# Intracranial Infections

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1. Introduction

Infections of the Central Nervous System (CNS) present a clinical challenge for specialists across many disciplines, from primary health care providers, to surgeons and infectious disease doctors, to health policy advocates. Regional variation of disease burden requires physicians to be familiar with new infectious trends while keeping abreast of local infection patterns and susceptibilities. The advent of HIV/AIDS in the 1980’s provides an example of how a new infectious agent and its CNS manifestations forced local health networks to think beyond the challenges they had faced in preceding years.

Such ‘Neuroinfections’ are reported globally by 26.5% of all World Health Organization’s member states and by 50% of countries in parts of Africa and South-East Asia. While these statistics may be subject to bias, most interpret these results as representing a disproportionate burden of disease in the developing world.(1) This is also the area of the world with the least number of Neurosurgeons. There are an average of 0.01 Neurosurgeons per 100,000 population in Africa in comparison to 0.76 Neurosurgeons per 100,000 population in the Americas.(1) As a consequence of this disproportional burden of disease and expert care, many qualified surgeons (although not trained in Neurosurgery) are undertaking neurosurgical procedures such as treatment of epidural abscesses. As such, this review is not only aimed at Neurosurgeons (either in-training or fully qualified) but also at General Surgeons who find they are undertaking the treatment of intracranial infections.

When considering intracranial infections, it is perhaps best to follow a classification scheme that encompasses both location within the skull and infectious etiology. Here, we review intracranial infections using the following layout:

- Skull and scalp infections
- Epidural Abscess
- Subdural Empyema
- Brain Abscess
- Infections in the setting of HIV/AIDS
- CNS Tuberculosis
- Neurocysticercosis
- Cerebral Malaria
Bacterial Meningitis

The above list encompasses infections from bacterial, viral, fungal and protozoa origin. We will review each of these areas with regard to clinical presentation and management strategies. The management of each of these conditions should encompass both a medical and surgical strategy. Due to space constraints we have focused this review to either conditions that may require surgical intervention or those that are highly prevalent. Other important neuroinfections, such as poliomyelitis, rabies, and leprosy neuropathy are beyond the scope of this review.

2. Methods

We carried out a Medline search for articles published between 1996 and July 2009. We matched keywords of chosen topic headings (for example epidural abscess, subdural empyema, etc.) to Medical Subject headings (MeSH) and cross-referenced this with the MeSH ‘developing countries’. In accordance with the principle of full-online access mandated by Surgery in Africa, we limited our search to articles available in full text through the University of Toronto library system, available free online to Ptolemy account holders. All languages were included. In some instances this search strategy did not yield sufficient information to provide an adequate overview of the topic. In such cases we extended the search prior to 1996 and included paper only resources.

3. Infections of the Scalp

3.1. Background and Clinical Presentation

While there are a host of dermatological conditions that can affect the scalp, scalp infections requiring the intervention of a surgeon are exceedingly rare. In the setting of preceding trauma or previous neurosurgical procedure this rate increases and one should watch for discharge around old traumatic scars or surgical incisions. Risk factors for surgical site infections include immunosuppression, diabetes mellitus, or contaminated wounds.

3.2. Surgical Management

The scalp is very well vascularized and because of this most minor infections can be treated with antibiotics alone (described below). In the setting of preceding trauma or neurosurgical procedure, one should acquire a CT scan of the head (with contrast) to ensure that the infection has not penetrated the bone, epidural or subdural space. If CT is not available, plain skull X-rays may reveal abnormalities of the skull. If the infection appears extensive, (for example with visible bone or necrotic skin edges) one should consider intra-operative irrigation and debridement followed by a longer course of antibiotics. In very rare cases skin grafting or skin flaps may be required to treat long-standing, poorly managed infections.

3.3. Medical Management

Scalp infections such as folliculitis can often be treated conservatively or with topical antibiotics alone. Deeper infections such as cellulitis typically require systemic antibiotics covering usual skin organisms, namely Staphylococcus aureus or Streptococcal species. Other soft tissue infections like impetigo can affect the face, particularly in children. Again, gram-positive skin organisms like S. aureus, and also Group A Streptococci should be considered. Penicillinase-resistant penicillins with anti-staphylococcal activity or cephalosporins should be used.
Soft tissue infections in the post-neurosurgical setting are important to consider. The most likely pathogens are again *S. aureus* and Coagulase-negative staphylococcus (CoNS). A first-generation cephalosporin like cefazolin is often sufficient, though in some centers with high rates of methicillin-resistant *S. aureus*, vancomycin is recommended. Hardware present at the surgical site increases the risk of treatment failure, indicating that removal of the hardware may be necessary to eradicate infection.

4. Skull Infections

4.1. Background and Clinical Presentation

Osteomyelitis is defined as an inflammation of the bone that began as an infection of the medullary cavity and spread to involve the haversian system and the periosteum of the affected area. Perhaps the two most common clinical situations in which a clinician encounters infections of the skull, are post-trauma and post-neurosurgery. Other important aspects of a patient’s history include: 1) any local treatments that may have affected the vascularity of the bone, such as radiation or malignancy (2); and 2) any conditions that may have altered the patient’s immune status, such as diabetes, anemia or malnutrition.(3)

For practical purposes, osteomyelitis of the skull can be divided into the easily accessible calvaria (frontal, parietal, occipital and temporal bones) and the skull base.

The etiology of infection of the easily accessible calvaria is limited. Post-traumatic and post-neurosurgical bacterial infections are the most common; while rare conditions such as tuberculosis can present as calvarial lesions, although this represents only about 1% of all bony tuberculosis cases.(4) Diagnosis of these lesions is made with a combination of clinical history and imaging. Clinically, the patient may present with a discharging sinus tract and a tender scalp. X-ray or CT will yield bony destruction; while MRI may show more extensive soft tissue involvement.

The etiology of infection of the skull base is more extensive and usually involves spread from one of the surrounding paranasal sinuses or an otologic origin. A recent review (8) of a pediatric series demonstrated that acute frontal sinusitis resulted in approximately 30% more intracranial complications than an acute sinusitis at other locations. Prior to the advent of systemic antimicrobial therapy, the spread of these infections to the cranial base was most often fatal.(6) In contrast to infection of the calvarium, skull base lesions are often insidious in onset and have little clues to offer on either clinical exam or standard radiographic imaging. There have been reports of such infections presenting with lower cranial nerve deficits. (7)

Malignant otitis externa is an infection that begins in the soft tissues of the external ear canal and spreads via the fissures of Santorini and the tympanomastoid suture to involve the stylomastoid and jugular foramen. It occurs most commonly in uncontrolled diabetes and has been reported to be fatal if not treated early. (9) This infection usually presents with unremitting, throbbing ear pain that tends to be worse at night. Headache and temporomandibular joint pain can occur. A conductive hearing loss may be present. Physical examination reveals an erythematous, swollen external auditory canal. Lower cranial nerve palsies may be present. If left untreated it can spread along fascial planes and lead to venous thrombosis.

MRI is often needed to detect these lesions. In the absence of gross sinus or otologic infection it is difficult to distinguish an infectious etiology from a malignancy. If feasible, a CT or MRI guided biopsy is warranted to make a diagnosis. This is usually not possible as more often than not these lesions are inaccessible by such means. In such cases one may resort to an open surgical biopsy (see below).
4.2. Surgical Treatment

Surgical treatment of calvaria lesions rests on these principles: removal of necrotic bone and tissue, obtaining cultures or biopsy in order to identify the cause, managing the dead-space created by the debridement and ensuring stability of the bone. The first three points are addressed by taking the patient to the operating room and performing a standard craniectomy around the affected area. Attending to the integrity of the cranium requires a case-by-case decision that adheres to the following principle: if suspicious of an active infectious process then one should delay placing any implants. If an implant is required to replace a large cranial defect then methyl-methacrylate or a wire-mesh is typically used if available. If these are not available autologous rib may also be split length-wise to construct “planks” to reconstruct a defect. In very rare cases of long-standing persistent osteomyelitis involving the scalp, free muscle flaps may be considered but should be done only in the hands of an experienced surgical team involving both Neurosurgeons and Plastic surgeons. (5)

Surgical treatment of suspected skull base lesions is more complicated and should involve consultation with an appropriate Otolaryngology surgeon. Often a combined endoscopic and open approach is needed to make a diagnosis, especially if the infection stems from the paranasal sinuses. Debridement of as much tissue as possible without causing neurological damage to the patient is recommended.

4.3. Medical Treatment

The chronicity of skull infections creates a relatively avascular and ischemic environment. The lower oxygen tension not only creates opportunity for anaerobic bacterial growth, but also impairs the penetration of antibiotics, highlighting the importance of surgical removal of necrotic tissue. (3)

Medical management of osteomyelitis in the skull should be culture-driven whenever possible. Typical species encountered include *S. aureus* and *Streptococcal* spp., particularly *S. pneumoniae* and *S. pyogenes*. Anaerobes, *Klebsiella* spp. and *Pseudomonas aeruginosa* can also cause infection, particularly from otologic spread. Fungal and tuberculous possibilities need to be considered and cultured. (6) Infections spreading from nonotologic sources require coverage for *S. aureus*. Otologic infections must ensure coverage for *Pseudomonas*. Prolonged courses of third-generation cephalosporins or oral fluoroquinolones are generally used. Duration of treatment is typically six weeks, but can be extended in certain clinical circumstances. (3)

5. Epidural Abscess

5.1. Background and Clinical Presentation

Epidural abscess has a tendency to occur in three populations: children in the range of 12 – 16 years, patients who undergo a neurosurgical procedure, and those who suffer traumatic injury to the cranium. Infection develops in the potential space between the inner table of the cranium and the dura mater by way of direct extension or hematogenous spread, usually from skin, soft tissue, urinary, or respiratory sources. Differentiating acute or chronic abscess is not clinically useful as it neither indicates an etiological agent nor does it change choice of treatment or prognosis.

A number of predisposing conditions have been reported in the literature, mainly in the form of case reports or small case series. Risk factors can be classified as those involving compromised immunity (diabetes mellitus, age, renal failure, malignancy, HIV/AIDS, and alcoholism), those involving disruption of normal anatomy (congenital sinus dermal tract, traumatic cranial fracture, insertion of tongs for cervical traction, or prior neurosurgical procedure), or those involving a source of infection...
(mastoiditis, chronic otitis media, paranasal and frontal sinusitis, or orbital cellulitis). (25)

Clinical presentation can vary from headache, nausea, vomiting and lethargy to fever, meningismus, periorbital swelling and scalp tenderness. Spinal epidural abscesses are more often characterized by back pain, localized spinal tenderness, fever, and neurological symptoms or paresis. Investigation should include an CT scan with contrast if available; this will reveal a hypodense center with a ring of enhancement. The bone is not usually involved. Lumbar puncture is of little or no value and has been reported to cause deleterious consequences including seeding of the meninges and subdural space in the case of spinal epidural abscess, or herniation if the infection has spread to the subdural or subarachnoid spaces. (10) In resource-poor settings, however, it may be necessary to rule out other causes of symptoms. (25) MRI, if available, may be of benefit if there is a diagnostic dilemma or if the infection is particularly small. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), though nonspecific, can be followed to assess response to treatment if they are available. Blood cultures should be obtained, although they are negative in about half cases. Potential distant sources of infection, such as urine or sputum should be cultured as well if clinically indicated.

5.2. Surgical Management

Epidural abscess requires surgical evacuation and prolonged antibiotic administration. If the patient’s clinical situation is stable and surgical evacuation can be arranged in a timely manner then it is best to identify the organism prior to beginning antibiotic therapy. Such collections are best treated with a craniotomy that uncovers the majority of the collection to allow for adequate removal and irrigation. Burr hole treatment is not sufficient. If osteomyelitis is present in the setting of severe infection one must consider discarding the bone flap. Cosmetic defects can be corrected at a later time (after the infection has been adequately treated – usually a period of six months) with autologous rib graft or a bone substitute such as methyl methacrylate or wire mesh. The use of a postoperative surgical drain is not recommended, as adequate irrigation of the cavity should be accomplished in the operating room.

5.3. Medical Management

Data on epidural abscesses in resource-poor settings is lacking. Case series from mainly Western sources show that the majority of epidural abscesses are caused by S. aureus (60% of cases), followed by gram-negative rods such as Escherichia coli, Pseudomonas aeruginosa, and Klebsiella spp. Streptococcus spp. including the Viridans group, S. agalactiae, and S. pneumoniae, as well as enterococcus, Coagulase negative staphylococci, and anaerobes. In endemic settings, mycobacterial causes need to be suspected. Increasingly, rarer organisms are becoming culprits, such as Prevotella oris, Listeria mycopathogenes, Mycobacterium avium intracellulare, and Nocardia spp. The HIV pandemic and changes in bacterial flora in the antibiotic era may be contributing factors. (25) In HIV-endemic settings, culture-based therapy is necessary due to the expanded differential of causative organisms including fungi and parasites.

There are no clear guidelines directing treatment, and recommendations are generally based on case series, retrospective data, and expert opinion. Antibiotics should be tailored to cultures whenever available. Empiric antimicrobials should cover S. aureus, streptococci, and gram-negative bacilli, must penetrate bone, and have sufficiently low toxicity to allow for a prolonged course. (25) Examples include amoxicillin-clavulanate or cefuroxime. An alternative is a third generation cephalosporin with or without metronidazole while awaiting cultures. If the patient is an intravenous drug user, Pseudomonas coverage must be included. Synergistic doses of aminoglycosides can be considered if there is an ability to monitor for renal toxicity. Azoles or amphotericin B should be used for fungal infections. (26) There is insufficient evidence to recommend steroids for bacterial epidural abscesses. (25)
There are several factors to consider when deciding on the duration of antibiotics, including other comorbidities, concurrent surgical intervention, the organism isolated, the bactericidal efficacy of the available agents, and the presence of concomitant vertebral osteomyelitis. If there is no osteomyelitis, 4-6 weeks of antibiotics with at least 3-4 weeks of parenteral treatment is recommended. If osteomyelitis is present, the patient should receive at least 6-8 weeks of intravenous therapy and a total course of antibiotics lasting 8-12 weeks. Ideally, the patient should be reimaged 4-8 weeks after therapy completion to ensure resolution. (25,26)

6. Subdural Empyema

6.1. Background and Clinical Presentation
The etiology of subdural infection is similar to that of epidural infection with one distinction: subdural empyema most commonly occurs after cranial surgery, particularly after burr hole drainage of a chronic subdural hematoma in the elderly. Infection of the subdural space can also occur in the setting of shunts because of the presence of a foreign body and the propensity for bacteria to adhere to foreign material. Infection can also spread from the posterior table of the frontal sinus by retrograde thrombophlebitis of mucosal veins that communicate with dural venous sinuses via emissary veins. Sinusitis-associated subdural empyema tends to present more acutely than that which occurs post-surgery.

Acute subdural empyema tends to present with rapid encephalopathy, meningismus, seizures and focal neurological deficits. Subacute empyema tends to manifest itself as low grade fever and headache lasting several weeks. (27) Thrombosis of cortical veins can occur, resulting in cerebral infarction. Infratentorial subdural empyemas can cause an obstructive hydrocephalus and the symptoms associated with it. Treatment of such lesions should be expedited, as the mortality rate can reach 20%. (11)

Peripheral blood work will reveal a leukocytosis and cultures may be positive. As with epidural infections, lumbar puncture (LP) is of little value and may result in a herniation syndrome if intracranial pressure (ICP) is high. If an LP is performed, it demonstrates low-grade pleocytosis, normal glucose, and normal protein. CSF cultures are negative unless there is concomitant meningitis. (27) Investigation of choice is either a CT or MRI with contrast. CT reveals a hypodense lesion with peripheral enhancement. MRI will reveal a collection that has decreased T1 signal and increased T2 signal. In the case of patients with a ventricular shunt, MRI is important to distinguish subdural effusions from subdural infections.

6.2. Surgical Management
Surgery combined with antibiotic therapy directed at a specific organism is the appropriate treatment, as there is very limited experience with conservative management with antibiotics alone.(28) A recent series of close to 700 patients reported that craniotomy with evacuation of pus and irrigation was the preferred surgical approach in comparison to either burr holes or craniectomy. (10) Burr holes may be used in medically unstable patients (i.e. septic shock) in order to obtain a diagnosis and start appropriate antibiotic therapy. Craniotomy should follow such treatment as soon as it is safe to do so as mortality rates are higher with burr hole treatment alone.

6.3. Medical Management
Antibiotic selection should take into consideration local prevalence rates as well as likely pathogens based on the source of infection. When caused by sinusitis, the most likely pathogens are aerobic and anaerobic Streptococci (particularly the S. milleri group), anaerobes, S. aureus, Haemophilus species, and Enterobacteriaceae.(27,28) In this situation, Penicillin (PCN) G and chloramphenicol may be most relevant to a resource-poor environment. Some groups have suggested third-generation cephalosporins
and metronidazole, while others suggest the addition of vancomycin to this regimen. (27,28) When caused by otitis, coverage should again include aerobic and anaerobic Streptococci, anaerobes and Enterobacteriaceae. PCN G and chloramphenicol, or alternatively metronidazole with a third-generation cephalosporin may be used. In the post-traumatic setting, coverage needs to be expanded to include CoNS, S. aureus, Enterobacteriaceae, and clostridium spp, typically with vancomycin and a third-generation cephalosporin.

The duration of parenteral therapy may be as short as 2 weeks, followed by 4 weeks of oral therapy when there is improvement in radiographic findings, fever, and ESR. More often at least 3 weeks of IV therapy are followed by 3 weeks of oral treatment. If there is osteomyelitis, intravenous therapy should be extended to 6-8 weeks. Seizures should be treated with anticonvulsant medication; some groups recommend prophylactic seizure medications. Corticosteroids or osmotic agents such as mannitol should be reserved for the setting of life-threatening elevated ICP. (27)

7. Brain Abscess

7.1. Background and Clinical Presentation

The cause of brain abscess can go undetermined in about one-third of all cases.(12) Nonetheless, specific patient populations and mechanisms have been identified in the pathogenesis of these lesions: 1) systemic disease such as immunodeficiency (e.g. HIV/AIDS and transplant patients), and congenital heart disease with right to left shunts (e.g. tetralogy of Fallot); 2) contiguous spread from paranasal sinus, middle ear and mastoid air cell infection; 3) hematogenous dissemination via other infectious sources such as osteomyelitis, dental abscess, respiratory infection, acute diverticulitis and bacterial endocarditis. The location and number of abscesses can provide clues as to the source. A frontal lobe abscess usually indicates direct extension from either the frontal or paranasal sinuses. Temporal lobe abscesses usually result from middle ear or mastoid infections. Multiple abscesses usually indicate hematogenous spread or immunodeficiency.

Presentation of intracerebral abscesses is similar to that of an intracranial mass lesion (i.e. tumor) but the symptoms tend to progress much more quickly. Headache is invariably present and nausea, vomiting and seizures can occur in up to 50% of patients. Focal neurological deficits may be present and depend on the location of the abscess.

Laboratory tests are non-specific but can yield some information: an elevated white blood cell count, ESR and CRP often indicate an infectious process. Gram stain and culture of any specimen should be obtained. Immediate direct inoculation of pus into both aerobic and anaerobic culture medium may help increase yield. Fungal cultures and staining for acid-fast bacilli (AFB) should also be done. Blood, sputum, ear, or sinus cultures may be helpful. Tissue should also be examined histopathologically, as granulomas or parasitic sources may be identified. CT and MRI are the diagnostic modalities of choice. CT reveals a hypodense lesion with peripheral enhancement. MRI will reveal a collection that has decreased T1 signal and increased T2 signal (Figure 1).
7.2. Surgical Management

Surgical management is necessary to obtain an accurate microbiological diagnosis and is therapeutic in reducing the infectious burden, allowing better penetration of antibiotics. The primary goal of surgical treatment should be a balance of obtaining a diagnosis, draining the pus, and preserving neurological function. One must resort to the typical armamentarium of surgical options available ranging from a biopsy for lesions that are either deep-seated or in eloquent areas, to craniotomy with the goal of complete resection in superficial, non-eloquent areas. In the former case the most accurate way of accessing deep lesions is with a stereotactic frame or frameless navigation system. If these are not available the accuracy of a freehand biopsy and drainage can be improved using a sterile draped ultrasound device intra-operatively. Indwelling catheter drainage after surgical treatment is of little value as the purulent fluid is often too viscous and occludes the catheter. Requirement for repeated drainage of a brain abscess is a common occurrence depending on the patient's condition and the appearance of subsequent CT scans (see below).

One of the most feared aspects of brain abscesses or the treatment of such lesions is rupture into the ventricular system and the subarachnoid space. This can result in a far worse clinical status including prolonged seizures and hospital stay requiring intensive care unit support.

7.3. Medical Management

The microbial spectrum seen in brain abscesses is largely dependent on the source of infection. Polymicrobial infection can be seen in up to 30% of cases, particularly if the infection arose from an otogenic or mastoid source.\(^{(29)}\) Empiric treatment for bacterial abscesses consists of a third-generation cephalosporin, PCN G and metronidazole, covering most likely organisms. In resource poor settings, chloramphenicol is likely to be substituted for gram negative and anaerobic coverage. The use of corticosteroids is controversial as it may decrease antimicrobial penetration with prolonged use. There are no well-controlled randomized controlled trials, but generally steroids are recommended for life-threatening edema or impending herniation, with a goal of tapering as quickly as possible. Prolonged seizure prophylaxis is recommended until the patient is seizure-free for at least 2 years.\(^{(29,30)}\)

Contiguous otogenic or paranasal sinusitis-based infections typically involve Streptococcus spp.,
Enterobacteriaceae, or anaerobes. Hematogenously spread abscesses from the abdomen (usually caused by gram-negative bacteria or anaerobes), urinary tract (Enterobacteriaceae or Pseudomonas), and lungs (streptococcus, Corynebacterium, Fusobacterium, or Peptococcus species), can all be treated similarly with a third-generation cephalosporin, PCN G and metronidazole. If endocarditis or penetrating trauma is suspected, a beta-lactamase resistant PCN should be substituted for PCN G to cover S. aureus. Penetrating trauma may also be associated with Clostridium, Bacteroides, or Peptostreptococcus species. Lastly, in the postoperative setting, staphylococcal species (particularly S. aureus and S. epidermidis), Pseudomonas, and Enterobacteriaceae need to be covered. The recommended regimen is a third-generation cephalosporin and vancomycin, but in developing settings an anti-staphylococcal PCN may be more reasonable choice depending on regional rates of MRSA. For bacterial brain abscesses, 6-8 weeks of parenteral therapy are recommended. For multiple abscesses, 3-6 months of treatment may be necessary. CT scans should be repeated every 1-2 weeks during treatment when possible, followed by monthly scans until resolution of the abscess occurs.(29,30)

In the HIV/AIDS era, Nocardia asteroides is a growing cause for brain abscesses in individuals with impaired cell-mediated immunity. Its onset is more insidious than that of other bacterial infections, occurring over months. Mortality is threefold higher than for other bacterial abscesses. Because Nocardia is slow-growing in usual culture medium, the laboratory should be notified if suspected. Treatment is with high dose combination sulfa drugs. High doses should be continued for 3-6 weeks, when they can be changed based on clinical response for a total duration of 12 months. Some suggest ongoing suppressive therapy in the presence of ongoing immunosuppression. Patients on prolonged courses of sulfa drugs need to be monitored for rash and bone marrow suppression.(31)

Fungal infections are also becoming increasingly common in patients with HIV/AIDS. Cerebral aspergillosis and Mucormycosis (zygomycosis) deserve special mention for their virulence, and Candida species for their prevalence. Aspergillosis abscesses are associated with blood vessel invasion and cause thrombosis. “Mucor” usually presents fulminantly. Both fungi originate from lung or paranasal sinus sources. For these infections, in particular, surgical and medical treatments are essential. For neuroaspergillosis or candida the recommended regimen is amphotericin B and synergistic 5-flucytosine, which is usually unavailable in resource poor settings. Fungal infections should be treated with prolonged courses of antibiotics, ranging from 3-12 months depending on the organism and response to treatment.

8. Infections in the setting of HIV/AIDS

8.1. Background and Clinical Presentation

Surgeons will continue to play a role in the management of HIV patients for several reasons. As systemic treatments improve and anti-retroviral medications reach those in sub-Saharan Africa and other endemic regions, the length of time that people live with AIDS is increasing. Given this fact, there is increasing evidence that the CNS acts as a reservoir for HIV.(14) The differential diagnosis of CNS lesions in HIV-positive patients is presented in Table 1. As one can see, the sheer number of possibilities makes diagnosis extremely important prior to the initiation of treatment. CNS diseases specific to HIV include cerebral toxoplasmosis, cryptococcal meningitis, cytomegalovirus (CMV) encephalitis and polyradiculomyelitis, and progressive multifocal leukoencephalopathy. Medical management will be outlined briefly. CNS tuberculosis (TB) will be discussed later. Effective therapies have been established for approximately 90% of CNS lesions in patients with AIDS.(15) The majority of these therapies are medical, shifting the role of the surgeon towards biopsy rather than open surgical procedure. In fact, the need for a craniotomy in an AIDS patient should be limited to life saving operations required for the treatment of high intracranial pressure of a mass lesion or to other
intracranial lesions unrelated to the patient’s HIV that warrant surgical treatment.

An HIV+ patient who experiences neurological symptoms should be investigated with either CT or MRI. Despite the fact that certain CNS lesions are characteristic in the general population, it is recommended that the treating physician of HIV patients with CNS mass lesions strongly consider biopsy prior to medical therapy.\(^{(16)}\) Furthermore, it is recommended that one \textbf{not} assume that multiple CNS lesions are of the same etiology.

### 8.2. Surgical Management

Despite the fact that the differential diagnosis of CNS mass lesions in HIV patients is wide, there are certain infections that are more common than others. Toxoplasmosis is an example and is demonstrated by either single or multiple ring-enhancing lesions on a contrast enhanced CT. Several groups are advocating 2-3 weeks of empirical anti-Toxoplasma therapy \(^{(17)}\) (described below) to defer or avoid brain biopsy. This protocol is especially appropriate in the setting of limited neurosurgical resources.

If the treating physician is unable to make a diagnosis based on imaging, or the patient fails to respond to empiric Toxoplasmosis therapy, a biopsy should be considered. As mentioned above, there is little role for open surgical procedure, especially given the fact that HIV-positive patients with CNS lesions are often medically unstable.

### 8.3. Medical Management

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Table 1 CNS Lesions in HIV-positive patients. Adapted from Levy et al\(^{(13)}\)

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Neoplastic</th>
<th>Non-Infectious</th>
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<tr>
<td>Parasitic</td>
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<td>Non-Infectious</td>
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<td>Lymphoma (primary and secondary)</td>
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<td>Cysticercosis</td>
<td>Kaposi’s sarcoma</td>
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<td>Fungal</td>
<td>Glioma</td>
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<td>Cryptococcus</td>
<td>Metastatic carcinoma</td>
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Perhaps most importantly, the CNS diseases described here are considered opportunistic infections and warrant initiation of anti-retroviral therapy. Timing of therapy is controversial, as worsening of symptoms with immune reconstitution has been described. Once the acute illness is managed, secondary prophylaxis should be continued until there is a sustained and absolute increase in CD4+ count to >200 cells/ul for over 6 months. (32)

**Cerebral toxoplasmosis**

Cerebral toxoplasmosis is caused by the obligate intracellular protozoan parasite *Toxoplasma gondii*. Diagnosis is usually made on the basis of progressive neurological deficits, contrast enhancing mass lesion(s) on CT or MRI, and clinical and radiographical evidence of response to empiric anti-toxoplasmosis treatment within 2 weeks. In developed countries, the most likely causes for a ring-enhancing mass lesion in an HIV+ patient are toxoplasmosis or primary CNS lymphoma (PCNSL), which is the basis for the current recommendation that empiric toxoplasmosis treatment be attempted for 10-14 days. If there is no response at this point, biopsy is recommended. In the developing world, other endemic infections like TB are more common than PCNSL. (33) Recognizing that resource-poor settings may have financial constraints that restrict neurosurgical options for diagnosis, a group in South Africa developed an alternative algorithm for the management of CNS lesions in HIV+ patients that relies on epidemiological likelihood, CT scan findings, and limited serology. It has yet to be validated in larger trials, but may represent a more realistic option for many settings. (33)

Sulfa drugs are the mainstay of treatment for cerebral toxoplasmosis. While combination pyrimethamine and sulfadiazine is most commonly recommended (with folinic acid to prevent bone marrow toxicity), trimethoprim-sulfamethoxazole (TMP-SMX) 2.5-5mg/kg/d has been shown to be equally efficacious and is more readily available in resource-poor settings. It is important to know local patterns and guidelines, as there are considerable concerns in Sub-Saharan Africa regarding the development of malaria strains resistant to anti-folate drugs like sulfadoxine-pyrimethamine, as well as concerns of resistant strains of toxoplasma. If side effects limit use of sulfadiazine, clindamycin has been shown to be an effective substitute. Primary therapy should last for 6 weeks, followed by secondary prophylaxis with pyrimethamine-sulfadiazine or TMP-SMX. (34) Corticosteroids may be required if there is significant mass effect and impending herniation, but prolonged use may confound the diagnosis, as resolution of PCNSL lesions would occur due to steroid effect. Antiepileptics may be needed to treat and prevent further seizure activity, but valproate should be considered first-line treatment as both phenytoin and phenobarbital interact with antiretroviral therapy.

**Cryptococcal meningitis**

Cryptococcal meningitis is the leading cause of meningitis in central and southern Africa. (35) Caused by the yeast *Cryptococcus neoformans*, it presents subacutely. Typically patients are unwell for 2-4 weeks prior to presentation, experiencing fever, malaise, and headaches. This can progress to lethargy, altered mental status, personality changes, and memory loss. More rarely, cerebral infarcts, seizures, and extraocular muscle dysfunction can occur. Meningismus is often absent. It is characteristically associated with very high ICP, which can lead to blindness, hearing impairment, coma, or seizures. (36) Definitive diagnosis can be made in three ways: visualizing the fungus in CSF under India Ink stain (75-85% sensitive); CSF cryptococcal antigen by latex agglutination assay (95% sensitive); or positive CSF culture (relatively insensitive). Negative prognostic factors include an abnormal mental state at presentation, high organism titre by quantitative CSF culture or CSF antigen titer, a WBC <0.02 x109/L in CSF, positive cryptococcal blood cultures, or hyponatremia on presentation. (35,36)

Tragically, the recommended antimicrobial treatment for cryptococcal meningitis is largely unavailable in resource-poor settings. Recommended treatment is amphotericin B 0.7 mg/kg/day with or without
synergistic flucytosine 100mg/kg/d for two weeks as induction, followed by consolidation with fluconazole or itraconazole for 10 weeks. Flucytosine has not been shown to lessen mortality or the clinical course in randomized control trials, but is tolerated well and achieves better CSF sterilization. (35) Recent studies show promise with amphotericin B and fluconazole in combination. The alternative is fluconazole 800mg/d x3d followed by 600mg/d, which is better tolerated but results in more early deaths. Higher doses of fluconazole have been studied and tolerated well, though they still perform more poorly than amphotericin B. If amphotericin B is available, electrolytes, hemoglobin, and renal function must be monitored closely. There is no evidence to support the use of acetazolamide, mannitol, or corticosteroids; in fact, outcomes may actually be worse with the use of these adjuncts. (35)

Markedly elevated ICP associated with cryptococcal meningitis may warrant repeated therapeutic LPs to reduce ICP by 50%. (36) Insertion of a lumbar drain for refractory high ICP has been described, allowing continual controlled drainage of up to 200ml/day. While lumbar drainage is not without risk of infection or tentorial/tonsillar herniation, there is a relatively low risk of complications with adequate monitoring and training of medical and nursing staff. (35) An extraventricular shunt may be needed if neurological symptoms caused by the elevated ICP persist or progress. Upon completion of consolidation therapy, a repeat LP should be done to confirm cryptococcal negativity. Secondary prophylaxis with fluconazole 200mg/d should be initiated.

**Progressive Multifocal Leukoencephalopathy (PML)**

PML is caused by JC virus, a polyomavirus infecting oligodendrocytes and astrocytes. It presents as a demyelinating disorder with slowly progressive focal neurological deficits and white matter lesions on MRI. While brain biopsy is the gold standard, cerebrospinal fluid polymerase chain reaction (CSF-PCR) for JC virus is sufficient evidence of disease if this test is available. If PML is strongly suspected and CSF-PCR is negative, repeating the LP may improve yield. Combination antiretroviral therapy is the mainstay of treatment. There are some studies and case series describing the use of cidofovir, but no randomized clinical trials to recommend its use. (34)

**CMV Encephalitis and polyradiculomyelitis**

Cytomegalovirus (CMV) belongs to the herpes virus family, and is endemic in many populations. Most HIV positive patients demonstrate evidence of prior exposure. In immunocompromised patients, CMV infection can manifest itself as retinitis, gastrointestinal ulcers, encephalitis, or polyradiculomyelitis. CMV encephalitis usually presents as progressive encephalopathy and periventricular enhancement on CT or MRI studies. CMV polyradiculomyelitis involves lower back pain or sciatica and rapidly progressive paresthesias, sphincter dysfunction, distal sensory loss, and progressive ascending weakness. A history of prior CMV infection (i.e. retinitis) should alert the clinician to the possibility of CNS CMV infection. The diagnosis is strongly supported by CMV-DNA positive CSF-PCR (62-100% sensitive, 89-100% specific), or CMV culture which is notoriously insensitive. CSF may show a polymorphonuclear pleocytosis. Brain biopsy is generally not an option as the disease often involves the brainstem or periventricular areas. CNS CMV is treated with a three-week induction with intravenous ganciclovir or foscarnet, which are associated with hematologic and renal risks. Ganciclovir can be used as maintenance therapy, though the goal is to achieve restoration of CD4 counts with the use of combined antiretroviral therapy (cART). (34)

**9. CNS Tuberculosis**

**9.1. Background and Clinical Presentation**
While CNS tuberculosis (TB) comprises only 1% of all cases of TB globally, it is described in 10-20% of all HIV-related TB, highlighting its relevance in HIV-endemic nations. CNS TB develops as a result of hematogenous seeding to the brain, spinal cord, or meninges from primary sites including the lung, bone and gastrointestinal tract. The location of seeding, host response, and bacterial virulence determine whether clinical disease occurs and what form of CNS TB will be manifest. While there has been a dramatic decline in the incidence of tuberculosis in developed countries (attributable to improving anti-tuberculosis medications), and a less dramatic decline in developing countries, this infection is still often quoted as a leading cause of mortality from a single infection, especially since it plays a role in the AIDS syndrome.

CNS TB, particularly intracranial TB, can exist in several forms. If in the skull, it presents as an osteomyelitis (described above). If in the meningeal coverings, it presents as chronic meningitis - the most common form. If within the brain parenchyma, it can present as a tuberculoma, tubercular encephalopathy, or a tuberculous brain abscess. Vertebral TB osteomyelitis, known as Pott’s disease, can also occur. The bulk of this discussion will focus on parenchymal lesions.

Tuberculomas are tubercles in the brain parenchyma that have enlarged but not ruptured into the subarachnoid space. They can sometimes be associated with tuberculous meningitis. A tuberculoma is a granuloma of epithelial, giant, and lymphoid cells that forms an area of caseating necrosis, while a tuberculous abscess is rather an encapsulated collection of pus containing viable bacilli. Patients with intracranial tuberculomas tend to be younger than 30 years of age and present with symptoms suggestive of an intracranial mass lesion, including headache, seizures, focal findings and manifestations of elevated ICP. One should inquire about either active TB, a history of personal TB or close contact with individuals known to harbor TB. Fever and other constitutional signs are present in only a minority of cases and the clinical course may take a waxing and waning course, often of up to 6 months duration before being brought to the attention of a surgeon. In rare cases multiple intracranial tuberculomas may be present, and the symptoms associated with each affected brain region can be misleading prior to obtaining imaging.

A chest x-ray should be obtained in all suspected cases of CNS TB, as 30-50% of patients will have pulmonary TB. Tuberculin skin testing in HIV+ patients has lower sensitivity than in HIV-negative patients, as immunosuppression can lead to anergy and lack of response. CSF in patients with TB menigitis shows a lymphocytic predominance with low glucose and raised protein levels. TB can be demonstrated in the CSF in three ways: culture (25-86% sensitive); CSF smear (only 8-86% sensitive); or CSF-PCR (83-100% sensitive and 88-100% specific). Techniques to improve the sensitivity of AFB staining in CSF include staining the clot formed by standing CSF, spinning down the CSF, staining the sediment and examining at least 6 ml, for at least 30 minutes.

CT scan provides the diagnosis with the following features: a lesion isodense or slightly hyperdense to the brain; ring-enhancing with contrast; may have irregular margins (as compared with a bacterial abscess); may occur adjacent to the dura and appear as a meningioma. The degree of contrast enhancement can be used to follow response to treatment on repeat imaging within 4-6 weeks. If an MRI is available and can be obtained, T1 sequences reveal a hyperintense rim with a central iso- or hypointensity. T2 images can be hypo or hyperintense. MRI can also help distinguish a tuberculoma from a single degenerating cysticercus.

9.2. Surgical Management

Tuberculomas have the potential to cause life-threatening increased ICP and may need to be surgically excised on an urgent basis (including lesions causing obstructive hydrocephalus). On the other hand, lesions caught early or within eloquent areas are best treated with medical therapy and followed with...
serial clinical examinations and imaging. If the diagnosis is in question a biopsy or complete excision (if the lesion is superficial and in a non-eloquent area) should be performed. For patients with noncommunicating hydrocephalus, serial lumbar punctures, ventriculoperitoneal shunt, or external ventricular shunt may be needed. There is no evidence to suggest one ideal management strategy, though some suggest that HIV+ patients should preferentially be treated with external drainage since high complication rates with VP shunts have been described in these patients.

9.3. Medical Management

General management for patients with CNS TB is to initiate quadruple therapy with antituberculous medications - namely isoniazid, rifampin (or rifabutin if the patient is already on combination antiretroviral therapy), ethambutol, and pyrazinamide, with pyridoxine to prevent isoniazid-induced peripheral neuropathy. Both isoniazid and pyrazinamide can easily cross the blood-brain barrier. Cultures should be obtained whenever possible so that antibiotics can be tailored based on sensitivities. Quadruple therapy is continued for 2 months, after which isoniazid and rifampin are continued in susceptible strains, to complete 9-12 months of therapy in total. If the patient is unable to tolerate oral medications because of alterations in mental status, isoniazid, rifampin, and the second line agents, capreomycin and aminoglycosides, are available in intravenous form. Patients with CNS TB may actually deteriorate clinically for a brief period after initiating therapy, which does not necessarily mean they need a change in therapy. However, multi-drug resistant TB (MDRTB) is a significant concern, especially if patients have been previously exposed to TB medications, have had contact with a patient with known MDRTB, or who have poor response after 2 weeks of therapy despite a confirmed diagnosis and excellent adherence to therapy.(37) For tuberculoma patients with communicating hydrocephalus, acetazolamide or furosemide may be used, while surgical management is need for noncommunicating hydrocephalus.(37)

The devastating consequences of vertebral TB osteomyelitis deserve special mention. Diagnosis is usually delayed because of its insidious onset and lack of fever, and neurologic deficits are more severe than in bacterial osteomyelitis. Medical management with antituberculous antibiotics may need to be prolonged beyond the usual 10-12 months to ensure symptomatic and radiographic regression. Decompressive surgery is often necessary based on the degree of neurological dysfunction and kyphosis and patient age. If surgery is not planned, biopsy may be helpful in obtaining specimens for histopathology and culture. Pott’s disease typically takes longer to resolve than other CNS manifestations of TB, but if clinical symptoms, inflammatory markers (such as ESR, WBC) or radiographic findings persist or worsen at 3 months, it may be that the treatment is ineffective. The lack of improvement may warrant surgery, but also may reflect resistance to first line therapy, necessitating either a switch to second-line agents or verification of the diagnosis.(26)

Corticosteroids in TB meningitis are controversial in the developing world, as a large controlled trial demonstrated a decrease in mortality that did not extend to HIV+ patients in subgroup analysis.(38) While steroids are currently recommended by the Infectious Diseases Society of America for the treatment of TB meningitis, it is unclear if these conclusions apply to an African population with high HIV prevalence.

10. Neurocysticercosis

10.1. Background and Clinical Presentation

While many parasitic diseases have been reported to affect the CNS, cysticercosis is by far the most common. Its infestation has been reported in Africa, Eastern Europe, Indonesia, parts of Asia, Latin
America and parts of North America. *Taenia solium*, a porcine tapeworm can be ingested in the adult tapeworm form (usually from eating undercooked pork products) or in the larval form (via fecal-oral route). Larval infection occurs by ingesting food contaminated with *T. solium* eggs, each of which contains an active embryo or “oncosphere”. These oncospheres are liberated from the eggs by the human digestive process, penetrate the wall of the small intestine and small blood vessels and are carried to distant sites. The tissues mainly affected are muscle, skin, brain and eye.\(^{(39)}\)

After penetrating the CNS the oncospheres pass through different life stages: the encephalitic stage, the cystic stage, the racemose form, the partially degenerated stage and the totally degenerated stage.

The encephalitic stage occurs when the oncosphere initially penetrates into the brain and elicits a focal inflammatory response resulting in parenchymal edema. Symptoms that occur during this stage would include headache and possibly focal seizure. CT investigation at this stage reveals a hyperdense nodular mass. MRI will demonstrate a T1 hyperintense, nodular mass surrounded by edema. If the parasites are not destroyed by the immune reaction that occurs as they penetrate the blood-brain barrier, the next 60-70 days result in the development of larvae or “cysticerci”.

Cysticerci are usually ovoid in shape with a diameter of approximately 1 cm (but can vary from 5 mm to 5 cm), are enclosed by a fragile membrane and contain a fluid and a scolex (the tapeworm’s head) with both suckers and hooks. These cysts can live for long periods of time and are easily viewed on CT as hypodense, round lesions of various sizes and number throughout the brain. Single lesions are also seen. MRI often shows hypointense round lesions of various sizes. These are most often located within the brain parenchyma but can be found in the subarachnoid space or in the ventricular system.

The racemose stage does not occur in all cases. It is defined as a cyst in communication with the subarachnoid space and subsequent development of chronic meningitis and arachnoiditis. Communicating or non-communicating hydrocephalus often develops.

In the partially degenerated stage the cyst fluid becomes jelly-like and the parasite is no longer viable.

The totally degenerated stage is a progression of the partially degenerated stage and is identified by calcification of the cyst.

The clinical presentation of patients affected by neurocysticercosis depends on several factors, including the number, life-cycle stage, and location of parasites, as well as the severity of host response. It can range from a benign, self-limiting condition to a life-threatening disease. Late-onset epilepsy is the most common presentation, usually partial seizures that occasionally progress to secondary generalized seizures.\(^{(22)}\) Progressive intracranial hypertension also occurs, which presents as seizures, dementia, and focal signs due to hydrocephalus caused by arachnoiditis, intraventricular cysts, or granular ependymitis. A massive immune response triggered by many cysticerci can cause encephalitis. CSF usually shows an increased white blood cell count, eosinophilia, decreased glucose and increased protein. CSF can be tested for enzyme-linked immunoelectrotransfer blot evidence, which is 100% specific and 98% sensitive overall, but may be negative in patients with a single brain parasite. Imaging with either CT or MRI shows the lesions well.

### 10.2. Surgical Management

Surgical management is dependant on many factors and a decision to operate must be made in conjunction with the timing of medical therapy. As brain edema can play a large role, especially in the earlier stages of the life cycle, it is important to understand that anti-parasitic medications can exacerbate
this edema and neurological symptoms. Therefore, if the potential for life threatening increases in ICP
exist with the initiation of medical treatment, with many large intracranial cysts, surgery may be
warranted earlier. As a general rule, if the patient presents in the early acute encephalitic stage with
brain edema, therapy should primarily focus on adjunct steroids and anticonvulsants if seizures are
present.

If the lesion is intraparenchymal and if mass effect is causing symptoms (including seizures) the lesion
should be removed with microneurosurgical technique. Care should be taken to remove the cyst wall.
This applies to each of the cystic stage and the degenerating stages. If the lesion is not causing mass
effect then treatment should be with medication and adjuvant steroids and anticonvulsants, as required.

If the lesion is in the ventricular system it should be removed surgically if safe to do so. The concern
with this location is the eventual development of obstructive hydrocephalus. Resection has been
reported to be curative.(23)

Hydrocephalus as a result of inoperable intraventricular lesions or a chronic meningitis/arachnoiditis
should be treated with ventricular-peritoneal shunting. Because of increased protein content in the CSF,
shunt failure is common (some report failure in the range of 40%) and redo operations are often
necessary.(24)

10.3 Medical Management

The use of cysticidal drugs is not without risks and considerable controversy. Parasite death may lead to
a severe inflammatory reaction that can worsen intracranial hypertension and even cause death. In fact,
it may not even decrease seizures, arguably one of the major impetuses for treatment. Treatment with
antiparasitic agents depends largely on the location and number of cysts (Table 2). Antiepileptic drugs
are helpful, but the optimal duration of seizure prophylaxis is unclear since 50% of patients experience
recurrence of seizures once antiepileptics are withdrawn. For several forms of neurocysticercosis,
namely subarachnoid cysticerci, ventricular cysts, spinal cysts, and multiple parenchymal cysts, steroids
are necessary to prevent infarction caused by an inflammatory reaction occluding the leptomeningeal
arteries. Steroids in these cases are also needed to prevent acute hydrocephalus, spinal cord swelling,
and cerebral edema. They can also help manage the nausea and headache associated with effective
cysticidal drug treatment.(39)

Table 2: Treatment of Neurocysticercosis (Adapted from Garcia and Del Brutto, 2005)(39)

<table>
<thead>
<tr>
<th>Parenchymal Lesions</th>
<th>Antiparasitic</th>
<th>Duration</th>
<th>Steroid</th>
<th>Surgical</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single vesicular cyst</td>
<td>Albendazole 15mg/kg/d</td>
<td>1 week</td>
<td>If side-effects occur</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Moderate vesicular cyst *</td>
<td>Albendazole 15mg/kg/d</td>
<td>1 week</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy (&gt;100 vesicular cysts)*</td>
<td>Albendazole 15mg/kg/d</td>
<td>1 week</td>
<td>High dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single degenerating cyst</td>
<td>Albendazole 15mg/kg/d or none</td>
<td>1 week</td>
<td>If side-effects occur</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Moderate degenerating</td>
<td>Albendazole 15mg/kg/d</td>
<td>1 week</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
11. Cerebral Malaria

11.1. Background and Clinical Presentation

Malaria causes 1-3 million deaths annually, 90% of which occur in sub-Saharan Africa. Most deaths are due to severe anemia, which can be prevented even with only modest medical services, or from cerebral malaria, which is fatal 15-50% of the time, even in the best of circumstances. The more severe form of malaria infecting humans is caused by the protozoan parasite *Plasmodium falciparum*. It is transmitted by the Anopheles mosquito and starts its lifecycle in the liver, after which merozoites are released into circulation. They go on to infect red blood cells, where they undergo various stages of development over the next 48 hours before rupturing the RBC and being released as schizonts.

The majority of mild cases of malaria can be treated with oral medications, but some patients’ progress to develop severe disease requiring intravenous therapy. The World Health Organization (WHO) case definitions for severe malaria include cerebral malaria, severe anemia, respiratory distress, renal failure, shock, hypoglycemia, and impaired coagulation. Previously unexposed individuals, with little or no background immunity, (i.e. children in endemic countries and travelers to endemic areas) are more likely to develop severe infection. The degree of parasitemia, interestingly, is a poor predictor.

The WHO definition of cerebral malaria is unrousable coma (Glasgow Coma Scale <11/15), peripheral parasitemia with *Plasmodium falciparum*, and the exclusion of other causes of encephalopathy. Cerebral malaria occurs particularly in children up to 5 years old in areas of moderate transmission. Adults with severe malaria more frequently develop renal failure or pulmonary complications, but can

<table>
<thead>
<tr>
<th>Lesions</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalitis</td>
<td>None</td>
</tr>
<tr>
<td>Calcifications</td>
<td>None</td>
</tr>
<tr>
<td>Giant Cysts</td>
<td>Albendazole 15mg/kg/d</td>
</tr>
<tr>
<td>Basal subarachnoid</td>
<td>Albendazole 15mg/kg/d</td>
</tr>
<tr>
<td>Ventricular cysts</td>
<td>Controversial</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>None</td>
</tr>
<tr>
<td>Arachnoiditis, angiitis</td>
<td>None</td>
</tr>
<tr>
<td>Ependymitis</td>
<td>None</td>
</tr>
<tr>
<td>Spinal Cysts</td>
<td>Possibly</td>
</tr>
</tbody>
</table>

*Predictive of seizure recurrence*
still develop cerebral malaria.\textsuperscript{(42)} It commonly presents with 1-4 days of fever and seizures that can progress to coma. Vomiting and respiratory distress can also occur. Other findings consistent with bilateral upper motor neuron lesions are found. Retinal hemorrhages, papilledema, dysconjugate gaze, and jaw clenching can also occur in adults, while children tend to manifest signs of elevated ICP with flaccid tone and abnormal brainstem reflexes.\textsuperscript{(40,42)}

The diagnosis is made challenging by a wide differential diagnosis and the fact that an alternative diagnosis may exist in a parasitemic patient in endemic areas, as individuals with recurrent episodes of malaria may be able to tolerate some degree of parasitemia. Regardless, it is imperative to treat for cerebral malaria if it is suspected. Thick and thin smear microscopy is necessary for diagnosis. Thick films are sensitive for detecting low levels of parasitemia, but thin films can give insight into the degree of parasitemia through the percentage of infected RBCs and presence of infected neutrophils. Smears should be used for daily monitoring. CBC to monitor hemoglobin and platelets will help with decisions about the need for transfusion. Creatinine and electrolytes (including calcium and magnesium) need to be measured as renal failure and electrolyte abnormalities are common. Frequent glucose monitoring is vital as hypoglycemia is a well-documented side effect of quinine infusion as well as of malaria itself.

Most deaths occurring within the first 24 hours are from acidosis, respiratory failure, and uncontrollable ICP. Of survivors, 20% are left with neurological sequelae. Some studies suggest factors predictive of sequelae include hypoglycemia, prolonged raised ICP or coma, and protracted seizures.\textsuperscript{(42)} Patients with severe neurological deficits (spastic paresis or vegetative state) typically die within months. Increasingly, subtler cognitive, language, and behavioral sequelae are being recognized.

### 11.2. Medical Management

In malaria-endemic regions of the world where testing may not be available, the decision to treat as severe malaria is often based solely on clinical judgment. Any patient with prostration, impaired consciousness, convulsions, shock, decreased urinary output, respiratory distress or abnormal bleeding should be treated as having severe malaria with parenteral therapy. Furthermore, previously unexposed patients with parasitemia of 2% or greater can deteriorate quickly or unpredictably and may warrant IV therapy.\textsuperscript{(40)} Patients should also be treated empirically for meningitis if it is suspected clinically. A rise in parasitemia may occur in the first 18-24 hours, and does not necessarily indicate treatment failure.

The key treatment decision is between intravenous quinine or artemisinin derivatives, preferably IV artesunate. Since the rise in chloroquine resistance, quinine has become widely used in resource-poor countries for severe malaria, although a randomized trial showed that artemisinin-based treatment has mortality benefit over quinine in adults.\textsuperscript{(43)} Quinine has been described to induce life-threatening arrhythmias, and also stimulates insulin secretion necessitating close glucose monitoring. Intravenous quinine is given until there is <1% parasitemia and the patient is able to tolerate oral medication, at which point oral quinine can be started. Quinine should be given for at least five days, and stopped when the patient is aperasitemic for two consecutive blood films taken 24 hours apart. The patient will then need to complete their course of treatment with doxycycline or clindamycin for 7 days, since quinine monotherapy is associated with recrudescence as well as tinnitus, deafness, nausea, vomiting, ataxia and blurred vision.\textsuperscript{(40)}

Intramuscular Artemether or intravenous artesunate (preferred) act on immature parasite forms, demonstrating improved parasitic clearance. They produce fewer episodes of hypoglycemia or arrhythmias and are simpler to administer. Unfortunately, they are not licensed in many developing countries. They can sometimes be accessed as second line agents if patients develop significant side effects on quinine-based therapy. Artemisinin derivatives should be given for at least 7 days until parasite clearance is documented and the patient is able to take oral medications. At this point they
should be switched to oral doxycycline, sulfadoxine/pyrimethamine, or clindamycin (in pregnant women or children) for 7 days to prevent recrudescence. Therapy should ideally be based on local resistance rates, as multidrug-resistant malaria has been described.

Several supportive therapies have been studied for use in severe malaria. There is no role for mannitol or corticosteroids, which have demonstrated no mortality reduction and may actually prolong coma. Seizures should be treated with benzodiazepines. Superimposed bacterial or viral infections in the context of immunosuppression may occur, commonly with HSV, pneumococci, salmonella, *Escherichia coli* and other Gram-negative organisms. Clinicians should have a low threshold to start broad-spectrum antibiotics in response to a change in clinical status.(40

Patients should be carefully rehydrated, as they are often extremely volume depleted but also predisposed to pulmonary edema and elevations in ICP. Urine output should be monitored closely. Respiratory distress should be managed quickly, bearing in mind that possible causes include acidosis, ARDS, edema, and anemia. Mechanical ventilation has been shown to reduce mortality, and is beneficial from a respiratory, acidemia, and ICP standpoint. Acidosis management may include transfusion or even haemofiltration if dialysis is available. Electrolyte disturbances, including hyponatremia, hypokalemia and hypercalcemia are common. Hypoglycemia may warrant an IV dextrose infusion. Massive intravascular hemolysis and hemoglobinuria (known as blackwater fever) can occur, necessitating hydration and transfusion if Hb <70 or sooner in children. Coagulation parameters are often abnormal, but disseminated intravascular coagulation is uncommon. Platelet transfusion is usually not necessary unless the patient is actively bleeding or the counts are < 10 × 10⁹/μl. Exchange transfusion and erythrocytapheresis have been used with mixed results shown in the literature with no randomized trials, and this modality is unlikely to be available in most resource poor settings. Adjuvants such as iron chelation and anti-TNF agents are not beneficial. Concerted prevention efforts and removal of barriers to accessing first-line therapeutics would likely have a significant impact on malaria-related mortality globally.(40,42)

12. Bacterial Meningitis

12.1. Background and Clinical Presentation

Bacterial meningitis is ten times more common in the developing world, and also more devastating. HIV+ patients generally fare worse and also have higher levels of antimicrobial resistance.(44) Symptoms usually develop over 24-48 hours. Neck stiffness occurs in 50-90% of adults, confusion in 75-85%, and focal deficits, rash, or seizures in less than 30%. Children more commonly present with nausea, vomiting, irritability, reduced consciousness, a bulging fontanelle, or poor feeding.(44) The triad of fever, headache, and photophobia is present in only 40% of patients, but the absence of all three is 99% specific.

The most common culprit pathogens in resource-poor settings remain *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitides*. Group B streptococci must be considered in neonates, and *Listeria monocytogenes* or *Enterobacteriaceae* species in the elderly or immunocompromised. Even in HIV+ patients, *S. pneumoniae* is most common, but non-typhi Salmonella species can cause acute meningitis. Parasitic infections with *Toxocara canis*, or viruses (such as herpes simplex, varicella zoster, and enteroviruses) can also cause meningitis.

Diagnosis is made particularly challenging by the fact that many patients may have received incomplete outpatient antibiotic treatment, which changes disease presentation from fulminate to the more subacute picture of partially treated meningitis. This makes bacterial meningitis harder to differentiate from TB or
cryptococcal disease. With limited laboratory facilities, it is also very hard to differentiate from cerebral malaria. Investigations should include a thick and thin smear for malaria, with a negative predictive value >95%. Blood cultures can be positive in up to 33%, and rapid HIV testing should be done if available. In resource-rich countries the LP is often deferred until imaging is done, but even negative imaging cannot rule out the possibility of herniation and in resource-poor settings the omission of an LP may carry greater risk of death from misdiagnosis.(44) Looking at turbidity alone is helpful in identifying bacterial meningitis only about 40% of the time. Microscopic examination of the cell count and differential is helpful, but may be varied in immunocompromised patients or children. Neutrophilia is seen in bacterial meningitis, but can also occur in early TB or cryptococcal meningitis. Raised CSF protein is a nonspecific finding. Low glucose is seen in bacterial and mycobacterial meningitis, but not in viral. If microscopic or biochemical analysis is unavailable, urine dipsticks can be used to look for glucose, protein, and leukocyte esterase, particularly in turbid CSF. Gram stain can help direct initial therapy.(44)

12.2. Medical Management

The WHO has recommended ceftriaxone as first line therapy but many developing countries rely on PCN and chloramphenicol as their primary armamentarium against bacterial meningitis. Rising rates of PCN and chloramphenicol resistance are seen in >20% of S. pneumoniae and H.influenzae isolates, with 10% resistant to both drugs. Furthermore, resistance may go unnoticed due to poor or unavailable laboratory facilities. Alternatives are otherwise limited, as vancomycin is usually cost-prohibitive, fluoroquinolones have not been studied for this purpose, and rifampicin, though effective poses the risk of promoting resistant strains of TB. Uncomplicated meningococcal disease can be treated with one dose of ceftriaxone or oily chloramphenicol, particularly in epidemics. This is usually extended to 5 days if the patient is under 2 years old or if fever, coma, or seizures last more than 24 hours. The optimum duration for antimicrobial therapy is unclear, and realistic possibilities vary between resource-rich and resource-poor nations. In the former, H. influenzae and meningococcal disease are treated for at least 7 days and S. pneumoniae for 10-14 days. There is limited evidence to support this, and in the developing world it is usually sufficient to treat for 5 days if patients are immunocompetent and demonstrating a rapid and uncomplicated recovery. If the patient is immunocompromised, is a child, or has persistent fevers, seizures, or coma, treatment should be extended to at least 7 days. Non-typhi salmonella should be treated for, at least three weeks.(44)

The use of dexamethasone in resource-poor countries is controversial, as most studies done in these settings have failed to show benefit. This is thought to reflect the higher proportion of late presentations, higher HIV prevalence, and high mortality.(44, 45) With respect to fluid resuscitation, studies suggest that intravenous isotonic hydration is preferred to fluid restriction (which was typically prescribed for hyponatremia) in the first 48 hours, particularly in resource poor settings.(46) While a detailed discussion about vaccination is outside the scope of this paper, there is strong evidence from several African nations that demonstrates nearly complete reduction or elimination of H. influenza meningitis after introduction of a mass vaccination program.(47) In sub-Saharan Africa, this is likely to be the greatest contributor to mortality reduction.

13. Conclusions and Recommendations

Intracranial infection represents a diverse collection of pathologies that warrants careful analysis and timely treatment in order to optimize outcome and preserve neurological function. The available evidence to guide management of such infections is largely limited to case reports and case series. While demographic data are available from the WHO regarding the incidence of such infections (1), little information is available on the regional variability of infectious agents and the success rate of different
treatment paradigms.

Here we present an overview of the background, clinical presentation, and medical and surgical management of intracranial infections based on location within the cranium and based on pathogens endemic in resource-poor nations. It is meant to act as a guide and to highlight the important aspects of diagnosis and treatment regardless of location of clinical practice around the globe. Certainly there will be regional variability in the incidence, diagnostic modalities available and treatment options. We encourage local practitioners who treat such conditions to report their experiences in order to build awareness to combat a leading cause of morbidity and mortality in the developing world. (1)

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