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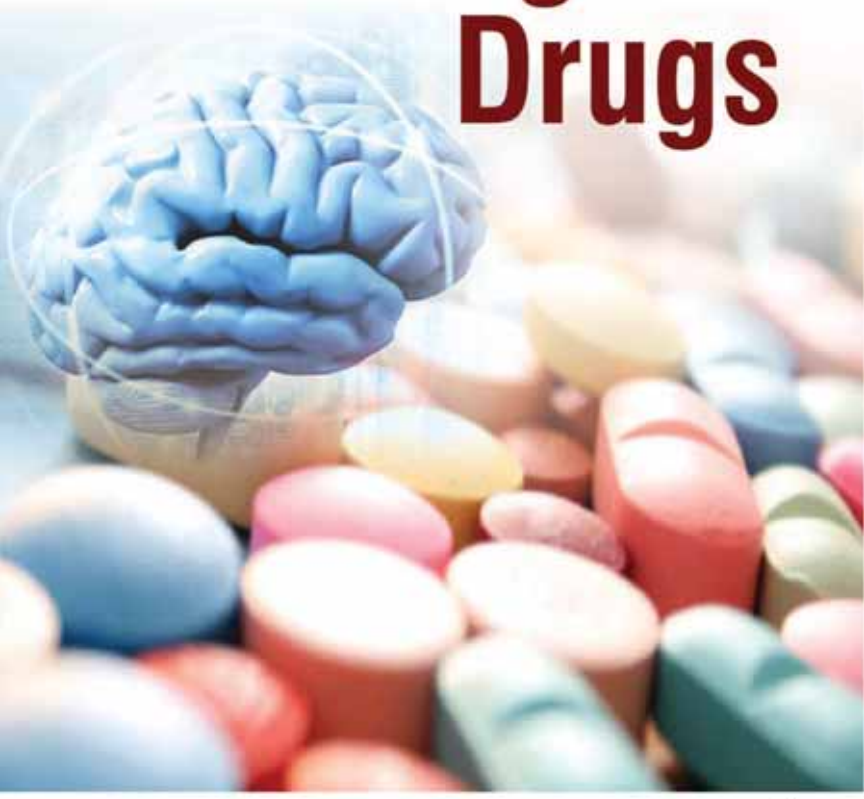
Neurological Drugs



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CHAPTER

15

Drug Treatment of Central Nervous System Infections

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INTRODUCTION

Central nervous system (CNS) infections are often life-threatening problems with high associated mortality and morbidity. The presentation may be acute, subacute, or chronic. Clinical findings are an interplay of anatomic site/s of involvement, infecting pathogens, and host response. Vulnerability of CNS to effects of inflammation and edema mandates prompt diagnosis with appropriate therapy if consequences to be minimized.[1]

Some of the infections are given following in Box 15.1.[2]

PATHOGENESIS[3]

Three common bacteria causing brain infections are: (1) *Haemophilus influenzae type b* (Hib), (2) *Neisseria meningitidis*, and (3) *Streptococcus pneumonia*. Vulnerable groups for meningitis include neonates, elderly, and immunosuppressed, etc.

Routes of entry could be hematogenous or neighboring focus, etc. The anatomic defect, e.g. congenital, traumatic,

Box 15.1: Common central nervous system (CNS) bacterial infections.[2]

- Bacterial meningitis
- Meningoencephalitis
- Brain abscess
- Subdural empyema
- Epidural abscess
- Septic venous sinus
- Thrombophlebitis.

or surgical can play important roles. Intraneural pathways could be important as well.

THERAPEUTIC AIMS IN ACUTE CENTRAL NERVOUS SYSTEM INFECTIONS[3,4]

One should promptly recognize the patient with an acute CNS infection syndrome and treat accordingly. Also, one has to rapidly initiate appropriate empiric therapy. In addition, attempts should be made to specifically identify the etiologic agent and adjust the therapies as indicated on prompt basis. One should optimize management of complicating features as well.

CLINICAL ASSESSMENT

Acute cases present within 24 hours while subacute within 7 days. Meningitis becomes chronic if it takes more than 4 weeks. History and physical examination can give useful clues to the cause. Box 15.2 gives details of clinical features of meningitis.

DIAGNOSIS

Cerebrospinal Fluid

One should note down color/clarity/cell counts/white blood cell (WBC) count, chemistries (protein, glucose),

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Box 15.2: Clinical features of meningitis.

- Fever
- Headache
- Nuchal rigidity
- Altered mental status
- Photophobia
- Nonspecific symptoms/signs
- Focal neurological signs
- Seizures
- Specific clinical stigmata according to etiological agent
- Children/elderly.

stains (e.g. Gram positive or negative), cultures (routine), and antigen screens, etc. *Streptococcus pneumoniae*, *Neisseria meningitidis*, and Hib could be positive in 50–100% of patients. Cryptoantigen screen detects *Cryptococcus neoformans*, and is positive in 90–95% of patients with cryptomeningitis. Low glucose could be due to higher bacterial load and suggests bacterial meningitis.

Every patient with meningitis should have cerebrospinal fluid (CSF) obtained unless the procedure is contraindicated. Chemistry and cytologic findings highly suggestive of bacterial meningitis include a CSF glucose concentration below 45 mg/dL, a protein concentration above 500 mg/dL, and a WBC count above 1,000/mm^3. A Gram stain should also be obtained and could be positive in up to 10% of patients. The following features are suggestive of dementia.

Opening pressure more than 180 mm H_2O and WBCs 10–10,000/L. It is important to that in infective bacterial meningitis, neutrophils predominate. Red blood cells are absent in nontraumatic tap. Glucose levels below 40 mg/dL and CSF proteins more than 45 mg/dL are indicative of bacterial meningitis. Gram stains may be positive in more than 60% and CSF culture in more than 80%.

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Latex agglutination may be positive in patients with meningitis due to *Streptococcus pneumoniae*, *Neisseria meningitidis,* Hib, *Escherichia coli*, and group B streptococci. Limulus test may be positive in cases of Gram-negative meningitis. Polymerase chain reaction can detect bacterial deoxyribonucleic acid (DNA).

Lumbar Puncture

This is the single most important diagnostic test. It is a mandatory test, especially, if bacterial meningitis is suspected. If lumbar puncture is contraindicated (Box 15.3), one should obtain bacteria count and then begin empirical treatment. CSF features are summarized in Table 15.1.

Imaging

It is usually an overemployed diagnostic modality in the diagnosis of CNS infections. However, it leads to unnecessary delays in treatment and added costs. It is important to know that imaging *per se* is rarely indicated in patients with suspected acute meningitis. This is, however, mandatory in patients with possible focal infection. Increased sensitivity with contrast enhancement could be expected.

Box 15.3: Contraindications of lumbar puncture.

- *Absolute:*
  - Skin infection over site
  - Papilledema
  - Focal neurological signs.
- *Relative:*
  - Increased intracranial pressure (ICP) without papilledema
  - Suspicion of mass lesion
  - Spinal cord tumor
  - Spinal epidural abscess
  - Bleeding diathesis or ↓ platelets.

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TABLE 15.1: Cerebrospinal fluid (CSF) features of bacterial meningitis.

Cerebrospinal fluid parameters	*Typical findings*
Opening pressure	200–500 mm H_2O
White blood cell count	1,000–5,000/mm^3 (range = 100–10,000)
Percentage of neutrophils	≥80%
Protein	100–500 mg/dL
Glucose	≤40 mg/dL
CSF-to-serum glucose ratio	≤0.4
Gram stain	Positive in 60–90%
Culture	Positive in 70–85%
Polymerase chain reaction	Useful to detect bacteria

Box 15.4: Penetration of antibiotics inside blood–brain barrier.

- Penicillins
- Cephalosporins
- Chloramphenicol
- Rifampin
- Trimethoprim-sulfamethoxazole combination.

TREATMENT

The chosen antimicrobial must have good activity on the suspected pathogen(s) and should preferably be bactericidal. Adequate CSF diffusion is a good indicator of its potential efficacy and the drug should have acceptable risk of toxicity. The penetrations of antibiotics are given in Box 15.4.

Antibacterial Therapy

Bactericidal therapy is generally necessary to cure meningitis. Bacteriostatic drugs, such as clindamycin and tetracycline, may be inadequate for meningitis.

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Chloramphenicol is a bacteriostatic drug for most enteric Gram-negative rods; however, it is usually bactericidal for *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae* and has been extensively and successfully used to treat meningitis caused by these organisms.

Empirical Therapy

Selected third-generation cephalosporins such as cefotaxime and ceftriaxone have emerged as the beta-lactams of choice in the empiric treatment of meningitis. These drugs have potent activity against the major pathogens of bacterial meningitis with the notable exception of *Listeria*. Ceftazidime, another third-generation cephalosporin, is much less active against penicillin-resistant pneumococci than cefotaxime and ceftriaxone. Ceftriaxone 2 grams given intravenously (IV) very 12 hourly or cefotaxime 2 grams IV every 4–6 hourly plus vancomycin 15 mg/kg every 6–12 hourly can be used. If the patient is more than 50 years, one can also add ampicillin 2 grams IV every 4 hourly (for *Listeria*).

Streptococcus pneumoniae

The conventional approach to the treatment of pneumococcal meningitis was the administration of penicillin alone for 2 weeks in a dose of four million units IV every 4 hours. Good results have also been obtained with third-generation cephalosporins. However, the problem of treating pneumococcal meningitis has recently been compounded by the widespread and increasingly common reports of pneumococcal strains resistant to penicillin. Cefotaxime or ceftriaxone can be used if the minimal inhibitory concentration (MIC) for these drugs is less than 0.5 μg/mL. It is recommended that vancomycin (2 g/day) should be given with

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cefotaxime or ceftriaxone in the initial treatment of pneumococcal meningitis if there has been beta-lactam resistance noted locally.

Vancomycin should be continued if there is high level penicillin resistance and an MIC more than 0.5 μg/mL to third-generation cephalosporins. If corticosteroids are given, rifampin should be added as a third agent since it increases the efficacy of the other two drugs. The usual duration of therapy is 2 weeks.

Treatment is done using high doses of penicillin, e.g. 1.2 grams (2 million units) given 2 hourly. Please note that some strains have reduced susceptibility to penicillin and some are resistant. Polyvalent vaccines for risk groups, e.g. before splenectomy is available.

Haemophilus influenzae

Haemophilus is a Gram-negative coccobacillus, capsulated strains (type b used predominate). Peak incidence occurs in 2 years old (range = 3 months to 5 years). Incidence has declined greatly since the successful introduction of Hib vaccine. Condition has insidious onset, no rash, and has lower mortality. Treatment is done using cefotaxime or ceftriaxone.

A third-generation cephalosporin is the drug of choice for *Haemophilus influenzae* meningitis. Patients with *Haemophilus influenzae* meningitis should be treated for 5–7 days. For adults, a dose of 2 grams every 6 hours of cefotaxime and 2 grams every 12 hours of ceftriaxone is more than adequate therapy. Pharyngeal colonization persists after curative therapy and may require a short course of rifampin if there are other children in the household who are at risk for invasive *Haemophilus* infection. The recommended dose is 20 mg/kg/day (to a maximum of 600 mg/day) for 4 days.

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Neisseria meningitidis

This infection is best treated with penicillin although there are scattered case reports of *Neisseria meningitidis* resistant to penicillin, such strains are still very rare. A third-generation cephalosporin is an effective alternative to penicillin for meningococcal meningitis. A 5 days duration of therapy is usually considered adequate. When penicillin is used, there may still be pharyngeal colonization with the infecting strain which may take some more time for eradication or need alternative therapies. As a result, the index patient may need to take rifampin, a fluoroquinolone, or a cephalosporin.

If meningococcal meningitis confirmed then a change to high doses of benzylpenicillin can be considered. Close contacts in home, school/university, and nursery should be given antibiotic prophylaxis. Rifampicin 600 mg once daily for 2 days or ciprofloxacin 1,000 mg once daily is used. Hospital contacts only need prophylaxis if contact with secretions, e.g. mouth to mouth resuscitation.

Listeria monocytogenes

Listeria has been traditionally treated with ampicillin and gentamicin, as resistance to these drugs is quite rare. Ampicillin is given in typical meningitis doses (2 grams IV every 4–6 hours in adults) and gentamicin is used for synergy. An alternative in penicillin-allergic patients is trimethoprim-sulfamethoxazole (dose of 10/50 mg/kg/day in two or three divided doses). The usual duration of therapy is at least 3 weeks.

Enteric Gram-negative Rods

Prior to the availability of third-generation cephalosporins, it was often necessary to instill an aminoglycoside

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Neurological Drugs

Salient Features

- Presents the principles and practice of neurological drug therapy in a simplified way
- Gives an overview of common diagnostic entities and evidence-based therapy guidelines about the neurological conditions, especially emphasizes on headache, epilepsy, Parkinson's disease, dementia, etc.
- Includes the special chapters on adverse drug reactions, genetic disorders and rare neurological illnesses
- It is an attempt to ensure both basic and advanced learners in neuropharmacology get a fair idea about the drug treatment
- Encourages rational basis of pharmacotherapy.

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