq$ 38.0°C. Infants were discharged after an intramuscular (IM) injection ceftriaxone, 50 mg/kg, if they generally appeared to be well (not strictly defined) and had no ear, soft tissue, joint, or bone infections on physical examination. Furthermore, these patients had to have CSF with $\leq$ 10 WBC/hpf, microscopic UA with $\leq$ 10 WBC/hpf or urine dipstick negative for leukocyte esterase, a peripheral WBC count of $\leq$ 20,000/mm^3, and normal findings in patients in whom a chest radiograph was obtained (all tests except the chest radiograph were performed on all patients). Twenty-seven of

503 children (5.4%) were later found to have serious bacterial infection (bacterial gastroenteritis, urinary tract infection, and occult bacteremia). Only one of nine patients with occult bacteremia in this study were infected *S pneumoniae* [88].

Baker and colleagues [65] similarly sought to identify low-risk patients between 29 and 56 days old with temperatures of $\geq 38.2^{\circ}C$. Patients who appeared to be well (as defined by an Infant Observation Score of 10 or less), had a peripheral WBC count of $\leq 15{,}000/mm^3$, a band-to-neutrophil ratio of ≤ 0.2, a urinalysis (UA) with fewer than 10 WBC/hpf, few or no bacteria on a centrifuged urine specimen, CSF with fewer than 8 WBC/mm^3, a gram-negative stain, negative results on chest radiographs (obtained on all patients), and stool negative for blood and few or no WBCs on microscopy (ordered on those patients with watery diarrhea) were considered to have a negative screen and were not treated with antibiotics. Of the 747 consecutively enrolled patients, 65 (8.7%) had SBI. All 65 patients who had serious bacterial infection were identified using these screening criteria. These 65 patients had a total of 70 bacterial infection sites where a bacterial pathogen was identified, and four of these 70 infections were caused by *S pneumoniae* [65]. In a follow-up study (in which fever was defined as $\geq 38.0^{\circ}C$ rectally) of 422 consecutively enrolled febrile young infants, 43 (10%) had SBI, and all 101 patients who were identified as low risk had no SBI. All 43 patients who had SBI were identified prospectively as high risk using the Philadelphia criteria [89].

In the large studies by Baskin and Baker and colleagues, only a minority of patients with SBI had pneumococcal infection, and thus, children in this age group are unlikely to benefit directly from the PCV7 vaccine [65,88].

Evaluation of the febrile young infant

The clinical evaluation alone will result in a substantial number of missed SBI, so laboratory testing is required in this age group. The white blood cell count with differential, catheterized urinalysis, and blood and urine cultures should be obtained in all patients. Stool studies for white blood cell counts and stool cultures should be ordered in patients with diarrhea. Chest radiographs should be obtained only in young febrile infants with signs of pulmonary disease (tachypnea ≥ 50 breaths/minute, rales, rhonchi, retractions, wheezing, coryza, grunting, nasal flaring, or cough) [90,91].

Controversies in this age group surround the need for lumbar puncture. Although the Boston and Philadelphia criteria require CSF analysis, the Rochester criteria do not mandate lumbar puncture. The rarity of bacterial meningitis contributes to the controversy surrounding the utility of the lumbar puncture. However, the prevalence of bacterial meningitis in febrile infants less than 3 months old is 4.1 per 1000 patients, and neither the clinical examination nor the peripheral white blood cell count is reliable in diagnosing meningitis in this age group [68,92]; therefore, the LP should be strongly considered. Additional controversy surrounds the need for antibiotics in patients who are identified as low risk. Patients identified as low risk by the Philadelphia protocol were not given

antibiotics, whereas patients enrolled in the Boston studies were given intramuscular ceftriaxone. There is some concern that performing a lumbar puncture in a bacteremic patient may lead to meningitis [93,94], and published recommendations state that parenteral antibiotics should be "considered" if a lumbar puncture is performed [66].

The results of these tests help to risk-stratify these young children. The WBC count is considered abnormal if the count is $\geq 15{,}000/mm^3$ or $\leq 5000/mm^3$ and the band- to-neutrophil ratio is ≥ 0.2. The urine is considered abnormal if the urine dipstick is positive for nitrite or leukocyte esterase; or there are ≥ 5 WBC/hpf on microscopy; or organisms are seen on a Gram-stained sample of uncentrifuged urine. If obtained, there should be fewer than 5 WBC/hpf on the stool specimen, no evidence of pneumonia on chest x-ray, and fewer than 8 WBC/mm^3 and no organisms on Gram stain of the cerebrospinal fluid [66]. Of note, however, one recent study reported that four of 8300 children who underwent CSF analysis had bacterial meningitis and ≤ 8 WBC/mm^3 in the CSF [95].

The presence of a documented viral infection lowers but does not eliminate the likelihood of a serious bacterial infection in this age group. Young infants classified as high-risk patients using the Rochester criteria who had documented viral infection (enterovirus, respiratory virus, rotavirus, and herpesvirus) were at lower risk for SBI compared with patients who did not have an identified source (4.2% versus 12.3%) [96]. Similarly, a subgroup analysis of 187 febrile infants 28 to 60 days old showed a significantly lower rate of SBI in RSV-positive patients compared with RSV-negative patients (5.5% versus 11.7%) [75], confirming the results of similar studies in young infants who had bronchiolitis. Most of these bacterial infections were urinary tract infections [97,98]. Patients less than 90 days old who have enteroviral infections have a rate of concurrent serious bacterial infections (mostly UTI) of 7% [99].

Treatment and disposition of the febrile young infant

Assuming that the patient is an otherwise healthy term infant who appears to be well and who does not have any lab abnormalities, outpatient management may be considered. If the patient undergoes a reliable follow-up within 24 hours, the parents have a way of immediately accessing health care if there is a change in the patient's condition, and the parents and the primary care physician understand and agree with this plan of care, then the patient may be discharged home. The use of ceftriaxone, 50 mg/kg IV or IM, before discharge is acceptable, as is withholding antibiotics in these low-risk patients. Patients who did not undergo lumbar puncture in the ED should not receive antibiotics because this will confound the evaluation for meningitis if the patient is still febrile on follow-up examination. Close follow-up reevaluation must be assured before discharge.

For those patients who have abnormal test results or who appear to be ill, antibiotic therapy and hospitalization are warranted. Ceftriaxone, 50 mg/kg IM or IV (100 mg/kg if meningitis is suspected), is commonly used for these patients.

Additional antibiotics should be considered in select circumstances (eg, ampicillin or vancomycin for suspected infection by *Listeria*, gram-positive cocci, or enterococcus). Some studies suggest that patients in this age group who have urinary tract infections may be treated on an outpatient basis [100,101]; however, there are no prospective studies with a large number of young infants that address this question.

Older infants and toddlers: 3 to 36 months old

A temperature of $\geq 38.0^{\circ}C$ defines a fever, and in younger children, this temperature is the usual threshold beyond which diagnostic testing is initiated. However, in febrile children between 3 and 36 months old (some studies extend this group to include 2-month-old infants), a temperature of $\geq 39.0^{\circ}C$ is commonly used as the threshold temperature for initiating further evaluation. This higher temperature cutoff is used because of the increasing risk of occult bacteremia with increasing temperatures [40]. Large studies of occult bacteremia, widely referenced in the medical literature, use this temperature as the study entry criteria [25,26,102].

Evaluation of the child 3 to 36 months old

The history is often helpful in this age group. Patients are more likely to be able to communicate complaints, and the physical examination is more informative. Clinical assessment as to whether a child appears to be well, ill, or toxic is important. A well appearance does not completely exclude bacteremia [103], but children who appear toxic are much more likely to have serious illness compared with ill- or well-appearing children (92% versus 26% versus 3%, respectively) [104]. Many bacterial infections can be identified by history and physical examination alone, but some infections may be occult. The serious bacterial infections that may not be clinically apparent are bacteremia, urinary tract infection, and pneumonia. If no focal source of infection is identified and the cause is not believed to be viral, then diagnostic testing in this age group is undertaken for the purposes of identifying these occult bacterial infections.

Occult bacteremia

In the era before universal PCV7 vaccination, the pathogen that most commonly caused occult bacteremia was *S pneumoniae* [25,26]. The children at greatest risk for pneumococcal bacteremia are children between 6 and 24 months old. There has been much controversy about the role of blood testing in the evaluation of the febrile child, specifically regarding the value of blood testing in the identification of occult bacteremia. There is an increased risk of bacteremia

with an increasing white blood cell count [26,105,106], but the sensitivity and specificity of a white blood cell count $\geq 15{,}000/mm^3$ is only 80% to 86% and 69% to 77%, respectively. An absolute neutrophil count (ANC) of $\geq 10{,}000/mm^3$ is a stronger predictor of occult bacteremia than an elevated white blood cell count. Eight percent of patients who have an ANC $\geq 10{,}000/mm$ have occult pneumococcal bacteremia, whereas 0.8% of patients who have an ANC $\leq 10{,}000/mm^3$ have occult pneumococcal bacteremia [40]. Nevertheless, using an elevated WBC or ANC as a surrogate marker for occult bacteremia means that many patients will unnecessarily receive antibiotics.

The shifting epidemiology of bacteremia has prompted cost-effectiveness analyses of various management strategies. Using pre-PCV7 data, Lee and colleagues [107] analyzed five strategies for the 3- to 36-month-old febrile child who did not have an identifiable source of infection. Using a bacteremia prevalence rate of 1.5%, the authors concluded that the most cost-efficient strategy was to obtain CBCs and to selectively send blood cultures and treat patients empirically for WBC counts $>15{,}000/mm^3$. In their sensitivity analysis, the authors found that when the prevalence rate of pneumococcal bacteremia dropped to 0.5%, then clinical judgment (eg, the patient who was deemed to be at low risk clinically for occult pneumococcal bacteremia received no testing) was a more cost-effective strategy.

The role of antibiotics in children believed to be at high-risk for bacteremia is controversial as well. There is currently no way of prospectively identifying bacteremic patients, and practically, this means that at the time of the ED or office visit, many febrile children who are at risk for bacteremia must be treated to prevent a single serious bacterial infection. The use of both amoxicillin [108] and ceftriaxone [102,105] appears to shorten the duration of fever in bacteremic febrile children. However, there is a paucity of randomized, placebo-controlled data demonstrating that the use of either oral or parenteral antibiotics prevents significant, adverse infectious sequelae in these children. One study compared amoxicillin with placebo for the treatment of febrile children and showed no difference in the rates of subsequent focal infection [108]. Another retrospective study demonstrated that, in patients ultimately found to have bacteremia, treatment with oral or parenteral antibiotics reduced persistent fever, persistent bacteremia, and hospital admission [109]. A subsequent meta-analysis has shown that, although ceftriaxone prevents serious bacterial infection in patients with proven occult bacteremia, 284 patients at risk for bacteremia would need to be treated with antibiotics to prevent one case of meningitis [110]. Although oral antibiotics also decrease the risk of SBI in patients with occult bacteremia caused by *S pneumoniae*, it is unclear whether antibiotics reduce the risk of meningitis in these patients [111]. Additionally, there is no apparent difference in rates of serious bacterial infection in patients with occult pneumococcal bacteremia who are treated with oral versus parenteral antibiotics [112]. Complicating this analysis is the fact that in a majority of patients with pneumococcal bacteremia, the bacteremia will resolve spontaneously [25]. Focal infections develop in 17% of bacteremic children [25], and 2.7% to 5.8% of patients with occult

pneumococcal bacteremia develop meningitis [111,113]. These analyses were conducted on data obtained in the pre-PCV7 era, and it is likely, with the significant decrease in invasive pneumococcal disease, that many more febrile patients will need to be treated to prevent SBI.

There are relatively few data on occult bacteremia in the post-PCV7 era. In one retrospective cohort study of pediatric emergency department patients, three of 329 blood cultures in children between 2 to 36 months old were positive for S *pneumoniae.* One patient was infected with a nonvaccine serotype, one was not immunized with PCV7, and a third patient was infected with an unknown serotype [114].

Although pneumococcus has been the most common cause of occult bacteremia, other causes of bacteremia can be occult as well. *Salmonella* causes 4% of occult bacteremia, occurring in 0.1% of all children 3 to 36 months old who have temperatures $\geq 39.0^{\circ}C$ [25,26,102], and whereas the majority of patients with *Salmonella* bacteremia have gastroenteritis, 5% will have primary bacteremia [115]. One large retrospective study of non-*typhi Salmonella* bacteremia in children showed that 54% of bacteremic children had a temperature $\leq 39.0^{\circ}C$ and a median WBC count of 10,000/mm^3. These children had a 41% rate of persistent bacteremia on follow-up cultures, and the rates of persistent bacteremia were the same in patients who were treated with antibiotics at the initial visit and those who were not. Among immunocompetent patients, 2.5% of patients with *Salmonella* bacteremia had focal infections, and no difference in rates of focal infection were noted in children older and younger than 3 months of age [116].

Meningococcal infections are infrequent causes of bacteremia but are associated with high rates of morbidity and mortality. Combining the data from Boston and Philadelphia occult bacteremia studies, 0.02% of children who appeared to be nontoxic and had temperatures $\geq 39.0^{\circ}C$ had meningococcal disease [25,26]. Usually, these patients are overtly sick; however, 12% to 16% of patients with meningococcal disease have unsuspected infection [117,118]. Although there is an association between younger age and elevated band count with meningococcal disease, the positive predictive values of these variables are quite low, given the low prevalence of this disease, and authors of one large meningococcal disease study believe that routine screening for all young febrile children with CBCs for meningococcal bacteremia is not useful [117]. Patients who had unsuspected meningococcal disease who were treated empirically with antibiotics had fewer complications than patients who were untreated, but there were no differences in rates of permanent sequelae or death [119]. However, testing and empiric treatment may be warranted for children at higher risk for meningococcal disease. Risk factors for meningoccal bacteremia include contact with patients with meningoccal disease, periods of meningoccal disease outbreaks, and presence of fever and petechiae (although the majority of children with fever and petechiae do not have invasive bacterial disease) [120–122]. A new tetravalent meningococcal conjugate vaccine was licensed for use in the United States in 2005. Although clinical trials in infants and young children are in

progress, this vaccine has been licensed and recommended for routine administration only in children 11 years old and older [123].

Children who have positive blood cultures need to be reexamined. A patient who appears ill needs a repeat blood culture, lumbar puncture, intravenous antibiotics, and hospital admission. Patients with pneumococcal bacteremia who are afebrile on repeat evaluation can be followed on an outpatient basis [124] after repeated blood cultures and antibiotics. Children who have pneumococcal bacteremia and who are persistently febrile need repeat blood cultures and generally should undergo lumbar puncture and require hospital admission. The treatment and disposition for well-appearing children with *Salmonella* bacteremia are less clear, but patients with meningococcal bacteremia should be hospitalized for parenteral antibiotics [106].

Contaminated blood cultures are common, and in younger children, the rate of contaminated cultures frequently exceeds the rate of true positive cultures [25,26,114,125,126]. Although the average cost to the patient of a false-positive blood culture is rather small [127], false-positive blood cultures lead to further testing, use of antibiotics, and hospitalizations [128], along with the attendant iatrogenic complications [129]. The rates of blood culture contamination decline when cultures are drawn from a separate site rather than through a newly inserted intravenous catheter [126].

Given the observed decline in invasive pneumococcal disease, the relative infrequency of meningococcemia and *Salmonella* bacteremia, and the limited value of the white blood cell count in predicting the latter two diseases, the need for routine CBC, blood cultures, and empiric antibiotics have been called into question in fully immunized children [130,131]. Baraff, the author of the commonly referenced fever algorithms [66,132], has recently stated that children who have received three does of vaccine are at sufficiently low risk that they do not need blood testing or antibiotics and that patients who have received only two doses of the Hib and PCV7 vaccines are not at any significant risk for occult bacteremia [133]. It is reasonable to address parental preferences when devising a ''risk-minimizing'' versus a ''test-minimizing'' [134] approach to these children because parental perceptions and preferences regarding risk may differ from those of the treating clinician.

Occult urinary tract infection

UTIs are common sources of fever in young children, and children are at risk for permanent renal damage from UTIs. In older children, historical and examination features such as dysuria, urinary frequency, and abdominal and flank pain may suggest urinary tract infection. However, in young children, symptoms are usually nonspecific. Although the overall prevalence in children is 2% to 5% [135–137], certain subgroups of children are at higher risk for UTIs. Whites, girls, uncircumcised boys, no alternative source of fever, and temperatures $\geq 39.0^{\circ}C$ were associated with a higher risk; 16% of white girls less than 2 years

old with temperatures ≥39.0°C and fever without source had urinary tract infections [135,136]. UTIs were found in 2.7% to 3.5% of febrile children, even when there were other potential sources of fever (eg, gastroenteritis, otitis media, upper respiratory tract infection, and nonspecific rash) [135,136].

Based on these prevalence data, a clinical decision rule was derived and validated for febrile girls less than 24 months of age. Urine testing is indicated if two or more of the following risk factors are present: age less than 12 months, fever for 2 or more days, temperature ≥ 39.0°C, white, and no alternative source of fever [138]. This rule has a sensitivity of 95% to 99% and a false-positive rate 69% to 90% in detecting girls with UTI [138,139]. No similar clinical decision rules exist for boys, but because the prevalence in boys less than 6 months old is 2.7% [136], urine should be collected in all boys in this age group. The prevalence of UTIs in uncircumcised boys is 8 to 9 times higher than circumcised boys, so uncircumcised boys younger than 12 months old should also undergo urine testing [136,140,141].

Urine culture is the gold standard for the diagnosis of urinary tract infection, but results are not immediately available. Several rapid urine tests have very good sensitivity for detecting UTIs. Enhanced urinalysis (≥10 WBC/hpf or bacteria on Gram stained, uncentrifuged urine) [71,142] or a combination of ≥ 10 WBC/hpf and bacteriuria (on either centrifuged or uncentrifuged urine) [143] are both excellent screening tests. The more readily available urine dipstick (positive for either leukocyte esterase or nitrites) has a sensitivity of 88% [71]. Importantly, however, because no rapid screening test detected all UTIs, urine cultures should be ordered on all of these patients [74]. Any positive test results from a rapid test should lead to a presumptive diagnosis of a urinary tract infection, and antibiotic treatment should be initiated. Most patients with urinary tract infection who appear well can be treated on an outpatient basis. Empiric antibiotic therapy should be tailored to local bacterial epidemiology, but reasonable outpatient medications include cefixime (8 mg/kg twice on the first day of treatment, then 8 mg/kg/d, starting from the second day) or cephalexin (25–100 mg/kg/d divided into four doses). The duration of therapy should be from 7 to 14 days.

Occult pneumonia

Young children commonly develop pneumonia, and the most common pathogens are viruses and (based on pre-PCV7 data) *S pneumoniae* [144]. The diagnosis of pneumonia based on clinical examination can be difficult [145]. Multiple attempts have been made at deriving clinical decision rules for the accurate diagnosis of pneumonia, but none has been successfully validated [146–148]. The presence of any pulmonary findings on examination (eg, tachypnea, crackles, respiratory distress, or decreased breath sounds) increases the likelihood of pneumonia, and conversely, the absence of these findings decreases the likelihood of pneumonia [149–151]. The role of pulse oximetry in detecting pneumonia is unclear [152,153], and although the chest radiograph is often believed to be the

gold standard, there is variability in the interpretation of radiographs even by pediatric radiologists [154]. Radiographic findings cannot be used to distinguish reliably between bacterial and nonbacterial causes [155,156]. In one South African study, chest radiographs did not affect the clinical outcome in children meeting the World Health Organization definition of pneumonia [157].

Some cases of pneumonia are likely to be clinically occult. Bachur and colleagues [158] found that 19% to 26% of children younger than 5 years old who had a temperature of $\geq$39.0°C, a WBC count $\geq$20,000/mm^3, and no other source or only a "minor" bacterial source on examination had a pneumonia infection as seen on a chest radiograph. A clinical policy by the American College of Emergency Physicians states that a chest radiograph should be considered in children older than 3 months who have a temperature $\geq$39°C and a WBC count $\geq$20,000/mm^3 and that a chest radiograph is usually not indicated in febrile children older than 3 months who have a temperature $\leq$39°C without clinical evidence of acute pulmonary disease [90]. The British Thoracic Society similarly recommends that a chest radiograph should be considered in children younger than 5 years old who have a temperature $\geq$39°C caused by an unclear source of infection [159]. These recommendations may change based on the decline of the prevalence of pneumococcal pneumonia [160]. No decision rules exist for pediatric pneumonia that help with disposition decisions in children who have pneumonia, but the majority of patients are treated on an outpatient basis. Both amoxicillin (80 mg/kg/d divided twice or three times daily) and macrolide antibiotics (eg, azithromycin, 10 mg/kg by mouth on the first day, then 5 mg/kg/d for 4 more days) are acceptable. Treatment duration is usually from 7 to 10 days (with the exception of azithromycin), but no definitive evidence supports a specific duration of therapy [159].

Future directions and questions

The pneumococcal vaccine has already had a significant impact on the epidemiology of bacterial infection in young children, and this vaccine has already seems to have had some impact on the practice patterns of pediatricians. Pediatricians who were surveyed were found to order fewer blood and urine tests and were less likely to prescribe antibiotics in a hypothetical scenario of an 8-month-old febrile but otherwise healthy infant when the child had been fully immunized with PCV7 compared with a nonimmunized child [161]. Some authors have begun advocating a less aggressive approach to the evaluation of the immunized febrile child, given the decline in invasive pneumococcal disease with PCV7 [131,133]. Other investigators, however, are urging caution before changing evaluation and management strategies, postulating that invasive pneumococcal disease will persist for several reasons: not all serotypes are covered by vaccine, some children will not be able to mount an adequate immune response to form protective antibodies, and some children still will be incompletely immunized [162].

Other questions regarding PCV7 have arisen. Among the seven serotypes, the amount of disease reduction is variable [34–36]. Furthermore, although the overall rate of invasive pneumococcal disease is lower, there is an increase in the percentage of invasive pneumococcal disease caused by nonvaccine serogroups [33–36]. The clinical implications of this serotype replacement remains unclear but will depend on the capacity of the PCV7 vaccine to protect against these noncovered serotypes as well as the virulence of the nonvaccine strains. Pneumococcal conjugate vaccines intended to cover nine and 11 serotypes are in development [163]. Another question that remains unanswered is the duration of protection afforded to patients who are immunized. Finally, the approach to the patient who is not fully immunized is still unclear. Partial immunization likely provides some protection against pneumococcus; the majority of patients in the post-surveillance PCV7 studies were not fully immunized (ie, three vaccinations), but there was still a decline in invasive pneumococcal disease [33].

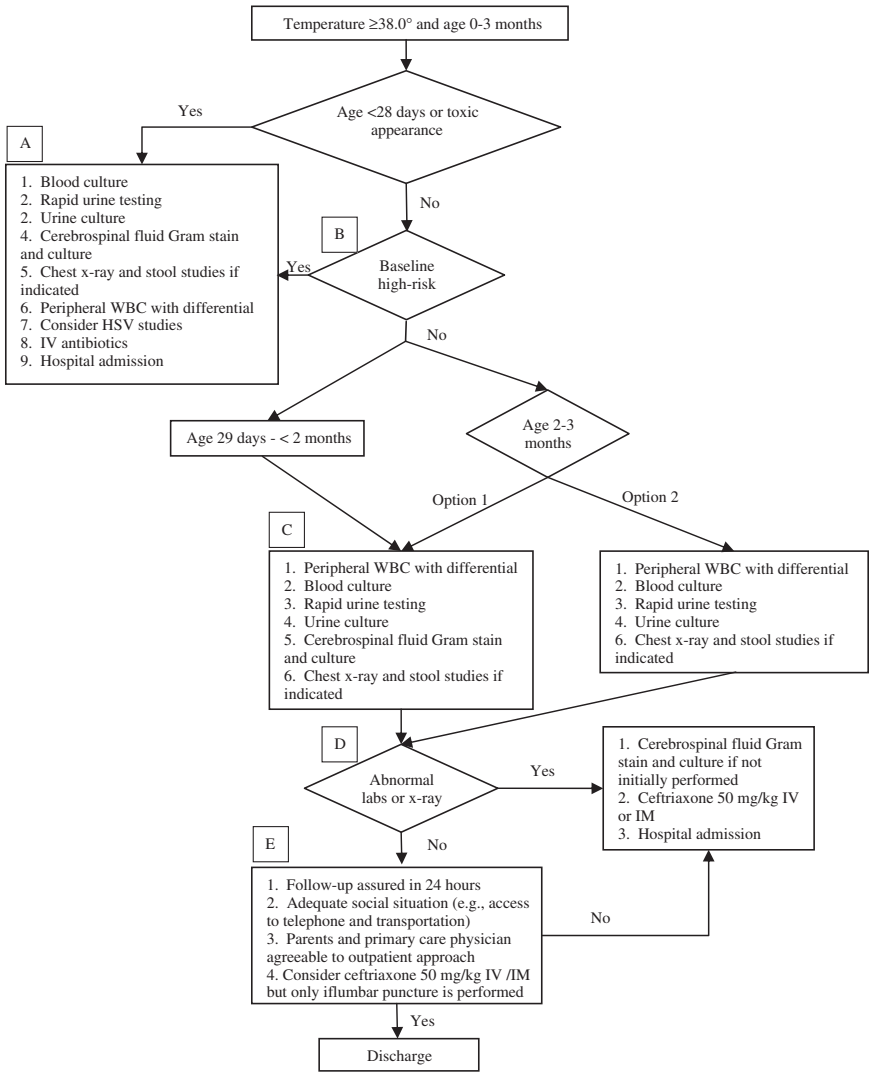
Despite the use of the PCV7 vaccine, patients will still develop bacteremia, and there will be still be a need for better tests to diagnose invasive bacterial disease. Several additional tests are being studied as potential surrogate markers for bacterial disease in young children: procalcitonin (not yet available in the United States), C-reactive protein, and interleukin-6 [164–171].

Summary

Most children 0 to 36 months of age who have fever without an obvious source have viral infections, but certain subsets of febrile children are at higher risk for more serious bacterial disease. The child who appears to be toxic, regardless of age, needs a comprehensive work-up, antibiotic coverage, and admission to the hospital. Generally, this entails a complete blood count with differential, blood culture, urinalysis and urine culture, lumbar puncture with cerebrospinal fluid analysis, Gram stain and culture, and, when indicated, chest radiographs and stool studies. These patients should receive broad-spectrum parenteral antibiotics before hospital admission. The febrile neonate (0–28 days old) is at high risk for serious bacterial infection, even with benign examination and normal screening laboratory results. Therefore, these patients also need a complete blood count with differential, blood culture, urinalysis and urine culture, lumbar puncture with cerebrospinal fluid analysis, Gram stain and culture, and, when indicated, chest radiographs and stool studies. Febrile neonates should receive empiric antibiotic coverage, typically with ampicillin (50 mg/kg IV, or 100 mg/kg if meningitis is suspected) and cefotaxime (50 mg/kg IV, or 100 mg/kg if meningitis is suspected) or gentamicin (2.5 mg/kg IV).

The febrile young infant (1–3 months old) is also at significant risk for bacterial infection. These patients need complete blood counts, blood cultures, urinalyses and urine cultures. A lumbar puncture with cerebrospinal fluid analysis, Gram stain, and culture should be strongly considered because laboratory

tests such as the white blood cell count are inaccurate in predicting which patients have meningitis. When they are clinically indicated, chest radiographs and stool studies should be obtained as well. If any of these test findings are abnormal (including peripheral WBC $\geq 15{,}000/mm^3$ or $\leq 5000/mm^3$, band-to-neutrophil ratio ≥ 0.2, a urine dipstick test positive for nitrite or leukocyte esterase, or ≥ 5 WBCs/hpf, or organisms seen on Gram stain; cerebrospinal fluid with ≥ 8 WBC/mm^3 or organisms on Gram stain; or ≥ 5 WBC/hpf on the stool specimen or evidence of pneumonia on a chest radiograph), these patients should receive ceftriaxone (50 mg/kg IV or IM, or 100 mg/kg IV if meningitis is suspected)



and should be admitted to the hospital. If these initial laboratory results are normal, a patient can be discharged if follow-up within 24 hours (or sooner if clinically worse) can be assured. The administration of ceftriaxone, 50 mg/kg IV or IM, should be considered if a lumbar puncture is performed, but if a lumbar puncture is not performed, antibiotics should be withheld. If a patient is 2 to 3 months old and the practitioner is comfortable with pediatric assessment skills, these children can be treated similarly to older febrile children.

The older infant or toddler (3–36 months old) who has a temperature of $\geq 39.0^{\circ}C$ may be treated more selectively. In this age group, if no febrile source is identified definitively, a catheterized urine specimen for evaluation (dipstick, urinalysis, microscopy, or Gram stain) and urine culture should be obtained in girls less than 2 years old, if two or more of the following risk factors are present: age less than 12 months old, fever for 2 or more days, temperature $\geq 39.0^{\circ}C$, white, and no alternative source of fever. All boys younger than 6 months old and all uncircumcised boys younger than 12 months old should also have catheterized urine sent for rapid urine testing and culture. Based on pre-PCV7 data, the most cost-effective approach to the child who has not had at least three PCV7 doses is to obtain a CBC. If the WBC count is $\geq 15{,}000/mm^3$, a blood culture should be ordered and the administration of ceftriaxone should be considered. Other options (eg, blood culture only or CBC and blood culture with selective antibiotic administration) are reasonable. However, in nontoxic children who have had three PCV7 immunizations and who are not at risk for meningococcal disease, some practitioners believe that obtaining any blood work is unnecessary. The current

Fig. 1. (*A*) Urine testing can be accomplished either by microscopy, Gram stain, or urine dipstick. Chest radiographs are indicated in patients with hypoxia, tachypnea, abnormal lung sounds, or respiratory distress. Stool studies are indicated in patients with diarrhea. Herpes simplex virus testing should be considered in the presence of risk factors (see text for details). HSV testing is best accomplished by polymerase chain reaction or viral culture. Neonates should receive both ampicillin (50 mg/kg IV, or 100 mg/kg IV if meningitis is suspected) and cefotaxime (50 mg/kg, or 100 mg/kg IV if meningitis is suspected) or gentamicin (2.5 mg/kg IV). Additionally, neonates with findings suggestive of HSV infection should receive acyclovir (20 mg/kg IV). Older children should receive ceftriaxone (50 mg/kg IV, or 100 mg/kg IV if meningitis is suspected). A WBC count with differential may be ordered, but the results should not dissuade the clinician from pursuing a full evaluation and treatment with antibiotics. (*B*) Young patients who have increased underlying risk include children who were premature, had prolonged hospital stays after birth, those with underlying medical conditions, patients with indwelling medical devices, fever lasting longer than 5 days, or patients already on antibiotics. (*C*) Urine testing can be accomplished either by microscopy, Gram stain, or urine dipstick. Chest radiographs are indicated in patients with hypoxia, tachypnea, abnormal lung sounds, or respiratory distress. Stool studies are indicated in patients with diarrhea. (*D*) Abnormal laboratory findings: peripheral WBC count $\leq 5{,}000/mm^3$ or $\geq 15{,}000/mm^3$ or band-to-neutrophil ratio ≥ 0.2; urine testing, ≥ 5 WBC/hpf, bacteria on Gram stain, or positive leukocyte esterase or nitrite; cerebrospinal fluid, ≥ 8 WBC/mm^3 or bacteria on Gram stain; stool specimen, ≥ 5 WBC/hpf; and chest radiograph, infiltrate detected. (*E*) Administering ceftriaxone (50 mg/kg IV or IM) is optional but should only be considered in patients who have undergone lumbar puncture. Patients who have not undergone lumbar puncture should not get ceftriaxone. (*Adapted from* Baraff L. Management of fever without source in infants and children. Ann Emerg Med 2000;36(6):602–14.)

evidence suggests that this may become a reasonable approach, but studies addressing this specific approach have not yet been published (Figs. 1 and 2).

Finally, it is critically important to recognize that there is no combination of clinical assessment and diagnostic testing that will successfully identify all patients with serious infection at the time of initial presentation. Therefore, the importance of timely reassessment cannot be overemphasized, and caretakers must be instructed to return to the ED or the office immediately for any deterioration in the child's condition. While strategies such as that described above may help guide the evaluation and treament of febrile young infants,

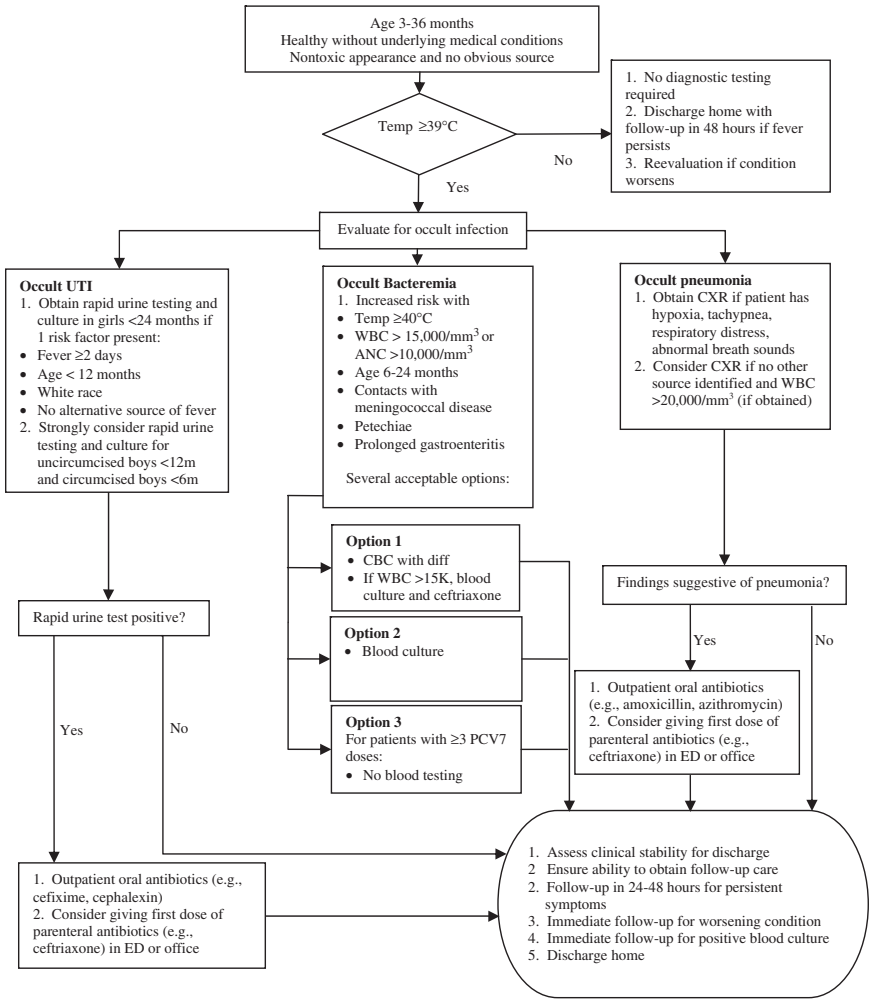


Fig. 2. Algorithm for treating children aged 3 to 36 months old (may be used for patients 2 to 3 months old as well; see text). (*Adapted from* Baraff L. Management of fever without source in infants and children. Ann Emerg Med 2000;36(6):602–14.)

no single approach can capture the nuances of all febrile young patients. Therefore, this approach should serve as an adjunct to, and not a replacement for clinician judgment.

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Corticosteroids for acute bacterial meningitis (Review)

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ABSTRACT

Background
In experimental studies, the clinical outcome of acute bacterial meningitis has been related to the severity of the inflammatory process in the subarachnoidal space. Treatment with corticosteroids can reduce this inflammatory response and thereby may improve outcome. We conducted a meta-analysis of randomised controlled trials (RCTs) of adjuvant corticosteroids in the treatment of acute bacterial meningitis.

Objectives
We conducted a systematic review examining the efficacy and safety of adjuvant corticosteroid therapy in acute bacterial meningitis.

Search strategy
In this updated review, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 2, 2006); MEDLINE (1966 to July 2006); EMBASE (1974 to June 2006); Current Contents (2001 to June 2006); and reference lists of all articles. We also contacted manufacturers and researchers in the field.

Selection criteria
Eligible published and non-published RCTs on corticosteroids as adjuvant therapy in acute bacterial meningitis. Patients of any age and in any clinical condition, treated with antibacterial agents and randomised to corticosteroid therapy (or placebo) of any type, could be included. At least case fatality rate or hearing loss had to be recorded for inclusion.

Data collection and analysis
Two review authors independently assessed trial quality and extracted data. Adverse effects were collected from the trials. Additional analyses were performed for children and adults, causative organisms, and low-income and developed countries.

Main results
Eighteen studies involving 2750 people were included. Overall, adjuvant corticosteroids were associated with lower case fatality (relative risk (RR) 0.83, 95% CI 0.71 to 0.99), lower rates of severe hearing loss (RR 0.65, 95% CI 0.47 to 0.91) and long-term neurological sequelae (RR 0.67, 95% CI 0.45 to 1.00). In children, corticosteroids reduced severe hearing loss (RR 0.61, 95% CI 0.44 to 0.86). In adults, corticosteroids gave significant protection against death (RR 0.57, 95% CI 0.40 to 0.81) and short-term neurological sequelae (RR 0.42, 95% CI 0.22 to 0.87). Subgroup analysis for causative organisms showed that corticosteroids reduced mortality in patients with meningitis due to *Streptococcus pneumoniae* (RR 0.59, 95% CI 0.45 to 0.77) and reduced severe hearing loss in children with meningitis due to *Haemophilus influenzae* (RR 0.37, 95% CI 0.20 to 0.68); subgroup analysis for patients with meningococcal showed a nonsignificant favourable trend in mortality (RR 0.71, 95% CI 0.31 to 1.62). Sub analyses for high-income and low-income countries of the effect of corticosteroids on mortality showed RRs of 0.83 (95% CI 0.52 to 1.05) and 0.87 (95% CI 0.72 to 1.05), respectively. Corticosteroids were protective against short-term neurological sequelae in patients with bacterial meningitis high-income countries (RR 0.56, 95% CI 0.3 to 0.84); in low-income countries this RR was 1.09 (95% CI 0.83 to 1.45). For children with bacterial meningitis admitted in high-income countries, corticosteroids showed a protective effect of on severe hearing loss (RR 0.61, 95% CI 0.41 to

0.90) and favourable point estimates for severe hearing loss associated with non-*Haemophilus influenzae* meningitis (RR 0.51, 95% CI 0.23 to 1.13) and short-term neurological sequelae (RR 0.72, 95% CI 0.39 to 1.33). For children in low-income countries, the use of corticosteroids was neither associated with benefit nor with harmful effects. Overall, adverse events were not increased significantly with the use of corticosteroids.

Authors' conclusions

Overall, corticosteroids significantly reduced rates of mortality, severe hearing loss and neurological sequelae. In adults with community-acquired bacterial meningitis, corticosteroid therapy should be administered in conjunction with the first antibiotic dose. In children, data support the use of adjunctive corticosteroids in children in high-income countries. We found no beneficial effect of corticosteroids for children in low-income countries.

PLAIN LANGUAGE SUMMARY

The corticosteroid dexamethasone can reduce hearing loss and death after meningitis for both children and adults

Acute bacterial meningitis is an infection of the membrane lining the brain that often causes hearing loss and is frequently fatal. It is usually caused by bacteria spreading from an ear or throat infection. Corticosteroids are drugs that can reduce inflammation caused by infection. Research on the use of corticosteroids for meningitis has had conflicting results. This review of trials found that the corticosteroid dexamethasone leads to a major reduction in hearing loss and death in both children and adults, without major adverse effects.

BACKGROUND

Acute bacterial meningitis remains a disease with a high mortality rate, ranging from 10 to 30% despite advances in critical care (Bohr 1983; Baraff 1993; van de Beek 2004b; van de Beek 2006a). Late sequelae such as cranial nerve impairment, especially hearing loss, occur in 5 to 40% of patients (Bohr 1983; Baraff 1993; van de Beek 2002; van de Beek 2004b; van de Beek 2006a). In experimental studies, the outcome has been related to the severity of the inflammatory process in the subarachnoidal space (Scheld 1980; Tauber 1985). Treatment with corticosteroids results in a reduction of the inflammatory response in the cerebrospinal fluid (CSF) (Scheld 1980; Tauber 1985). These pathophysiological insights prompted investigators to evaluate corticosteroids as an adjuvant therapy in acute bacterial meningitis. We conducted a meta-analysis of randomised controlled trials (RCTs) of adjuvant corticosteroids in the treatment of acute bacterial meningitis.

OBJECTIVES

To examine the efficacy and safety of adjuvant corticosteroid therapy in acute bacterial meningitis.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Eligible randomised controlled trials (RCTs) of corticosteroids as an adjuvant therapy in acute bacterial meningitis.

Types of participants

Participants of any age and in any clinical condition.

Types of intervention

Participants treated with antibacterial agents and randomised to corticosteroid therapy (or placebo) of any type.

Types of outcome measures

At least rates of case fatality rate or hearing loss had to be recorded for studies to be included.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Acute Respiratory Infections Group methods used in reviews.

In the first publication of this review , we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* issue 1, 2003); MEDLINE (1966 to April 2002); EMBASE (1974 to April 2002); HEALTHLINE (1988 to April 2002); Current Contents for trials published before the April

1st 2002, and reference lists of all articles. We also contacted manufacturers and researchers in the field (DvdB).

In this 2006 update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 2, 2006); MEDLINE (1966 to July 2006); EMBASE (1974 to June 2006); and Current Contents (2001 to June 2006).

MEDLINE was searched using the following keywords and MeSH terms in conjunction with the highly sensitive search strategy designed by the Cochrane Collaboration for identifying RCTs (Higgins 2005). The same strategy was used to search CENTRAL and adapted to search EMBASE (WebSpirs) and Current Contents (OVID).

MEDLINE (OVID)
1 exp Meningitis/
2 meningit$.mp.
3 or/1-2
4 exp Adrenal Cortex Hormones/
5 corticosteroid$.mp.
6 exp Steroids/
7 steroid$.mp.
8 exp Dexamethasone/
9 dexameth$.mp.
10 or/4-9
11 3 and 10

We performed the search without any language restrictions. In addition, we identified relevant trials by searching references listed in published studies, handsearching congress abstracts, personal communication with researchers and experts in the field and from literature lists of pharmaceutical companies. Two review authors did the assessment for inclusion in the methodological appraisal (DvdB, JdG).

METHODS OF THE REVIEW

Methodological appraisal

We performed the study appraisal using the Jadad scale (Jadad 1996). This is a validated 5-point scale evaluating randomisation (0 to 2 points), double blinding (0 to 2 points), and withdrawals and dropouts (0 to 1 point). Two experienced researchers, not working in the field of infectious diseases, performed a blinded appraisal. We resolved disagreements by consensus. All trials with 1 or 2 points for randomisation in the Jadad score were included in the analysis. In addition, allocation concealment was assessed as adequate, inadequate, unclear, or not used (by DvdB; 'Characteristics of included studies' table; Schulz 1995).

Extraction of data

Two review authors (DvdB, JdG) independently extracted the data, using a pre-determined protocol. We included all patients who were randomised or who started therapy in the intention-to-treat analysis. We included all patients who complied with the study protocol in the per-protocol analysis. Data were cross checked and differences were resolved by discussion.

Efficacy

Primary outcome measures were mortality, severe hearing loss and neurological sequelae. Hearing loss was defined as severe when there was bilateral hearing loss greater than 60 dB or requiring bilateral hearing aids. Neurological sequelae were defined as focal neurological deficits other than hearing loss, epilepsy (not present before meningitis onset), severe ataxia and severe memory or concentration disturbance. Children whose only non hearing deficit(s) were speech or language disturbances were not counted as having non-hearing deficits if these problems were associated with severe hearing loss. We analysed both short- and long-term neurological sequelae, other than hearing loss. Short-term neurological sequelae were defined as sequelae assessed between discharge and six weeks after hospital discharge. Long-term neurological sequelae were defined as sequelae assessed between 6 and 12 months after discharge. Whenever possible, we extracted data for both these outcomes.

We performed subgroup analyses regarding age, causative organism and time of administration of steroids. Two age groups were defined: patients younger than 16 years and those of 16 years and older. Four categories of causative organisms were defined: *Haemophilus influenzae (H. influenzae), Neisseria meningitidis (N. meningitidis), Streptococcus pneumoniae (S. pneumoniae)* and other pathogens (including patients with negative CSF culture).

Studies were analysed in two subsets divided into low-income and high-income countries. Low-income countries had a United Nations Human Development Index of less than 0.7 and high-income countries had an index of 0.7 or higher (UNHDI 2003).

Safety

Adverse events were defined as clinically evident gastrointestinal tract bleeding, reactive arthritis, pericarditis, herpes zoster or herpes simplex virus infection, fungal infection, secondary fever (defined as a temperature of 38°C or above occurring after at least one afebrile day during the course of hospitalisation) and persistent fever (defined as fever that continued longer than five consecutive days after initiation of appropriate antibiotic therapy). The total number of adverse events in each treatment group was calculated. The frequency of clinically evident gastrointestinal tract bleeding was evaluated separately.

Statistical analysis

Statistical analysis was performed using Review Manager 4.2 software. Chi-squared tests were used to test for heterogeneity on the basis of DerSimonian and Laird Q statistics; P values for heterogeneity among studies ranged from 0.6 to 1, so a fixed-effect model was chosen (Mantel-Haenszel visu-ratio method); these P values for sub analyses of high-income and low-income countries were sometimes lower than 0.6 (noted in-text). The effect of

steroids was expressed as relative risks (RR), where a value below 1.0 indicates a beneficial effect of steroids. Statistical uncertainty was expressed with 95% confidence intervals (CI).

DESCRIPTION OF STUDIES

Selection of studies

We identified 32 potential eligible trials, of which two were described in one paper (Lebel 1988a; Lebel 1988b). Nine trials which did not obtain the necessary points for randomisation on the Jadad score were excluded - see Additional Table 01(Baldy 1986; Daoud 1999; Gijwani 2002; Jensen 1969; Lepper 1959; Marguet 1993; Ozen 2006; Passos 1979; Shembesh 1997). Subsequently, one study which compared two dexamethasone regimens (Syrogiannopoulos1994) and two studies presenting insufficient data (communications during scientific meetings only) (Farina 1995; Peltola 2004) were excluded, leaving 20 eligible trials.

Characteristics of studies

Subjects over the age of 16 years were included in five studies (Bennett 1963; Bhaumik 1998; de Gans 2002; Girgis 1989; Thomas 1999). In two other studies, patients older than 12 years were considered adults (Bhaumik 1998; Girgis 1989). The study intervention consisted of dexamethasone in 17 of 20 studies; dosages ranged from 0.4 to 0.9 mg/kg and the duration ranged from two to four days (Additional Table 02). In the other studies hydrocortisone, prednisolone or a combination of both was given (Bademosi 1979; Bennett 1963; DeLemos 1969).

Study medication was administered with or before the first dose of antibiotic in nine studies (Bademosi 1979; de Gans 2002; Girgis 1989; Kanra 1995; Kilpi 1995; Molyneux 2002; Odio 1991; Qazi 1996; Schaad 1993) and in seven studies after the first doses. In four studies, the time of administration was not stated. Various antibiotic regimens were used and are listed in Additional Table 02. Third generation cephalosporins were most frequently prescribed.

A sample size calculation was given in four studies (de Gans 2002; Molyneux 2002; Qazi 1996; Thomas 1999). An intention-to-treat analysis was available from three studies (Bennett 1963; de Gans 2002; Molyneux 2002). In the other studies only per-protocol data were available to be ascertained. Therefore, the final analysis was based mostly upon per-protocol figures, including 2750 of 2961 (93%) randomised patients; in two studies, intention-to-treat figures were used (de Gans 2002; Molyneux 2002).

Mortality rates ranged between 0 and 45% (Table 02). In one study, patients who died during the first 18 hours of admission were excluded (Belsey 1969). Nevertheless these results were included in the analysis. Hearing was adequately assessed (by audiometry and/or brainstem auditory evoked potentials) in 1383 children. Definitions of adverse events were heterogeneous and the numbers of events were recalculated for each study.

METHODOLOGICAL QUALITY

The quality of included studies was high, with a median Jadad score of 4 (Additional Table 02).

RESULTS

Primary outcomes

The overall number of participants who died was significantly smaller in the corticosteroid group than in the placebo group (186 out of 1387 (13.4%) versus 220 out of 1363 (16.1%), RR 0.83, 95% CI 0.71 to 0.99) (Bademosi 1979; Belsey 1969; Bennett 1963; Bhaumik 1998; Ciana 1995; de Gans 2002; DeLemos 1969; Girgis 1989; Kanra 1995; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b; Lebel 1989; Molyneux 2002; Odio 1991; Qazi 1996; Schaad 1993; Thomas 1999; Wald 1995). The number of participants with severe hearing loss was significantly smaller in the corticosteroid group than in the placebo group (50 out of 884 (5.7%) versus 77 out of 863 (9.8%), RR 0.65, 95% CI 0.44 to 0.91) (Belsey 1969; Girgis 1989; Kanra 1995; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b;Girgis 1989;Lebel 1989; Molyneux 2002; Odio 1991; Qazi 1996; Schaad 1993; Wald 1995; Bhaumik 1998). Short-term neurological sequelae (other than hearing loss) were assessed in ten studies including 1175 participants (Bhaumik 1998; Ciana 1995; de Gans 2002; Kanra 1995; Kilpi 1995; Lebel 1988a; Lebel 1988b; Lebel 1989; Molyneux 2002; Thomas 1999); although the point estimate was favourable, there was no significant beneficial effect of corticosteroids (95% CI 0.68 to 1.08). The number of participants with long-term neurological sequelae was significantly less in the corticosteroid group than in the placebo group (36 out of 596 (6.0%) versus 51 out of 567 (9.0%), RR 0.67, 95% CI 0.45 to 1.00) (Girgis 1989; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b; Kanra 1995; Odio 1991; Qazi 1996; Schaad 1993; Wald 1995). Adverse events were equally divided between the treatment and placebo group (RR 1.08, 95% CI 0.90 to 1.29) (Bennett 1963; Belsey 1969; Bhaumik 1998; de Gans 2002; Kanra 1995; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b; Lebel 1989; Molyneux 2002; Odio 1991; Qazi 1996; Schaad 1993; Thomas 1999; Wald 1995). The risk for gastro-intestinal tract bleeding was not increased in patients treated with corticosteroids (data not shown).

Subgroup analyses

One hundred and forty-two out of 1051 (13.5%) children in the placebo group died, compared to 139 out of 1023 (13.6%) who received corticosteroids (RR 0.99, 95% CI 0.81 to 1.20) (Belsey 1969; Ciana 1995; DeLemos 1969; Girgis 1989; Kanra 1995; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b; Lebel 1989; Molyneux 2002; Odio 1991; Qazi 1996; Schaad 1993; Wald 1995). Corticosteroids prevented hearing loss in children: 76 of the 688 (11.0%) children in the control group had severe hearing loss, compared to 46 out of 695 (6.6%) who received corticosteroids (RR 0.61, 95% CI 0.44 to 0.86). Sub-analysis of chil-

dren gave a favourable point estimate for risk reduction of long-term sequelae by corticosteroids (which did not reach statistical significance). For adult participants, corticosteroids gave significant protection against death: 69 out of 315 (21.9%) adults in the placebo group died, compared to 36 out of 308 (11.7%) who received corticosteroids (RR 0.57, 95% CI 0.40 to 0.81) (Bhaumik 1998; Bennett 1963; de Gans 2002; Girgis 1989; Thomas 1999). In addition, there was protective effect of corticosteroids on short-term sequelae in adults (RR 0.42, 95% CI 0.22 to 0.78).

Case-fatality rates varied according to the bacteria. Of the 709 participants with meningitis due to *H. influenzae*, 70 died (9.9%); compared with 22 out of 517 participants with meningococcal meningitis (4.3%) and 160 out of 641 participants with pneumococcal meningitis (25.0%). Corticosteroids protected against death in pneumococcal meningitis (RR 0.59, 95% CI 0.45 to 0.77), as well as in meningitis caused by bacteria other than *H. influenzae* (including participants with negative CSF culture; RR 0.77, 95% CI 0.62 to 0.96); there was considerable heterogeneity among included studies in these analyses (P = 0.01 and 0.04, respectively). In patients with meningococcal meningitis, corticosteroids were associated with a non-significant reduction in mortality (RR 0.71, 95% CI 0.31 to 1.62). For children with meningitis caused by *H. influenzae*, hearing loss was significantly reduced by steroids (RR 0.37, 95% CI 0.20 to 0.68). For children with meningitis caused by bacteria other than *H. influenzae,* no significant beneficial effect was seen (RR 0.86, 95% CI 0.57 to 1.30). If data from the Malawi study were excluded, the RR was 0.42 (95% CI 0.20 to 0.89) (Molyneux 2002). There were too few participants with specified neurological sequelae (other than hearing loss) and a known causative organism to assess pathogen-specific effects.

Studies were analysed in two subsets divided into low-income (Bademosi 1979; Bhaumik 1998; Ciana 1995; Girgis 1989; Molyneux 2002; Qazi 1996) and high-income countries (Belsey 1969; Bennett 1963; de Gans 2002; DeLemos 1969; Kanra 1995; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b; Lebel 1989; Odio 1991; Schaad 1993; Thomas 1999; Wald 1995). On mortality, point estimates were 0.87 (95% CI 0.72 to 1.05) for low-income countries and 0.74 (95% CI 0.52 to 1.05) for high-income countries. The P value for heterogeneity among studies included in the analysis on mortality in low-income countries was 0.06, indicating considerable heterogeneity. Sub-analyses for children in high-income countries showed a protective effect of corticosteroids on severe hearing loss (RR 0.32, 95% CI 0.18 to 0.57); a favourable point estimate for severe hearing loss in meningitis caused by bacteria other than *H. influenzae* (6 of 175 (3.4%) versus 15 of 188 (8.0%); RR 0.48, 95% CI 0.20 to 1.15); and a favourable point estimate for short-term neurological sequelae (RR 0.76, 95% CI 0.45 to 1.27). For children in low-income countries, corticosteroids had no beneficial effect on mortality (RR 0.96, 95% CI 0.78 to 1.18), severe hearing loss (RR 1.04, 95% CI 0.66 to 1.63), and short-term neurological sequelae (RR 1.08, 95% CI 0.82 to 1.44).

Sub-analyses for timing of corticosteroids (before or with the first dose of antibiotics versus after the first dose of antibiotics) showed similar results for mortality (RR 0.84, 95% CI 0.70 to 1.02 and RR 0.80, 95% CI 0.70 1.02). Within the analysis of studies with administration before or with the first dose of antibiotics there was significant heterogeneity between studies (P = 0.05). For sub-analyses of severe hearing loss and short-term neurological sequelae, pooled studies with administration after the first dose of antibiotics had slightly more favourable point estimates than studies with early administration of corticosteroids.

DISCUSSION

This meta-analysis showed a beneficial effect of adjunctive corticosteroids in acute bacterial meningitis. Overall, corticosteroids significantly reduced rates of mortality, severe hearing loss and neurological sequelae.

In children with acute bacterial meningitis, corticosteroids reduced the rate of severe hearing loss from 11.0 to 6.6%. A large proportion of included children had meningitis due to *H. influenzae*, and Hib meningitis has virtually been eliminated in high-income countries since routine vaccination of children against this bacterium was started (Peltola 2000; van de Beek 2006b). Sub-analyses for children in high-income countries showed a protective effect of corticosteroids on severe hearing loss overall, and favourable point estimates for severe hearing loss in non-*Haemophilus* meningitis and for short-term neurological sequelae. Therefore, we recommend the use of adjunctive corticosteroids in children in high-income countries. For children in low-income countries, the use of corticosteroids was neither associated with benefit nor with harmful effects.

None of the studies in this analysis involved children younger than one month (neonatal meningitis). Since this is a specific group of patients with specific causative agents (Saez-Llorens 2003), the use of adjunctive corticosteroids is not recommended in neonates with acute bacterial meningitis. A RCT evaluating corticosteroids in neonatal meningitis should be performed.

In adults with acute bacterial meningitis, corticosteroids reduced mortality rate from 21.7 to 11.7%; so, 10 adult patients with acute bacterial meningitis would need to be treated with corticosteroids to save one additional life. On the basis of overall benefit, corticosteroid therapy should be commenced in adults with suspected or proven community-acquired bacterial meningitis (van de Beek 2006a).

There was a difference in efficacy of corticosteroids between high and low-income countries. This difference was mainly caused by inclusion of the Malawian study, which included children in whom

treatment began late, HIV-1 positive children, and children receiving inappropriate antibiotic therapy (Molyneux 2002). There may be several reasons for the difference in efficacy of corticosteroids, such as delayed presentation, clinical severity, underlying anemia, malnutrition, the antibiotic used and HIV-1 positive children. A recent study compared characteristics of children with culture-positive bacterial meningitis treated in the Royal Liverpool Children's Hospital and in the Children's Unit, Queen Elizabeth Central Hospital, Blantyre, Malawi (Molyneux 2006); the two cohort studies were derived from time-periods before the introduction of vaccines. Children in Malawi presented later and were more often comatose and malnourished, compared with children in Britain. Mortality from bacterial meningitis in children in Malawi was much higher than in children in Britain (41 versus 7%), even when infected with the same organisms. A meta-analysis of individual patient data should try to define the reasons for differing outcomes in high versus low income countries and identify those children in low-income countries who could benefit from corticosteroids.

Several biases may have diminished the reliability of our results. The first confounding factor is selection bias. Several included studies on childhood bacterial meningitis had exceptional low mortality rates; nine studies had mortality rates of 3% or less. Mortality rates of childhood bacterial meningitis in previously reported studies ranged from 8 to 20% (Baraff 1993; Bohr 1983). Inclusion of patients in the meta-analysis with a less severe illness, as reflected in very low case fatality rates, will probably underestimate the protective effect of corticosteroids (Glasziou 1995). Few included studies had high mortality rates but in three studies, mortality rates were over 30%. For patients admitted in a late stage of disease, adjuvant corticosteroids are less protective and might even be harmful (Prasad 1995). Inclusion of such patients will again lead to an underestimate of the treatment effect.

A second bias is introduced when participants are withdrawn (Prasad 1995; Qazi 1996). The analysis was based upon per-protocol figures, as intention-to-treat figures were available for only three studies. In total, 211 participants were withdrawn after the randomisation process, often for unknown reasons. Reasons for withdrawal include ineligibility according to trial criteria or inability to complete the treatment-protocol (Prasad 1995). Withdrawals on the grounds on ineligibility may have been influenced by knowledge of outcome; if so, this would advantage the corticosteroid regimen. Excluding participants, because of an inability to complete the course of corticosteroids due to side effects (for example, upper gastro-intestinal bleeding) clearly introduces bias in favour of the study medication, whereas withdrawals due to loss to follow up might favour the placebo group. In the Egyptian study, which was not placebo-controlled and not double-blinded, only three pathogens were cultured from the cerebral spinal fluid of enrolled participants, suggesting withdrawal of patients with other bacteria culture form CSF and those with negative CSF cultures (Girgis 1989).

A third bias might be introduced by including only RCTs as assessed by the previous validated Jadad scale (Jadad 1996). Studies that used quasi-randomisation, such as alternate allocation, were excluded (Gijwani 2002). Although the quality of included studies was high, reflected in a high median Jadad score, several included studies suffered from methodological flaws and drawbacks. Quality assessment and methods of its incorporation into systemic reviews remain controversial; nevertheless, its importance is clearly accepted (Moher 1998).

A fourth bias is introduced by competitive risks. The comparisons of hearing loss and neurologic sequelae (other than hearing loss) were made excluding all patients who died. Since mortality is possibly a treatment-related outcome, the treatment groups that exclude fatality cases may not be comparable. Competitive risks in this analysis will lead to an underestimation of the treatment effect of corticosteroids.

Finally, the included studies were heterogeneous with respect to study protocol. The first study was published in 1963 (Bennett 1963), the last two in 2002 (de Gans 2002; Molyneux 2002). Several different study interventions were used. Therefore, study population effect-sizes were calculated as relative risks.

The use of steroids was associated with only few side effects. However, definitions of adverse events used in the studies were heterogeneous and most studies had no specified criteria in advance, so under ascertainment is possible. The relative risk for gastro-intestinal bleeding did not reach statistical significance. Concerns have been raised over the interference by corticosteroids on CSF eradication of meningeal pathogens by reducing the blood brain barrier permeability and thereby the penetration of antibiotics in the subarachnoid space. Although in children with acute bacterial meningitis, treatment of dexamethasone did not reduce vancomycin levels in the CSF (Klugman 1995), therapeutic failures have been described in adults treated with standard doses of vancomycin and adjunctive dexamethasone (Viladrich 1991). Therefore, patients with pneumococcal meningitis who are treated with vancomycin and dexamethasone should be carefully observed throughout therapy (van de Beek 2006a).

In adults who survive acute bacterial meningitis, cognitive impairment occurs frequently (van de Beek 2002; van de Beek 2006a). As corticosteroids may potentiate ischaemic injury to neurons (Sapolsky 1985), it is important to know whether corticosteroids have beneficial effects on hearing loss and mortality but worsen cerebral cortical functioning (van de Beek 2006b). Neuropsychological outcome was recently evaluated in patients included in the European Dexamethasone Study who survived pneumococcal or meningococcal meningitis (Weisfelt 2006). In 87 out of 99 eligible patients, 46 (53%) of whom were treated with dexamethasone and 41 (47%) of whom received placebo, no significant differences in outcome were found between patients in the dexamethasone and placebo groups (median time between meningitis and testing was eight years). In another recent study on long-term neuropsychological outcome and dexamethasone in children, children after pneumococcal meningitis who were treated with corti-

costeroids showed better academic achievements compared with children with pneumococcal meningitis who were not treated with adjunctive corticosteroids (Ozen 2006).

The available studies do not address two important other issues - the minimum duration of corticosteroid therapy or the maximum length of time after parenteral antibiotic therapy for commencement of corticosteroid therapy. In most studies, a four-day regimen of dexamethasone (0.4 or 0.6 mg/kg/day) divided into four daily doses was used. One randomised, prospective study involving 118 children with bacterial meningitis showed a two-day and four-day regimen of dexamethasone to be similarly effective (Syrogiannopoulos1994). In this study, physicians were not blinded for treatment groups. Long-term neurological sequelae, or moderate hearing impairment (or both), were found in 1.8 and 3.8% of patients treated with dexamethasone for two and four days, respectively. It is unlikely that a RCT will be performed to answer the question of whether a two-day or four-day should be used in bacterial meningitis; such a clinical trial would need a very large number of patients enrolled to detect significant differences between groups. Since most studies used a four-day regimen (without increase of side-effects) we advice the use of the four-days of corticosteroid therapy.

Subanalyses for timing of corticosteroids (before or with the first dose of antibiotics versus after the first dose of antibiotic) showed no differences in efficacy of corticosteroids. In previous reports, administration of corticosteroids before or with the first dose of parenteral antibiotics seemed to be more effective than administration after the first dose of antibiotics (King 1994; McIntyre 1997). A RCT involving 3301 adults with bacterial meningitis in European countries showed a beneficial effect of the corticosteroid dexamethasone on unfavourable outcome and mortality (de Gans 2002). In this European study, dexamethasone or placebo was administered before or with the first dose of antibiotic (de Gans 2002). The beneficial effect of dexamethasone on mortality was most apparent in patients with pneumococcal meningitis. In a post hoc analysis of this study, the beneficial effect of dexamethasone on mortality in patients with pneumococcal meningitis was attributable to a reduction in systemic complications (van de Beek 2004a). Although speculative and not supported by clinical data, one implication of this finding might be that the effect of dexamethasone is not restricted to the first hours after administration (van de Beek 2006b). In experimental pneumococcal meningitis, CSF bacterial concentrations appeared to be more important than the timing of dexamethasone therapy in influencing the antibacterial-induced inflammatory response (Lutsar 2003). Hence, there is a time period beyond which corticosteroid loses its effectiveness after the first (parenteral) administration of an antibiotic agents but this time interval has not clearly been defined. Upcoming RCTs and a meta-analysis of individual patient data might provide an answer about pretreatment with (parenteral) antibiotic therapy and the effect of adjunctive corticosteroid therapy. On basis of available evidence, dexamethasone should be preferably started before of with the first dose of antibiotic therapy.

The beneficial effect of corticosteroids was most apparent in meningitis due to *H. influenzae* and *S. pneumoniae*. Subgroup analysis for patients with meningococcal showed a favourable trend in mortality. In clinical practice, the causative organisms in many cases will not be known when treatment is started. On basis of the overall benefit and absence of excess of adverse events, if corticosteroids are indicated, a four-day regimen of dexamethasone therapy should be given, regardless of bacterial aetiology.

Despite these encouraging results, the use of adjunctive corticosteroids in acute bacterial meningitis remains controversial in certain other patient subgroups. The role of corticosteroids for patients who present with both evidence of acute bacterial meningitis and septic shock remains unclear. Lower doses of corticosteroids have shown to be beneficial in septic shock (Annane 2002), while higher doses have shown to be either of no benefit or have a trend towards increased mortality (Cronin 1995; Lefering 1995).

Results of one study in children comparing placebo, adjunctive corticosteroids, glycerol and the combination of corticosteroids and glycerol, were presented during a scientific meeting in 2004 (Peltola 2004); however, results are not yet published. Two other RCTs on the effect of adjunctive corticosteroids in lower-income countries studies were recently performed. Peer-reviewed results of these three RCT are eagerly awaited.

AUTHORS' CONCLUSIONS

Implications for practice

In summary, the consistency and degree of benefit identified in this analysis merits the use of corticosteroids in adults with acute bacterial meningitis and in children with acute bacterial meningitis in high-income countries with good access to services. We recommend a four-day regimen of dexamethasone (0.6 mg/kg daily) given before or with the first dose of antibiotics.

Implications for research

(1) Trials of adjuvant dexamethasone in adults with acute bacterial meningitis in low-income countries with non-optimal access to medical services are needed. Results of upcoming RCTs are eagerly awaited.

(2) RCTs are required to assess the use of corticosteroids in neonatal meningitis.

(3) A meta-analysis of individual patient data should try to define the reasons for differing outcomes in high- versus low-income countries and identify those children in low-income countries who could benefit from corticosteroids.

(4) This individual meta-analysis may further define patient groups in whom the effect of adjunctive corticosteroids is uncer-

tain; international RCTs should be performed in these patient groups.

(5) Case series are needed to determine the effect of adjunctive dexamethasone therapy in patients with pneumococcal meningitis caused by highly penicillin- or cephalosporin-resistant strains.

FEEDBACK

Progress

Summary

Is the review due for publication in the near future? I note it was submitted over 12 months ago.

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Author's reply

It will be published 07-21-2003.

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Contributors

Dr Anna Holdgate

Paper by Shembesh et al

Summary

I have not seen the full text article, but in the medline abstract it states ages 1 month to 10 years are included. Table 01 states all ages were included.

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Author's reply

Patients of any age could be included in our review (as stated in the Pubmed abstract). In the study of Shembesh et al, patients aged 1 month to 10 years were included. However, this is only one of the 29 potential eligible trials evalutated in our review.

Diederik van der Beek

Contributors

Andrew Webster

POTENTIAL CONFLICT OF INTEREST

None.

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- Dept. of Neurology, Academic Medical Center, University of Amsterdam NETHERLANDS

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TABLES

Characteristics of included studies

Study	**Bademosi 1979**
Methods	Randomized, unblinded
Participants	10 to 59 years; bacteriologically proven pneumococcal meningitis
Interventions	Hydrocortisone, 100 mg; followed by prednisolone 60 mg/d, 14 d
Outcomes	Mortality
Notes	Jadad score and additional study characteristics in Additional Table 2
Allocation concealment	D – Not used

Study	**Belsey 1969**
Methods	Randomized, double-blind
Participants	0 to 17 years; purulent meningitis
Interventions	DXM 1.2 mg/M2/d, 4 d
Outcomes	Mortality, hearing loss, adverse events
Notes	
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	**Bennett 1963**
Methods	Randomized, double-blind
Participants	All ages; life-threatening infectious diseases, subgroup meningitis
Interventions	Hydrocortisone scheme, 7 d
Outcomes	Mortality, adverse events
Notes	
Allocation concealment	A – Adequate

Study	**Bhaumik 1998**
Methods	Randomized, unblinded
Participants	12 to 75 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 16 mg/day, 4 d; plus 3 d scheme
Outcomes	Mortality, neurological sequelae, adverse events
Notes	
Allocation concealment	D – Not used

Study	**Ciana 1995**
Methods	Randomized, unblinded
Participants	2 months to 6 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 0.4 mg/kg, 3 d
Outcomes	Mortality, neurological sequelae
Notes	
Allocation concealment	D – Not used

Study	**DeLemos 1969**
Methods	Randomized, double-blind
Participants	1 month to 17 years; diagnosis bacterial meningitis
Interventions	Methylprednisolone 120 mg/d, 3 d
Outcomes	Mortality
Notes	
Allocation concealment	A – Adequate

Study	**Girgis 1989**
Methods	Randomized, unblinded
Participants	3 months to 70 years; diagnosis bacterial meningitis
Interventions	DXM 16 -24 mg/d, 4 d
Outcomes	Mortality, hearing loss, neurological sequelae
Notes	
Allocation concealment	D – Not used

Study	**Kanra 1995**
Methods	Randomized, double-blind

Characteristics of included studies (*Continued*)

Participants	2 to 6 years; bacteriologically proven pneumococcal meningitis
Interventions	DXM 0.6 mg/kg/d, 4 d
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events
Notes	
Allocation concealment	A – Adequate

Study	**Kilpi 1995**
Methods	Randomized, unblinded
Participants	3 months to 15 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 1.5 mg/kg/d, 3 d
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events
Notes	
Allocation concealment	D – Not used

Study	**King 1994**
Methods	Randomized, double-blind
Participants	1 month to 13 years; suspected bacterial meningitis with CSF or blood criterion; also patients with suspected bacterial meningitis who were too unstable for a LP
Interventions	DXM 0.6 mg/kg/d, 4 d
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events
Notes	
Allocation concealment	B – Unclear

Study	**Lebel 1988a**
Methods	Randomized, double-blind
Participants	2 months to 16 years; suspected or proven bacterial meningitis
Interventions	DXM 0.6 mg/kg/d, 4 d
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events
Notes	
Allocation concealment	A – Adequate

Study	**Lebel 1988b**
Methods	Randomized, double-blind
Participants	2 months to 16 years; suspected or proven bacterial meningitis
Interventions	DXM 0.6 mg/kg/d, 4 d
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events
Notes	
Allocation concealment	A – Adequate

Study	**Lebel 1989**
Methods	Randomized, double-blind
Participants	2 months to 16 years; suspected or proven bacterial meningitis

Characteristics of included studies (*Continued*)

Interventions	DXM 0.6 mg/kg/d, 4 d
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events
Notes	
Allocation concealment	A – Adequate

Study	**Molyneux 2002**
Methods	Randomized, double-blind
Participants	2 months to 13 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 0.8 mg/kg/d, 2 d
Outcomes	Mortality, hearing loss, neurological sequelae
Notes	
Allocation concealment	A – Adequate

Study	**Odio 1991**
Methods	Randomized, double-blind
Participants	6 weeks to 16 years; culture proved bacterial meningitis or suspected bacterial meningitis with CSF inflammation
Interventions	DXM 0.6 mg/kg/d, 4 d
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events
Notes	
Allocation concealment	A – Adequate

Study	**Qazi 1996**
Methods	Randomized, double-blind
Participants	2 months to 12 years;suspected bacterial meningitis with CSF criteria
Interventions	DXM 0.6 mg/kg/d, 4 d
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events
Notes	
Allocation concealment	A – Adequate

Study	**Schaad 1993**
Methods	Randomized, double-blind
Participants	3 months to 16 years; suspected or proven bacterial
Interventions	DXM 0.8 mg/kg/d, 2 d
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events
Notes	
Allocation concealment	A – Adequate

Study	**Thomas 1999**
Methods	Randomized, double-blind
Participants	17 to 99 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 40 mg/d, 3 d

Outcomes	Mortality, neurological sequelae, adverse events
Notes	
Allocation concealment	A – Adequate

Study	**Wald 1995**
Methods	Randomized, double-blind
Participants	2 months to 12 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 0.6 mg/kg/d, 4 d
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events
Notes	
Allocation concealment	A – Adequate

Study	**de Gans 2002**
Methods	Randomized, double-blind
Participants	Older than 16 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 40 mg/d, 4 d
Outcomes	Mortality, neurological sequelae, adverse events
Notes	
Allocation concealment	A – Adequate

Characteristics of excluded studies

Study	**Reason for exclusion**
Baldy 1986	Score on Jadad-scale of 0 for randomisation Jadad score and additional study characteristics in the additional Table 1
Daoud 1999	Score on Jadad-scale of 0 for randomisation
Farina 1995	Not enough data for inclusion (abstract only)
Gijwani 2002	Score on Jadad-scale of 0 for randomisation
Gupta 1996	Score on Jadad-scale of 0 for randomisation
Jensen 1969	Score on Jadad-scale of 0 for randomisation
Lepper 1959	Score on Jadad-scale of 0 for randomisation
Marguet 1993	Score on Jadad-scale of 0 for randomisation
Ozen 2006	Score on Jadad-scale of 0 for randomisation
Passos 1979	Score on Jadad-scale of 0 for randomisation
Peltola 2004	Not enough data for inclusion
Shembesh 1997	Score on Jadad-scale of 0 for randomisation
Syrogiannopoulos1994	Compared 2-day 4-day regimen of dexamethasone

ADDITIONAL TABLES

Table 01. Quality assessment and characteristics of excluded studies

Year (author)	1. Randomisation (0-	2. Blinding (0-2)	3. Withdrawals (0-1)	Total Jadad (0-5)	Age of patients	Antibiotics (AB)	DXM before/with AB	Death %
1959 (Lepper)	0	0	0	0	All ages	Pen or pen/strep	NS	13
1969 (Jensen)	0	0	0	0	All ages	Sulf/pen	NS	19
1979 (Passos)	0	0	0	0	All ages	Pen	NS	0
1986 (Baldy)	0	0	0	0	All ages	Amp or pen	NS	0
1993 (Marguet)	0	0	0	0	1 month to 14 years	Ceph	No	5
1994 (Syrogian)	2	0	0	2	2 months to 15 years	Various	No	0
1995 (Farina)	1	1	0	2	NG	NG	No	NG
1996 (Gupta)	0	0	0	0	12 to 70 years	Pen/chlor/gent	NS	23
1997 (Shembesh)	0	0	0	0	> 1month	Ceph	NS	13
1999 (Daoud)	0	0	0	0	Neonates	Amp+ceph	Yes	25
2002 (Gijwani)	0	0	0	0	Adults	Ceph	Yes	15
2004 (Peltola)	1	0	0	1	Children	NG	NS	NS
2006 (Ozen)	0	0	0	0	Children	NG	NS	NA

Table 02. Quality assessment and characteristics of included studies

Year (author)	1. Randomisation (0-	2. Blinding (0-2)	3. Withdrawals (0-1)	Total Jadad (0-5)	Age of patients	Antibiotics (AB)	Intervention	DXM before/with AB	Deaths %
1963 (Bennet)	2	2	0	4	All ages	NS	Hydrocortison scheme, 7 d	No	45
1969 (deLemos)	1	1	0	2	1 month to 17 years	Chlor/sulf/pen	Methylprednisolone 120 mg/d	No	3

Table 02. Quality assessment and characteristics of included studies (*Continued*)

Year (author)	1. Randomisation (0-	2. Blinding (0-2)	3. Withdrawals (0-1)	Total Jadad (0-5)	Age of patients	Antibiotics (AB)	Intervention	DXM before/with AB	Deaths %
							, 3d		
1969 (Belsey)	1	1	0	2	0 to 17 years	Clor/sulf/pen	DXM 1.2 mg/M2/d, 4 d	NS	3
1979 (Bademosi)	1	0	0	1	10 to 59 years	Sulf/pen	Hydrocortisone, 100 mg; followed by prednisolone 60 mg/d, 14 d	Yes	44
1988 (Lebel)	2	2	1	5	2 months to 16 years	Ceph	DXM 0.6 mg/kg/d, 4 d	No	2
1989 (Lebel)	2	2	1	5	3 months to 16 years	Ceph	DXM 0.6 mg/kg/d, 4 d	No	2
1989 (Girgis)	1	0	0	1	3 months to 70 years	Ampi/chlor	DXM 16-24 mg/d, 4 d	Yes	15
1991 (Odio)	2	2	0	4	6 weeks to 16 years	Ceph	DXM 0.6 mg/kg/d, 4 d	Yes	2
1993 (Schaad)	2	2	1	5	3 months to 16 years	Ceph	DXM 0.8 mg/kg/d, 2 d	Yes	0
1994 (King)	1	2	0	3	1 month to 13 years	Various	DXM 0.6 mg/kg/d, 4 d	No	1
1995 (Kilpi)	2	0	0	2	3 months to 15 years	Ceph	DXM 1.5 mg/kg/d, 3 d	Yes	2
1995 (Ciana)	1	0	1	2	2 months to 6 years	Ampi/chlor	DXM 0.4mg/kg, 3 d	NG	28
1995 (Wald)	2	2	1	5	2 months to 12 years	Ceph	DXM 0.6 mg/kg/d, 4 d	No	1
1995 (Kanra)	2	2	1	5	2 to 6 years	Sulf/amp	DXM 0.6 mg/kg/d, 4 d	Yes	5

Table 02. Quality assessment and characteristics of included studies (*Continued*)

Year (author)	1. Randomisation (0-	2. Blinding (0-2)	3. Withdrawals (0-1)	Total Jadad (0-5)	Age of patients	Antibiotics (AB)	Intervention	DXM before/with AB	Deaths %
1996 (Qazi)	2	2	1	5	2 months to 12 years	Ampi/ chlor	DXM 0.6 mg/kg/d, 4 d	Yes	19
1998 (Baumik)	1	0	0	1	12 to 75 years	Pen/chlor or ceph	DXM 16 mg/d, 4 d; plus 3 d scheme	No	13
1999 (Thomas)	1	2	1	4	17 to 99 years	Amox	DXM 40 mg/d, 3 d	No	13
2002 (de Gans)	2	2	1	5	Older than 16 years	Various	DXM 40 mg/d, 4 d	Yes	11
2002 (Molyneux)	2	2	1	5	2 months to 13 years	Pen/chlor	DXM 0.8 mg/kg/d, 2 d	Yes	31

ANALYSES

Comparison 01. All patients

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mortality	20	2750	Relative Risk (Fixed) 95% CI	0.83 [0.71, 0.99]
02 Severe hearing loss	14	1747	Relative Risk (Fixed) 95% CI	0.65 [0.47, 0.91]
03 Short-term neurological sequelae	10	1175	Relative Risk (Fixed) 95% CI	0.86 [0.68, 1.08]
04 Long-term neurological sequelae	10	1163	Relative Risk (Fixed) 95% CI	0.67 [0.45, 1.00]
05 Adverse events	15	1484	Relative Risk (Fixed) 95% CI	1.08 [0.90, 1.29]

Comparison 02. Children

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mortality	15	2074	Relative Risk (Fixed) 95% CI	0.99 [0.81, 1.20]
02 Severe hearing loss	13	1383	Relative Risk (Fixed) 95% CI	0.61 [0.44, 0.86]

Comparison 03. Adults

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mortality	5	623	Relative Risk (Fixed) 95% CI	0.57 [0.40, 0.81]
02 Short-term neurological sequelae	3	339	Relative Risk (Fixed) 95% CI	0.42 [0.22, 0.78]

Comparison 04. Causative species

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mortality			Relative Risk (Fixed) 95% CI	Subtotals only
02 Severe hearing loss in children - non-Haemophilus influenzae species	11	660	Relative Risk (Fixed) 95% CI	0.86 [0.57, 1.30]
04 Severe hearing loss in children - Haemophilus influenzae species	9	663	Relative Risk (Fixed) 95% CI	0.37 [0.20, 0.68]

Comparison 05. Income of countries

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mortality - all patients	20	2750	Relative Risk (Fixed) 95% CI	0.83 [0.71, 0.99]
02 Severe hearing loss - all patients	14	1747	Relative Risk (Fixed) 95% CI	0.65 [0.47, 0.91]
03 Short-term neurological sequelae - all patients	10	1175	Relative Risk (Fixed) 95% CI	0.86 [0.68, 1.08]
04 Mortality - children	15	2074	Relative Risk (Fixed) 95% CI	0.99 [0.81, 1.20]
05 Severe hearing loss - children	12	1311	Relative Risk (Fixed) 95% CI	0.61 [0.43, 0.86]
06 Short-term neurological sequelae -children	7	836	Relative Risk (Fixed) 95% CI	0.99 [0.77, 1.26]
07 Severe hearing loss in children due to non-Heamophilus influenzae species	11	660	Relative Risk (Fixed) 95% CI	0.86 [0.57, 1.30]

Comparison 06. Timing of steroids

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mortality	18	2594	Relative Risk (Fixed) 95% CI	0.84 [0.70, 0.99]
02 Severe hearing loss	13	1664	Relative Risk (Fixed) 95% CI	0.66 [0.47, 0.92]
03 Short-term neurologic sequelae	9	1125	Relative Risk (Fixed) 95% CI	0.87 [0.69, 1.10]

INDEX TERMS

Medical Subject Headings (MeSH)

Adolescent; Anti-Inflammatory Agents [*therapeutic use]; Dexamethasone [therapeutic use]; Glucocorticoids [*therapeutic use]; Hearing Loss [etiology; prevention & control]; Meningitis, Bacterial [complications; *drug therapy]; Prednisolone [therapeutic use]; Randomized Controlled Trials

MeSH check words

Child; Humans

COVER SHEET

Title Corticosteroids for acute bacterial meningitis

Authors van de Beek D, de Gans J, McIntyre P, Prasad K

Contribution of author(s)	Diederik van de Beek (DvdB) was responsible for co-designing and writing the review, selecting studies, extracting and analysing data. Jan de Gans (JdG) was responsible for co-designing, co-writing the review, selecting studies, extracting data. Peter McIntyre (PM) was responsible for co-writing the protocol, co-writing the review and extracting data. Kameshwar Prasad (KP) was responsible for co-writing the protocol and co-writing the review.
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Review first published	2003/3
Date of most recent amendment	16 November 2006
Date of most recent SUBSTANTIVE amendment	10 November 2006
What's New	2006 updated review: two large new clinical trials were included.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	10 July 2006
Date authors' conclusions section amended	Information not supplied by author
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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 All patients, Outcome 01 Mortality

Review: Corticosteroids for acute bacterial meningitis

Comparison: 01 All patients

Outcome: 01 Mortality

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bademosi 1979	11/28	12/24		5.8	0.79 [0.43, 1.45]
Belsey 1969	2/43	1/43		0.4	2.00 [0.19, 21.24]
Bennett 1963	16/38	22/47		8.8	0.90 [0.56, 1.46]
Bhaumik 1998	1/14	3/16		1.3	0.38 [0.04, 3.26]
Ciana 1995	8/34	12/36		5.2	0.71 [0.33, 1.51]
de Gans 2002	11/157	21/144		9.8	0.48 [0.24, 0.96]
DeLemos 1969	2/54	1/63		0.4	2.33 [0.22, 25.03]
Girgis 1989	20/210	42/219		18.5	0.50 [0.30, 0.82]
Kanra 1995	2/29	1/27		0.5	1.86 [0.18, 19.38]
× Kilpi 1995	0/32	0/26		0.0	Not estimable
King 1994	0/50	1/51		0.7	0.34 [0.01, 8.15]
Lebel 1988a	0/51	1/49		0.7	0.32 [0.01, 7.68]
× Lebel 1988b	0/51	0/49		0.0	Not estimable
Lebel 1989	0/31	1/30		0.7	0.32 [0.01, 7.63]
Molyneux 2002	96/305	91/291		41.8	1.01 [0.79, 1.28]
Odio 1991	1/52	1/49		0.5	0.94 [0.06, 14.65]
Qazi 1996	12/48	5/41		2.4	2.05 [0.79, 5.33]
× Schaad 1993	0/60	0/55		0.0	Not estimable
Thomas 1999	3/31	5/29		2.3	0.56 [0.15, 2.14]
Wald 1995	1/69	0/74		0.2	3.21 [0.13, 77.60]
Total (95% CI)	1387	1363		100.0	0.83 [0.71, 0.99]

Total events: 186 (Treatment), 220 (Control)

Test for heterogeneity chi-square=16.96 df=16 p=0.39 I^2 =5.7%

Test for overall effect z=2.12 p=0.03

Analysis 01.02. Comparison 01 All patients, Outcome 02 Severe hearing loss

Review: Corticosteroids for acute bacterial meningitis

Comparison: 01 All patients

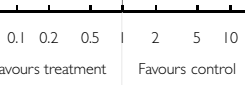
Outcome: 02 Severe hearing loss

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Belsey 1969	0/41	1/42		1.9	0.34 [0.01, 8.14]
Bhaumik 1998	2/13	2/13		2.6	1.00 [0.16, 6.07]
Girgis 1989	2/190	5/177		6.6	0.37 [0.07, 1.90]
× Kanra 1995	0/29	0/27		0.0	Not estimable
Kilpi 1995	1/32	3/26		4.2	0.27 [0.03, 2.45]
King 1994	2/50	3/50		3.8	0.67 [0.12, 3.82]
Lebel 1988a	2/51	9/48		11.9	0.21 [0.05, 0.92]
Lebel 1988b	1/51	6/49		7.9	0.16 [0.02, 1.28]
Lebel 1989	1/31	2/29		2.7	0.47 [0.04, 4.89]
Molyneux 2002	31/181	27/189		33.9	1.20 [0.75, 1.93]
Odio 1991	3/51	7/48		9.3	0.40 [0.11, 1.47]
Qazi 1996	1/36	1/36		1.3	1.00 [0.07, 15.38]
Schaad 1993	2/60	4/55		5.4	0.46 [0.09, 2.40]
Wald 1995	2/68	7/74		8.6	0.31 [0.07, 1.45]
Total (95% CI)	884	863		100.0	0.65 [0.47, 0.91]

Total events: 50 (Treatment), 77 (Control)

Test for heterogeneity chi-square=13.57 df=12 p=0.33 I^2 =11.6%

Test for overall effect z=2.51 p=0.01



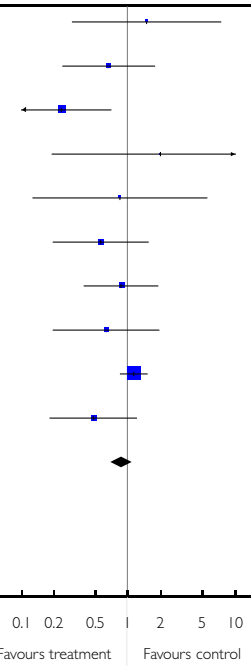
Analysis 01.03. Comparison 01 All patients, Outcome 03 Short-term neurological sequelae

Review: Corticosteroids for acute bacterial meningitis

Comparison: 01 All patients

Outcome: 03 Short-term neurological sequelae

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bhaumik 1998	3/13	2/13		1.7	1.50 [0.30, 7.55]
Ciana 1995	5/26	7/24		6.0	0.66 [0.24, 1.80]
de Gans 2002	4/143	14/118		12.7	0.24 [0.08, 0.70]
Kanra 1995	2/27	1/27		0.8	2.00 [0.19, 20.77]
Kilpi 1995	2/31	2/26		1.8	0.84 [0.13, 5.55]
Lebel 1988a	5/48	8/43		7.0	0.56 [0.20, 1.58]
Lebel 1988b	9/47	10/45		8.4	0.86 [0.39, 1.92]
Lebel 1989	4/31	6/29		5.1	0.62 [0.20, 1.99]
Molyneux 2002	69/223	57/209		48.6	1.13 [0.84, 1.52]
Thomas 1999	5/28	9/24		8.0	0.48 [0.18, 1.23]
Total (95% CI)	617	558		100.0	0.86 [0.68, 1.08]
Total events: 108 (Treatment), 116 (Control)					
Test for heterogeneity chi-square=12.53 df=9 p=0.19 I^2 =28.2%					
Test for overall effect z=1.31 p=0.2					



Analysis 01.04. Comparison 01 All patients, Outcome 04 Long-term neurological sequelae

Review: Corticosteroids for acute bacterial meningitis

Comparison: 01 All patients

Outcome: 04 Long-term neurological sequelae

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Girgis 1989	1/190	2/177		4.0	0.47 [0.04, 5.09]
Kanra 1995	2/29	1/27		2.0	1.86 [0.18, 19.38]
Kilpi 1995	2/32	2/26		4.2	0.81 [0.12, 5.38]
King 1994	5/37	3/44		5.2	1.98 [0.51, 7.75]
Lebel 1988a	3/38	3/34		6.0	0.89 [0.19, 4.14]
Lebel 1988b	2/43	6/41		11.7	0.32 [0.07, 1.49]
Odio 1991	5/51	15/48		29.5	0.31 [0.12, 0.80]
Qazi 1996	9/48	8/41		16.5	0.96 [0.41, 2.26]
Schaad 1993	3/60	5/55		10.0	0.55 [0.14, 2.19]
Wald 1995	4/68	6/74		11.0	0.73 [0.21, 2.46]
Total (95% CI)	596	567		100.0	0.67 [0.45, 1.00]

Total events: 36 (Treatment), 51 (Control)

Test for heterogeneity chi-square=7.65 df=9 p=0.57 I^2 =0.0%

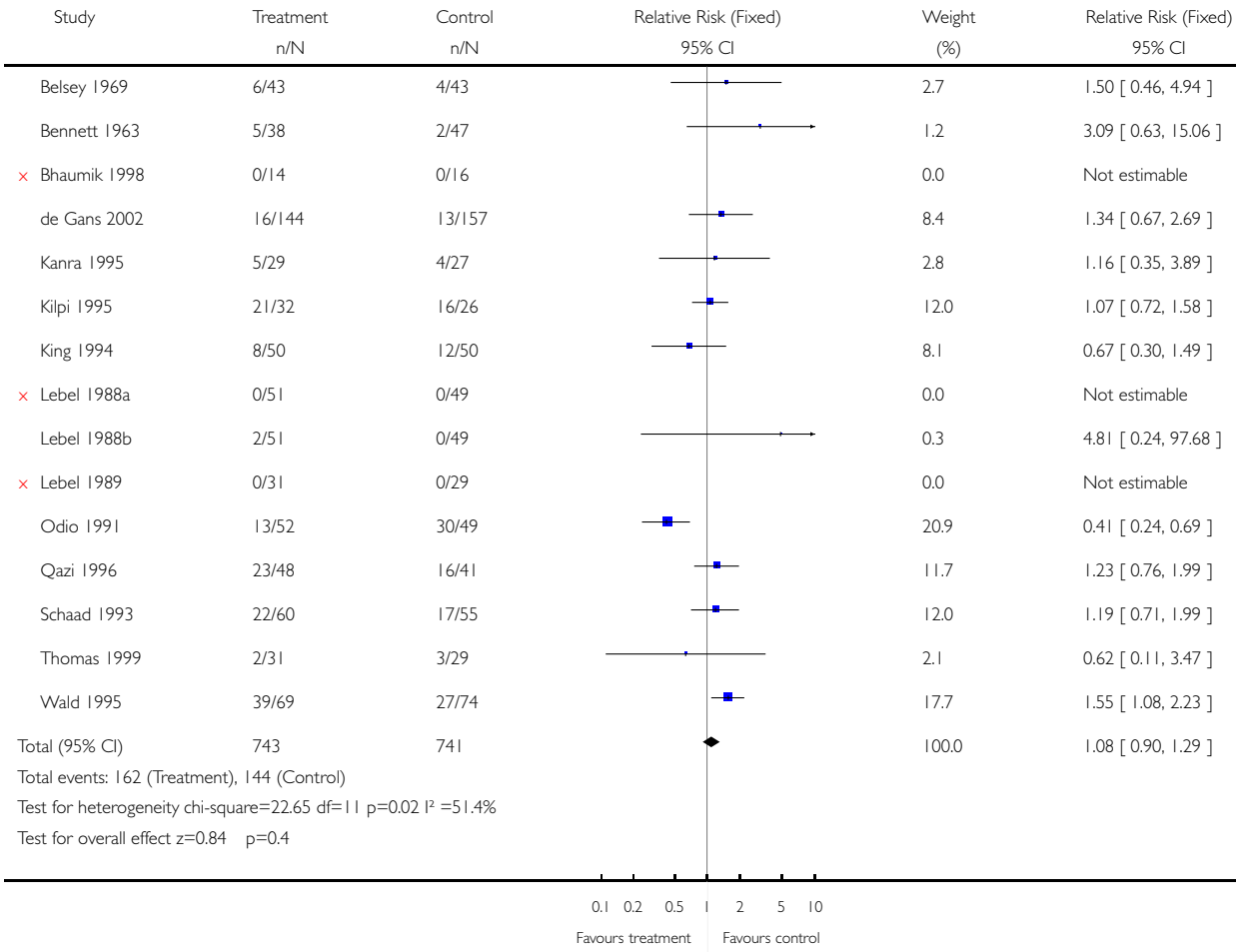
Test for overall effect z=1.96 p=0.05

Analysis 01.05. Comparison 01 All patients, Outcome 05 Adverse events

Review: Corticosteroids for acute bacterial meningitis

Comparison: 01 All patients

Outcome: 05 Adverse events



Analysis 02.01. Comparison 02 Children, Outcome 01 Mortality

Review: Corticosteroids for acute bacterial meningitis

Comparison: 02 Children

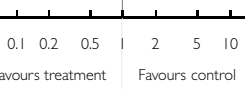
Outcome: 01 Mortality

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Belsey 1969	2/43	1/43		0.7	2.00 [0.19, 21.24]
Ciana 1995	8/34	12/36		8.2	0.71 [0.33, 1.51]
DeLemos 1969	4/54	2/63		1.3	2.33 [0.44, 12.25]
Girgis 1989	16/142	24/140		16.9	0.66 [0.37, 1.18]
Kanra 1995	2/29	1/27		0.7	1.86 [0.18, 19.38]
× Kilpi 1995	0/32	0/26		0.0	Not estimable
King 1994	0/50	1/51		1.0	0.34 [0.01, 8.15]
× Lebel 1988a	0/51	0/49		0.0	Not estimable
Lebel 1988b	0/51	1/49		1.1	0.32 [0.01, 7.68]
× Lebel 1989	0/31	0/29		0.0	Not estimable
Molyneux 2002	96/305	91/291		65.2	1.01 [0.79, 1.28]
Odio 1991	1/52	1/49		0.7	0.94 [0.06, 14.65]
Qazi 1996	12/48	5/41		3.8	2.05 [0.79, 5.33]
× Schaad 1993	0/60	0/55		0.0	Not estimable
Wald 1995	1/69	0/74		0.3	3.21 [0.13, 77.60]
Total (95% CI)	1051	1023		100.0	0.99 [0.81, 1.20]

Total events: 142 (Treatment), 139 (Control)

Test for heterogeneity chi-square=7.95 df=10 p=0.63 I^2 =0.0%

Test for overall effect z=0.14 p=0.9



Analysis 02.02. Comparison 02 Children, Outcome 02 Severe hearing loss

Review: Corticosteroids for acute bacterial meningitis

Comparison: 02 Children

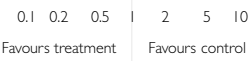
Outcome: 02 Severe hearing loss

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Belsey 1969	0/41	1/42		1.9	0.34 [0.01, 8.14]
Girgis 1989	0/16	4/15		6.0	0.10 [0.01, 1.79]
Kanra 1995	0/27	2/27		3.2	0.20 [0.01, 3.98]
Kilpi 1995	1/32	3/26		4.2	0.27 [0.03, 2.45]
King 1994	2/50	3/50		3.9	0.67 [0.12, 3.82]
Lebel 1988a	2/51	9/48		11.9	0.21 [0.05, 0.92]
Lebel 1988b	1/51	6/49		7.9	0.16 [0.02, 1.28]
Lebel 1989	1/31	2/29		2.7	0.47 [0.04, 4.89]
Molyneux 2002	31/181	27/189		33.9	1.20 [0.75, 1.93]
Odio 1991	3/51	7/48		9.3	0.40 [0.11, 1.47]
Qazi 1996	1/36	1/36		1.3	1.00 [0.07, 15.38]
Schaad 1993	2/60	4/55		5.4	0.46 [0.09, 2.40]
Wald 1995	2/68	7/74		8.6	0.31 [0.07, 1.45]
Total (95% CI)	695	688		100.0	0.61 [0.44, 0.86]

Total events: 46 (Treatment), 76 (Control)

Test for heterogeneity chi-square=15.44 df=12 p=0.22 I^2 =22.3%

Test for overall effect z=2.81 p=0.005



Analysis 03.01. Comparison 03 Adults, Outcome 01 Mortality

Review: Corticosteroids for acute bacterial meningitis

Comparison: 03 Adults

Outcome: 01 Mortality

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bennett 1963	16/38	22/47		29.7	0.90 [0.56, 1.46]
Bhaumik 1998	1/14	3/16		4.2	0.38 [0.04, 3.26]
de Gans 2002	11/157	21/144		33.1	0.48 [0.24, 0.96]
Girgis 1989	5/68	18/79		25.2	0.32 [0.13, 0.82]
Thomas 1999	3/31	5/29		7.8	0.56 [0.15, 2.14]
Total (95% CI)	308	315		100.0	0.57 [0.40, 0.81]
Total events: 36 (Treatment), 69 (Control)					
Test for heterogeneity chi-square=5.27 df=4 p=0.26 I^2 =24.1%					
Test for overall effect z=3.14 p=0.002					

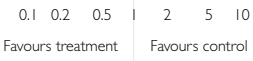
Analysis 03.02. Comparison 03 Adults, Outcome 02 Short-term neurological sequelae

Review: Corticosteroids for acute bacterial meningitis

Comparison: 03 Adults

Outcome: 02 Short-term neurological sequelae

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bhaumik 1998	3/13	2/13		7.4	1.50 [0.30, 7.55]
de Gans 2002	4/143	14/118		56.7	0.24 [0.08, 0.70]
Thomas 1999	5/28	9/24		35.9	0.48 [0.18, 1.23]
Total (95% CI)	184	155		100.0	0.42 [0.22, 0.78]
Total events: 12 (Treatment), 25 (Control)					
Test for heterogeneity chi-square=3.55 df=2 p=0.17 I^2 =43.7%					
Test for overall effect z=2.73 p=0.006					

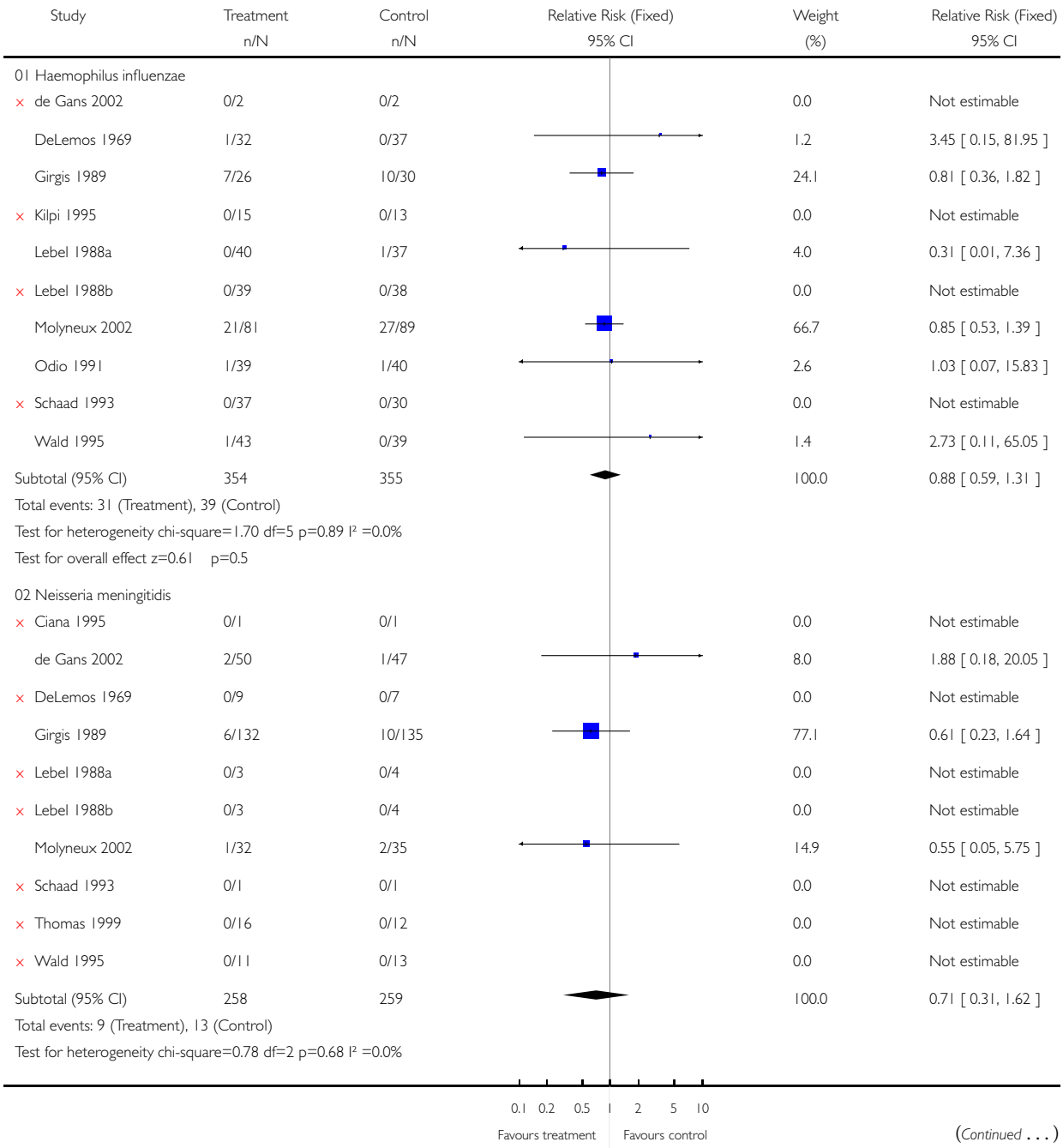


Analysis 04.01. Comparison 04 Causative species, Outcome 01 Mortality

Review: Corticosteroids for acute bacterial meningitis

Comparison: 04 Causative species

Outcome: 01 Mortality



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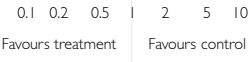
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=0.82 p=0.4					
03 Streptococcus pneumoniae					
Bademosi 1979	1/28	12/24		12.8	0.07 [0.01, 0.51]
de Gans 2002	8/58	17/50		18.0	0.41 [0.19, 0.86]
DeLemos 1969	1/5	1/8		0.8	1.60 [0.13, 20.22]
Girgis 1989	7/52	22/54		21.3	0.33 [0.15, 0.71]
Kanra 1995	2/29	1/27		1.0	1.86 [0.18, 19.38]
× Kilpi 1995	0/1	0/5		0.0	Not estimable
× Lebel 1988a	0/4	0/6		0.0	Not estimable
× Lebel 1988b	0/4	0/3		0.0	Not estimable
Molyneux 2002	46/132	42/106		46.1	0.88 [0.63, 1.22]
× Odio 1991	0/4	0/4		0.0	Not estimable
× Schaad 1993	0/5	0/6		0.0	Not estimable
× Wald 1995	0/13	0/13		0.0	Not estimable
Subtotal (95% CI)	335	306		100.0	0.59 [0.45, 0.77]
Total events: 65 (Treatment), 95 (Control)					
Test for heterogeneity chi-square=14.75 df=5 p=0.01 I^2 =66.1%					
Test for overall effect z=3.85 p=0.0001					
04 All other species than H. influenzae					
Bademosi 1979	11/28	12/24		9.8	0.79 [0.43, 1.45]
de Gans 2002	11/155	21/142		16.5	0.48 [0.24, 0.96]
DeLemos 1969	1/22	1/25		0.7	1.14 [0.08, 17.11]
Girgis 1989	13/184	32/189		23.8	0.42 [0.23, 0.77]
× Kilpi 1995	0/17	0/13		0.0	Not estimable
× Lebel 1988a	0/11	0/12		0.0	Not estimable
× Lebel 1988b	0/12	0/11		0.0	Not estimable
Molyneux 2002	71/226	62/204		49.2	1.03 [0.78, 1.37]
× Odio 1991	0/13	0/19		0.0	Not estimable
× Schaad 1993	0/23	0/25		0.0	Not estimable
× Wald 1995	0/26	0/35		0.0	Not estimable
Subtotal (95% CI)	717	699		100.0	0.77 [0.62, 0.96]
Total events: 107 (Treatment), 128 (Control)					
Test for heterogeneity chi-square=9.85 df=4 p=0.04 I^2 =59.4%					
Test for overall effect z=2.28 p=0.02					



Analysis 04.02. Comparison 04 Causative species, Outcome 02 Severe hearing loss in children - non-Haemophilus influenzae species

Review: Corticosteroids for acute bacterial meningitis

Comparison: 04 Causative species

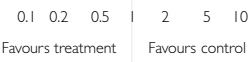
Outcome: 02 Severe hearing loss in children - non-Haemophilus influenzae species

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Belsey 1969	0/41	1/42		3.5	0.34 [0.01, 8.14]
Girgis 1989	0/16	4/15		11.1	0.10 [0.01, 1.79]
Kilpi 1995	1/17	2/13		5.4	0.38 [0.04, 3.77]
King 1994	1/21	1/22		2.3	1.05 [0.07, 15.69]
Lebel 1988a	1/17	2/19		4.5	0.56 [0.06, 5.63]
Lebel 1988b	0/12	2/14		5.5	0.23 [0.01, 4.38]
Lebel 1989	0/6	1/9		2.9	0.48 [0.02, 10.07]
Molyneux 2002	27/132	21/134		49.7	1.31 [0.78, 2.19]
Odio 1991	0/13	1/9		4.2	0.24 [0.01, 5.26]
Schaad 1993	1/23	3/25		6.9	0.36 [0.04, 3.24]
Wald 1995	2/25	2/35		4.0	1.40 [0.21, 9.28]
Total (95% CI)	323	337		100.0	0.86 [0.57, 1.30]

Total events: 33 (Treatment), 40 (Control)

Test for heterogeneity chi-square=8.00 df=10 p=0.63 I^2 =0.0%

Test for overall effect z=0.72 p=0.5



Analysis 04.04. Comparison 04 Causative species, Outcome 04 Severe hearing loss in children - Haemophilus influenzae species

Review: Corticosteroids for acute bacterial meningitis

Comparison: 04 Causative species

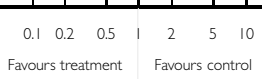
Outcome: 04 Severe hearing loss in children - Haemophilus influenzae species

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kilpi 1995	0/15	1/13		4.6	0.29 [0.01, 6.60]
King 1994	1/29	2/28		5.8	0.48 [0.05, 5.03]
Lebel 1988a	1/34	7/29		21.6	0.12 [0.02, 0.93]
Lebel 1988b	1/39	4/35		12.0	0.22 [0.03, 1.91]
Lebel 1989	1/25	1/20		3.2	0.80 [0.05, 12.01]
Molyneux 2002	4/81	6/89		16.3	0.73 [0.21, 2.50]
Odio 1991	3/38	6/39		16.9	0.51 [0.14, 1.91]
Schaad 1993	1/37	1/30		3.2	0.81 [0.05, 12.43]
Wald 1995	0/43	5/39		16.5	0.08 [0.00, 1.45]
Total (95% CI)	341	322		100.0	0.37 [0.20, 0.68]

Total events: 12 (Treatment), 33 (Control)

Test for heterogeneity chi-square=4.56 df=8 p=0.80 I^2 =0.0%

Test for overall effect z=3.21 p=0.001

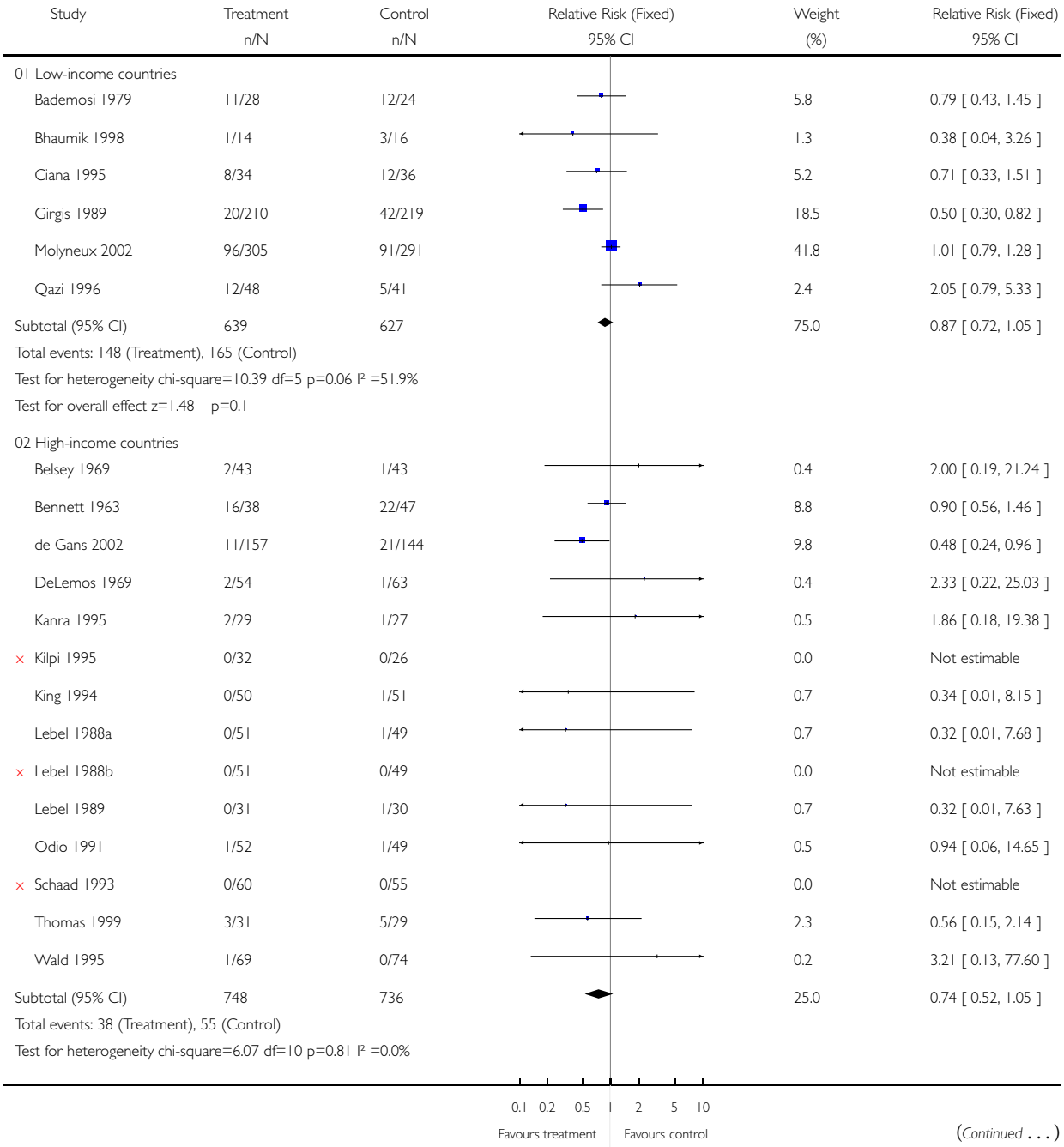


Analysis 05.01. Comparison 05 Income of countries, Outcome 01 Mortality - all patients

Review: Corticosteroids for acute bacterial meningitis

Comparison: 05 Income of countries

Outcome: 01 Mortality - all patients



Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Low-income countries					
Bademosi 1979	11/28	12/24		5.8	0.79 [0.43, 1.45]
Bhaumik 1998	1/14	3/16		1.3	0.38 [0.04, 3.26]
Ciana 1995	8/34	12/36		5.2	0.71 [0.33, 1.51]
Girgis 1989	20/210	42/219		18.5	0.50 [0.30, 0.82]
Molyneux 2002	96/305	91/291		41.8	1.01 [0.79, 1.28]
Qazi 1996	12/48	5/41		2.4	2.05 [0.79, 5.33]
Subtotal (95% CI)	639	627		75.0	0.87 [0.72, 1.05]
Total events: 148 (Treatment), 165 (Control)					
Test for heterogeneity chi-square=10.39 df=5 p=0.06 I² =51.9%					
Test for overall effect z=1.48 p=0.1					
02 High-income countries					
Belsey 1969	2/43	1/43		0.4	2.00 [0.19, 21.24]
Bennett 1963	16/38	22/47		8.8	0.90 [0.56, 1.46]
de Gans 2002	11/157	21/144		9.8	0.48 [0.24, 0.96]
DeLemos 1969	2/54	1/63		0.4	2.33 [0.22, 25.03]
Kanra 1995	2/29	1/27		0.5	1.86 [0.18, 19.38]
× Kilpi 1995	0/32	0/26		0.0	Not estimable
King 1994	0/50	1/51		0.7	0.34 [0.01, 8.15]
Lebel 1988a	0/51	1/49		0.7	0.32 [0.01, 7.68]
× Lebel 1988b	0/51	0/49		0.0	Not estimable
Lebel 1989	0/31	1/30		0.7	0.32 [0.01, 7.63]
Odio 1991	1/52	1/49		0.5	0.94 [0.06, 14.65]
× Schaad 1993	0/60	0/55		0.0	Not estimable
Thomas 1999	3/31	5/29		2.3	0.56 [0.15, 2.14]
Wald 1995	1/69	0/74		0.2	3.21 [0.13, 77.60]
Subtotal (95% CI)	748	736		25.0	0.74 [0.52, 1.05]
Total events: 38 (Treatment), 55 (Control)					
Test for heterogeneity chi-square=6.07 df=10 p=0.81 I² =0.0%					

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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=1.67 p=0.1					
Total (95% CI)	1387	1363		100.0	0.83 [0.71, 0.99]
Total events: 186 (Treatment), 220 (Control)					
Test for heterogeneity chi-square=16.96 df=16 p=0.39 I^2 =5.7%					
Test for overall effect z=2.12 p=0.03					

Analysis 05.02. Comparison 05 Income of countries, Outcome 02 Severe hearing loss - all patients

Review: Corticosteroids for acute bacterial meningitis

Comparison: 05 Income of countries

Outcome: 02 Severe hearing loss - all patients

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Low-income countries					
Bhaumik 1998	2/13	2/13		2.6	1.00 [0.16, 6.07]
Girgis 1989	2/190	5/177		6.6	0.37 [0.07, 1.90]
Molyneux 2002	31/181	27/189		33.9	1.20 [0.75, 1.93]
Qazi 1996	1/36	1/36		1.3	1.00 [0.07, 15.38]
Subtotal (95% CI)	420	415		44.4	1.06 [0.69, 1.63]
Total events: 36 (Treatment), 35 (Control)					
Test for heterogeneity chi-square=1.85 df=3 p=0.60 I^2 =0.0%					
Test for overall effect z=0.26 p=0.8					
02 High-income countries					
Belsey 1969	0/41	1/42		1.9	0.34 [0.01, 8.14]
× Kanra 1995	0/29	0/27		0.0	Not estimable
Kilpi 1995	1/32	3/26		4.2	0.27 [0.03, 2.45]
King 1994	2/50	3/50		3.8	0.67 [0.12, 3.82]
Lebel 1988a	2/51	9/48		11.9	0.21 [0.05, 0.92]
Lebel 1988b	1/51	6/49		7.9	0.16 [0.02, 1.28]
Lebel 1989	1/31	2/29		2.7	0.47 [0.04, 4.89]
Odio 1991	3/51	7/48		9.3	0.40 [0.11, 1.47]
Schaad 1993	2/60	4/55		5.4	0.46 [0.09, 2.40]

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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Wald 1995	2/68	7/74		8.6	0.31 [0.07, 1.45]
Subtotal (95% CI)	464	448		55.6	0.33 [0.18, 0.58]
Total events: 14 (Treatment), 42 (Control)					
Test for heterogeneity chi-square=1.82 df=8 p=0.99 I^2 =0.0%					
Test for overall effect z=3.77 p=0.0002					
Total (95% CI)	884	863		100.0	0.65 [0.47, 0.91]
Total events: 50 (Treatment), 77 (Control)					
Test for heterogeneity chi-square=13.57 df=12 p=0.33 I^2 =11.6%					
Test for overall effect z=2.51 p=0.01					

Analysis 05.03. Comparison 05 Income of countries, Outcome 03 Short-term neurological sequelae - all patients

Review: Corticosteroids for acute bacterial meningitis

Comparison: 05 Income of countries

Outcome: 03 Short-term neurological sequelae - all patients

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Low-income countries					
Bhaumik 1998	3/13	2/13		1.7	1.50 [0.30, 7.55]
Ciana 1995	5/26	7/24		6.0	0.66 [0.24, 1.80]
Molyneux 2002	69/223	57/209		48.6	1.13 [0.84, 1.52]
Subtotal (95% CI)	262	246		56.2	1.09 [0.83, 1.45]
Total events: 77 (Treatment), 66 (Control)					
Test for heterogeneity chi-square=1.18 df=2 p=0.55 I^2 =0.0%					
Test for overall effect z=0.63 p=0.5					
02 High-income countries					
de Gans 2002	4/143	14/118		12.7	0.24 [0.08, 0.70]
Kanra 1995	2/27	1/27		0.8	2.00 [0.19, 20.77]
Kilpi 1995	2/31	2/26		1.8	0.84 [0.13, 5.55]
Lebel 1988a	5/48	8/43		7.0	0.56 [0.20, 1.58]
Lebel 1988b	9/47	10/45		8.4	0.86 [0.39, 1.92]
Lebel 1989	4/31	6/29		5.1	0.62 [0.20, 1.99]

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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Thomas 1999	5/28	9/24		8.0	0.48 [0.18, 1.23]
Subtotal (95% CI)	355	312		43.8	0.56 [0.37, 0.84]
Total events: 31 (Treatment), 50 (Control)					
Test for heterogeneity chi-square=5.03 df=6 p=0.54 I^2 =0.0%					
Test for overall effect z=2.81 p=0.005					
Total (95% CI)	617	558		100.0	0.86 [0.68, 1.08]
Total events: 108 (Treatment), 116 (Control)					
Test for heterogeneity chi-square=12.53 df=9 p=0.19 I^2 =28.2%					
Test for overall effect z=1.31 p=0.2					

Analysis 05.04. Comparison 05 Income of countries, Outcome 04 Mortality - children

Review: Corticosteroids for acute bacterial meningitis

Comparison: 05 Income of countries

Outcome: 04 Mortality - children

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Low-income countries					
Ciana 1995	8/34	12/36		8.2	0.71 [0.33, 1.51]
Girgis 1989	16/142	24/140		16.9	0.66 [0.37, 1.18]
Molyneux 2002	96/305	91/291		65.2	1.01 [0.79, 1.28]
Qazi 1996	12/48	5/41		3.8	2.05 [0.79, 5.33]
Subtotal (95% CI)	529	508		94.1	0.96 [0.78, 1.18]
Total events: 132 (Treatment), 132 (Control)					
Test for heterogeneity chi-square=4.79 df=3 p=0.19 I^2 =37.4%					
Test for overall effect z=0.39 p=0.7					
02 High-income countries					
Belsey 1969	2/43	1/43		0.7	2.00 [0.19, 21.24]
DeLemos 1969	4/54	2/63		1.3	2.33 [0.44, 12.25]
Kanra 1995	2/29	1/27		0.7	1.86 [0.18, 19.38]
× Kilpi 1995	0/32	0/26		0.0	Not estimable
King 1994	0/50	1/51		1.0	0.34 [0.01, 8.15]
× Lebel 1988a	0/51	0/49		0.0	Not estimable

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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Lebel 1988b	0/51	1/49		1.1	0.32 [0.01, 7.68]
× Lebel 1989	0/31	0/29		0.0	Not estimable
Odio 1991	1/52	1/49		0.7	0.94 [0.06, 14.65]
× Schaad 1993	0/60	0/55		0.0	Not estimable
Wald 1995	1/69	0/74		0.3	3.21 [0.13, 77.60]
Subtotal (95% CI)	522	515		5.9	1.40 [0.59, 3.33]
Total events: 10 (Treatment), 7 (Control)					
Test for heterogeneity chi-square=2.44 df=6 p=0.87 I² =0.0%					
Test for overall effect z=0.76 p=0.4					
Total (95% CI)	1051	1023		100.0	0.99 [0.81, 1.20]
Total events: 142 (Treatment), 139 (Control)					
Test for heterogeneity chi-square=7.95 df=10 p=0.63 I² =0.0%					
Test for overall effect z=0.14 p=0.9					

Analysis 05.05. Comparison 05 Income of countries, Outcome 05 Severe hearing loss - children

Review: Corticosteroids for acute bacterial meningitis

Comparison: 05 Income of countries

Outcome: 05 Severe hearing loss - children

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Low-income countries					
Girgis 1989	0/16	4/15		6.0	0.10 [0.01, 1.79]
Molyneux 2002	31/181	27/189		34.4	1.20 [0.75, 1.93]
Subtotal (95% CI)	197	204		40.4	1.04 [0.66, 1.63]
Total events: 31 (Treatment), 31 (Control)					
Test for heterogeneity chi-square=2.87 df=1 p=0.09 I² =65.1%					
Test for overall effect z=0.15 p=0.9					
02 High-income countries					
Belsey 1969	0/41	1/42		1.9	0.34 [0.01, 8.14]
Kanra 1995	0/27	2/27		3.3	0.20 [0.01, 3.98]
Kilpi 1995	1/32	3/26		4.3	0.27 [0.03, 2.45]
King 1994	2/50	3/50		3.9	0.67 [0.12, 3.82]

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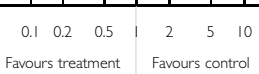
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Lebel 1988a	2/51	9/48		12.1	0.21 [0.05, 0.92]
Lebel 1988b	1/51	6/49		8.0	0.16 [0.02, 1.28]
Lebel 1989	1/31	2/29		2.7	0.47 [0.04, 4.89]
Odio 1991	3/51	7/48		9.4	0.40 [0.11, 1.47]
Schaad 1993	2/60	4/55		5.4	0.46 [0.09, 2.40]
Wald 1995	2/68	7/74		8.7	0.31 [0.07, 1.45]
Subtotal (95% CI)	462	448		59.6	0.32 [0.18, 0.57]
Total events: 14 (Treatment), 44 (Control)					
Test for heterogeneity chi-square=1.94 df=9 p=0.99 I^2 =0.0%					
Test for overall effect z=3.92 p=0.00009					
Total (95% CI)	659	652		100.0	0.61 [0.43, 0.86]
Total events: 45 (Treatment), 75 (Control)					
Test for heterogeneity chi-square=15.38 df=11 p=0.17 I^2 =28.5%					
Test for overall effect z=2.83 p=0.005					



Analysis 05.06. Comparison 05 Income of countries, Outcome 06 Short-term neurological sequelae -children

Review: Corticosteroids for acute bacterial meningitis

Comparison: 05 Income of countries

Outcome: 06 Short-term neurological sequelae -children

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Low-income countries					
Ciana 1995	5/26	7/24		7.7	0.66 [0.24, 1.80]
Molyneux 2002	69/223	57/209		62.5	1.13 [0.84, 1.52]
Subtotal (95% CI)	249	233		70.2	1.08 [0.82, 1.44]
Total events: 74 (Treatment), 64 (Control)					
Test for heterogeneity chi-square=1.03 df=1 p=0.31 I^2 =3.1%					
Test for overall effect z=0.55 p=0.6					
02 High-income countries					
Kanra 1995	2/27	1/27		1.1	2.00 [0.19, 20.77]
Kilpi 1995	2/31	2/26		2.3	0.84 [0.13, 5.55]
Lebel 1988a	5/48	8/43		9.0	0.56 [0.20, 1.58]

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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Lebel 1988b	9/47	10/45		10.9	0.86 [0.39, 1.92]
Lebel 1989	4/31	6/29		6.6	0.62 [0.20, 1.99]
Subtotal (95% CI)	184	170		29.8	0.76 [0.45, 1.27]
Total events: 22 (Treatment), 27 (Control)					
Test for heterogeneity chi-square=1.20 df=4 p=0.88 I^2 =0.0%					
Test for overall effect z=1.06 p=0.3					
Total (95% CI)	433	403		100.0	0.99 [0.77, 1.26]
Total events: 96 (Treatment), 91 (Control)					
Test for heterogeneity chi-square=3.71 df=6 p=0.72 I^2 =0.0%					
Test for overall effect z=0.12 p=0.9					

Analysis 05.07. Comparison 05 Income of countries, Outcome 07 Severe hearing loss in children due to non-Heamophilus influenzae species

Review: Corticosteroids for acute bacterial meningitis

Comparison: 05 Income of countries

Outcome: 07 Severe hearing loss in children due to non-Heamophilus influenzae species

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Low-income countries					
Girgis 1989	0/16	4/15		11.1	0.10 [0.01, 1.79]
Molyneux 2002	27/132	21/134		49.7	1.31 [0.78, 2.19]
Subtotal (95% CI)	148	149		60.7	1.09 [0.67, 1.77]
Total events: 27 (Treatment), 25 (Control)					
Test for heterogeneity chi-square=3.09 df=1 p=0.08 I^2 =67.6%					
Test for overall effect z=0.33 p=0.7					
02 High-income countries					
Belsey 1969	0/41	1/42		3.5	0.34 [0.01, 8.14]
Kilpi 1995	1/17	2/13		5.4	0.38 [0.04, 3.77]
King 1994	1/21	1/22		2.3	1.05 [0.07, 15.69]
Lebel 1988a	1/17	2/19		4.5	0.56 [0.06, 5.63]
Lebel 1988b	0/12	2/14		5.5	0.23 [0.01, 4.38]
Lebel 1989	0/6	1/9		2.9	0.48 [0.02, 10.07]

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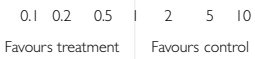
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Odio 1991	0/13	1/9		4.2	0.24 [0.01, 5.26]
Schaad 1993	1/23	3/25		6.9	0.36 [0.04, 3.24]
Wald 1995	2/25	2/35		4.0	1.40 [0.21, 9.28]
Subtotal (95% CI)	175	188		39.3	0.51 [0.23, 1.13]
Total events: 6 (Treatment), 15 (Control)					
Test for heterogeneity chi-square=2.10 df=8 p=0.98 I^2 =0.0%					
Test for overall effect z=1.65 p=0.1					
Total (95% CI)	323	337		100.0	0.86 [0.57, 1.30]
Total events: 33 (Treatment), 40 (Control)					
Test for heterogeneity chi-square=8.00 df=10 p=0.63 I^2 =0.0%					
Test for overall effect z=0.72 p=0.5					



Analysis 06.01. Comparison 06 Timing of steroids, Outcome 01 Mortality

Review: Corticosteroids for acute bacterial meningitis

Comparison: 06 Timing of steroids

Outcome: 01 Mortality

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Before or with first dose antibiotic					
Bademosi 1979	11/28	12/24		6.2	0.79 [0.43, 1.45]
de Gans 2002	11/157	21/144		10.4	0.48 [0.24, 0.96]
Girgis 1989	20/210	42/219		19.6	0.50 [0.30, 0.82]
Kanra 1995	2/29	1/27		0.5	1.86 [0.18, 19.38]
× Kilpi 1995	0/32	0/26		0.0	Not estimable
Molyneux 2002	96/305	91/291		44.3	1.01 [0.79, 1.28]
Odio 1991	1/52	1/49		0.5	0.94 [0.06, 14.65]
Qazi 1996	12/48	5/41		2.6	2.05 [0.79, 5.33]
× Schaad 1993	0/60	0/55		0.0	Not estimable
Subtotal (95% CI)	921	876		84.0	0.84 [0.70, 1.02]
Total events: 153 (Treatment), 173 (Control)					
Test for heterogeneity chi-square=12.82 df=6 p=0.05 I^2 =53.2%					
Test for overall effect z=1.78 p=0.08					

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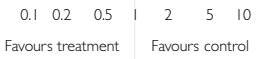
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
02 After first dose antibiotic					
Bennett 1963	16/38	22/47		9.4	0.90 [0.56, 1.46]
Bhaumik 1998	1/14	3/16		1.3	0.38 [0.04, 3.26]
DeLemos 1969	2/54	1/63		0.4	2.33 [0.22, 25.03]
King 1994	0/50	1/51		0.7	0.34 [0.01, 8.15]
Lebel 1988a	0/51	1/49		0.7	0.32 [0.01, 7.68]
× Lebel 1988b	0/51	0/49		0.0	Not estimable
Lebel 1989	0/31	1/30		0.7	0.32 [0.01, 7.63]
Thomas 1999	3/31	5/29		2.5	0.56 [0.15, 2.14]
Wald 1995	1/69	0/74		0.2	3.21 [0.13, 77.60]
Subtotal (95% CI)	389	408		16.0	0.80 [0.52, 1.22]
Total events: 23 (Treatment), 34 (Control)					
Test for heterogeneity chi-square=3.38 df=7 p=0.85 I^2 =0.0%					
Test for overall effect z=1.03 p=0.3					
Total (95% CI)	1310	1284		100.0	0.84 [0.70, 0.99]
Total events: 176 (Treatment), 207 (Control)					
Test for heterogeneity chi-square=16.23 df=14 p=0.30 I^2 =13.8%					
Test for overall effect z=2.04 p=0.04					

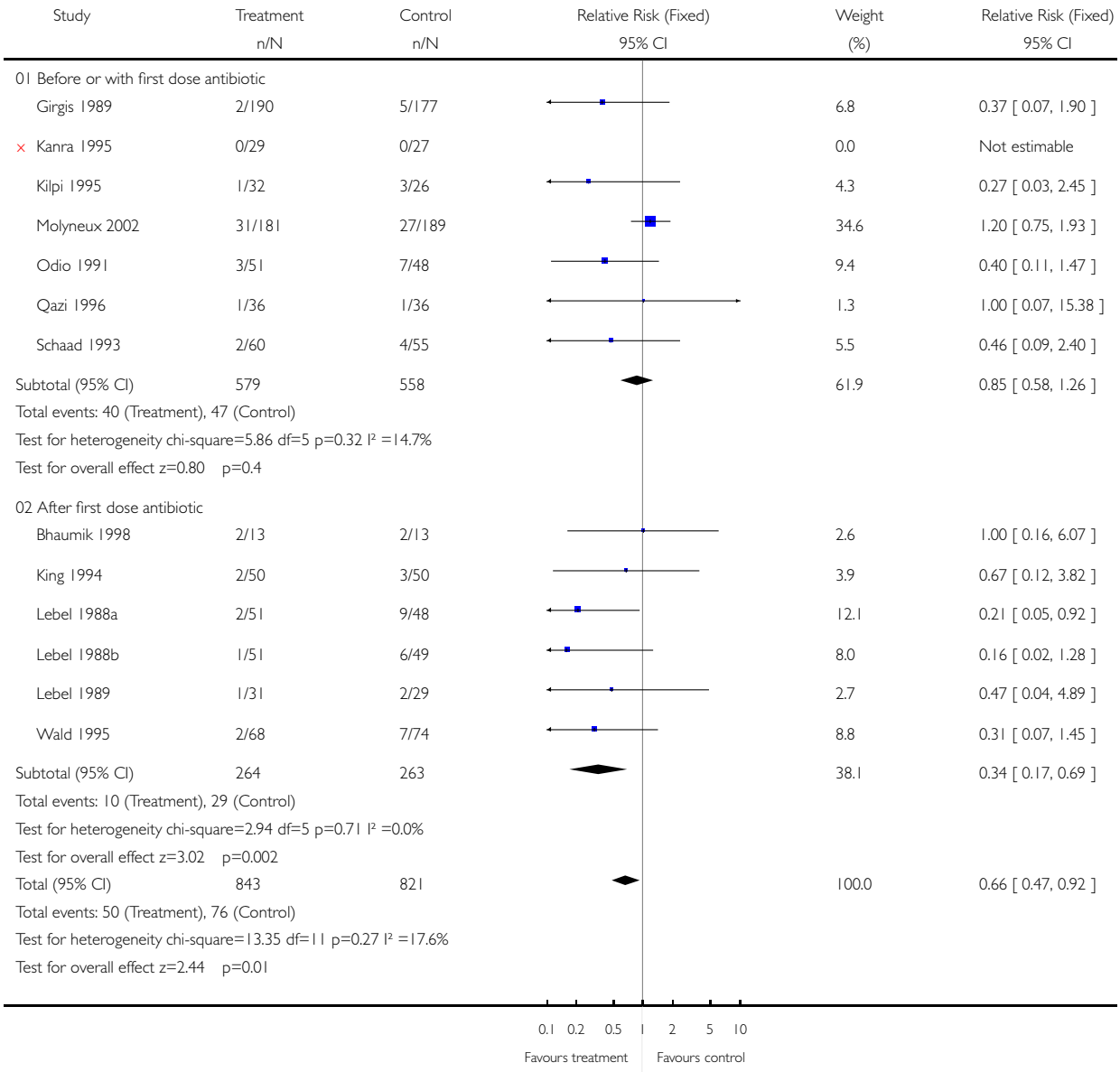


Analysis 06.02. Comparison 06 Timing of steroids, Outcome 02 Severe hearing loss

Review: Corticosteroids for acute bacterial meningitis

Comparison: 06 Timing of steroids

Outcome: 02 Severe hearing loss



Analysis 06.03. Comparison 06 Timing of steroids, Outcome 03 Short-term neurologic sequelae

Review: Corticosteroids for acute bacterial meningitis

Comparison: 06 Timing of steroids

Outcome: 03 Short-term neurologic sequelae

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Before or with first dose antibiotic					
de Gans 2002	4/143	14/118		13.5	0.24 [0.08, 0.70]
Kanra 1995	2/27	1/27		0.9	2.00 [0.19, 20.77]
Kilpi 1995	2/31	2/26		1.9	0.84 [0.13, 5.55]
Molyneux 2002	69/223	57/209		51.7	1.13 [0.84, 1.52]
Subtotal (95% CI)	424	380		67.9	0.96 [0.73, 1.26]
Total events: 77 (Treatment), 74 (Control)					
Test for heterogeneity chi-square=8.07 df=3 p=0.04 I^2 =62.8%					
Test for overall effect z=0.30 p=0.8					
02 After first dose antibiotic					
Bhaumik 1998	3/13	2/13		1.8	1.50 [0.30, 7.55]
Lebel 1988a	5/48	8/43		7.4	0.56 [0.20, 1.58]
Lebel 1988b	9/47	10/45		9.0	0.86 [0.39, 1.92]
Lebel 1989	4/31	6/29		5.4	0.62 [0.20, 1.99]
Thomas 1999	5/28	9/24		8.5	0.48 [0.18, 1.23]
Subtotal (95% CI)	167	154		32.1	0.68 [0.43, 1.08]
Total events: 26 (Treatment), 35 (Control)					
Test for heterogeneity chi-square=1.95 df=4 p=0.74 I^2 =0.0%					
Test for overall effect z=1.64 p=0.1					
Total (95% CI)	591	534		100.0	0.87 [0.69, 1.10]
Total events: 103 (Treatment), 109 (Control)					
Test for heterogeneity chi-square=12.15 df=8 p=0.14 I^2 =34.1%					
Test for overall effect z=1.15 p=0.2