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REVIEW ARTICLE

Emergency Neurologic Life Support: Meningitis and Encephalitis

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Abstract Bacterial meningitis and viral encephalitis, particularly herpes simplex encephalitis (HSE), are severe neurological infections that, if not treated promptly and effectively, lead to poor neurological outcome or death. Because treatment is more effective if given early, the topic of meningitis and encephalitis was chosen as an Emergency Neurological Life Support protocol. This protocol provides a practical approach to recognition of and urgent treatment for bacterial meningitis and HSE, including imaging and spinal fluid analysis, and discusses the choice of empirical treatments until the cause of infection is determined. Though uncommon in its full form, the typical clinical triad of headache, fever, and neck stiffness should alert the clinical practitioner to the syndromes. Early attention to the airway and maintaining normotension is crucial in treatment of these patients, as is rapid treatment with anti-infectives and, in some cases, corticosteroids.

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Introduction

Meningitis and encephalitis are potentially life-threatening central nervous system (CNS) diseases, the first presentation of which is frequently to the emergency department (ED). The annual incidence of bacterial meningitis in adults in the U.S. is approximately 4–6 cases per 100,000 [1–3]. Encephalitis is a less common disease than meningitis: while accurate estimates of incidence are difficult to obtain, its overall incidence is lower, and the non-herpes varieties display seasonal variation.

Bacterial meningitis and bacterial or viral encephalitis are medical, neurologic, and, occasionally, neurosurgical emergencies, which carry substantial morbidity, and mortality despite modern approaches. In one study, 48 % of patients with bacterial meningitis presented within 24 h of the onset of symptoms [2]. Therefore, patients who have a hyper-acute (hours) to acute (hours to days) onset of headache and altered mental status should be considered as potentially having meningitis or encephalitis.

Although fever is a major feature in this infectious illness, additional symptoms including stiff neck (typically elicited by neck flexion), fever, new rash, focal neurological findings, or new seizures should increase the clinical suspicion of CNS infection. In a large series of 696 adult patients with bacterial meningitis, the classic triad of fever, neck stiffness, and change in mental status was present in only 44 % of patients, but 95 % of patients had at least two symptoms when a fourth symptom—headache—was added to the classic triad [2]. In contrast, another report pooling adult studies of patients with meningitis demonstrated that

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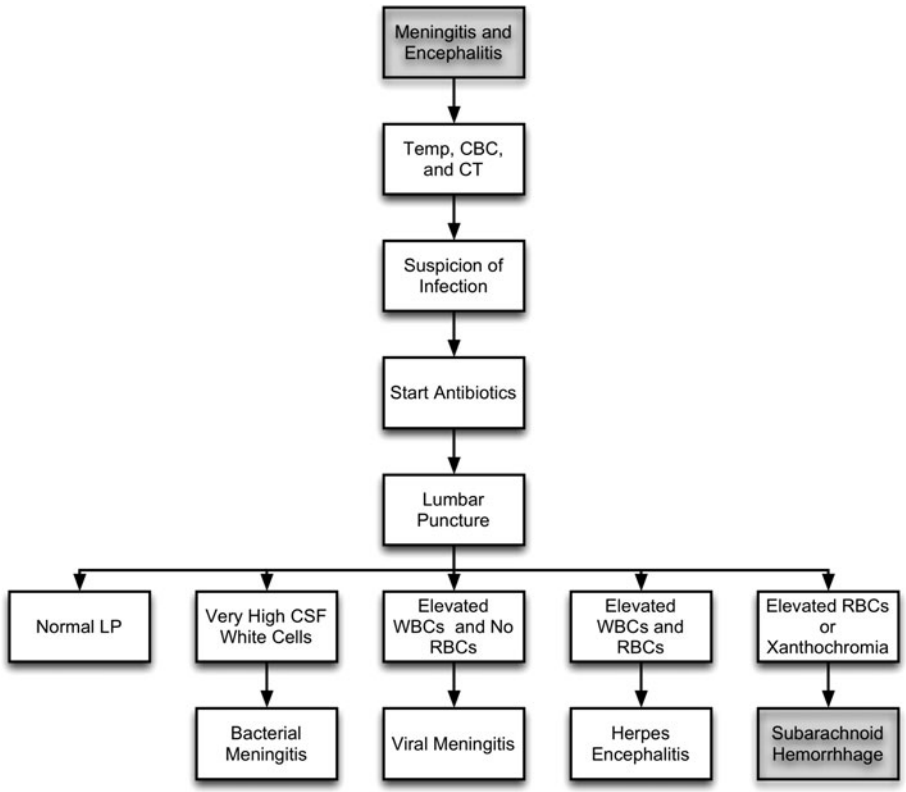

Fig. 1 ENLS meningitis and encephalitis protocol

95 % of patients had at least two of the three elements of the classic triad [4].

A challenge in diagnosing meningitis or encephalitis is that there is no single definitive clinical symptom or sign. A review of papers on adult meningitis published between 1966 and 1997 found that Kernig's sign was the sign most frequently elicited when evaluating a patient for possible meningitis. Kernig's sign is performed with the patient lying supine, hips, and knees flexed to 90°, and the clinician then extending the patient's knee [4]. A positive sign is present when extension of the leg at the knee produces lower back or posterior thigh discomfort. Brudzinski's sign, in contrast, is performed by placing the patient in a supine position, then passively flexing the patient's neck and observing whether this triggers flexion at the hips and knees.

Despite the fact that physicians learn these signs and are asked about them on rounds, the review found that the signs have not been sufficiently studied in a systematic fashion to comment on their sensitivity and specificity for diagnosing meningitis. A similar result from another study of 297 patients with suspected meningitis demonstrated the minimal utility of these maneuvers, except in patients with fulminant meningitis (i.e., CSF WBC $>$ 1,000 cells/ml) [5]. Therefore, the absence of these signs should not be used to rule out meningitis.

The Emergency Neurological Life Support (ENLS) suggested algorithm for the initial management of meningitis and encephalitis is shown in Fig. 1. Suggested items to complete within the first hour of evaluating a patient with meningitis and encephalitis are shown in Table 1.

Table 1 Meningitis and encephalitis checklist for the first hour

☐ Vital signs, history, examination
☐ IV access
☐ Labs: CBC, platelets, PT/PTT, chemistries, blood cultures, lactate
☐ IV fluids, treat shock
☐ Immediately administer dexamethasone followed by appropriate antibiotics for presumptive bacterial meningitis
☐ Head CT, if patient neurological exam is abnormal
☐ LP, if CT and results are available
☐ If meningococcus, exposure prophylaxis

Initial Assessment

As with all acute medical and neurological events, the basic ABCs of resuscitation (airway, breathing, circulation) should be evaluated immediately on presentation to the ED. Vital signs including temperature, blood pressure, heart rate, and respiratory rate, along with peripheral oxygen saturation, a pain scale, assessment of the Glasgow Coma Scale (GCS), and a rapid check of the patient's serum glucose level, should be quickly obtained at triage.

Patients with altered mental status are at risk for aspiration, have decreased ability to maintain a patent airway, and should be monitored for the need for endotracheal intubation. Patients with bacterial meningitis are at risk for lung or bloodstream infections with the same pathogen, further reinforcing the need to closely monitor vital signs and hemodynamics.

Meningitis is strictly defined as inflammation of the meninges, while encephalitis is strictly defined as inflammation of the brain. If both are inflamed, the patient has meningoencephalitis. Meningitis causes fever, meningismus, and pain (e.g., headache and neck pain), but other than depressing a patient's mental status, does not affect any cortical function (e.g., aphasia, seizure, and hemiparesis). Alternately, encephalitis typically causes cortical disturbance, particularly seizures.

Most of the patients have a predominance of one or the other, but many have features of the combined meningoencephalitis syndrome. The two conditions that are most important to recognize in the first hour are bacterial meningitis and herpes encephalitis, as these diseases have specific treatments that can improve patient outcome if administered quickly.

After vital signs, including core body temperature, are assessed in triage, patients at high risk for meningitis should have adequate intravenous (IV) access (a minimum of 2–18 gauge or larger peripheral IVs), and blood samples sent for laboratory analysis, including a peripheral white blood cell (WBC) count and differential, basic metabolic panel, serum lactate, and blood cultures.

As with a large percentage of patients with other bacterial infections, some patients with bacterial meningitis will be hypotensive. This is a result of the high percentage who are febrile, tachypneic, diaphoretic, and vomiting. In addition, bacterial meningitis, like other diseases causing severe sepsis and septic shock, can trigger a pronounced inflammatory response, eventually leading to vasodilation, capillary leak, and, in some patients, myocardial dysfunction.

The initial resuscitation strategy in critically ill patients with suspected meningitis or less likely, encephalitis should be identical to that recommended for other severe sepsis patients. For example, in guidelines focusing on initial resuscitation, the Surviving Sepsis Campaign recommends beginning resuscitation immediately in patients with hypotension (systolic blood pressure <90 mmHg) that persists after an initial fluid challenge (20–30 cc/kg of crystalloid over 30 min) or a serum lactate >4 mmol/l [6].

Further, the Campaign recommends a protocolized resuscitation strategy with specific resuscitation goals, including fluids until the patient is fluid unresponsive, a mean arterial pressure (MAP) >65 mmHg, urine output >0.5 ml/kg/h, and a central venous oxygen saturation ($ScvO_2$) >70 %.

One liter boluses of crystalloid over 30 min should be given repeatedly until these goals are reached, and the rate reduced once goals are achieved or when the patient demonstrates rising filling pressures (increased CVP) without improvements in systemic perfusion (persistently low $ScvO_2$ or rising serum lactate levels). Norepinephrine should be used to support mean arterial pressure (MAP) if the patient remains hypotensive despite initial resuscitation.

However, the optimal translation of these recommendations to the management of patients with CNS infections is unclear, and, in particular, the relationship between aggressive early volume resuscitation and cerebral edema should be systematically investigated.

Temperature, CBC and CT

If the patient has altered mental status, focal neurological deficits, papilledema, new onset seizures, or a history of neurological disease or immunosuppression, a cranial computed tomography (CT) should be expedited [7]. If circumstances permit, cranial CT should occur prior to lumbar puncture (LP) in patients with any of these concerning clinical signs.

In most instances, an oral temperature is adequate. Patients who are markedly tachypneic may not be able to keep their mouths closed during an oral temperature reading and require a rectal temperature to insure accuracy. Both fever (temperature >38 °C) and hypothermia (temperature <36 °C) are compatible with CNS infection.

If the patient is normothermic, the pre-test probability of bacterial meningitis or human immunodeficiency virus (HIV) encephalitis is decreased. However, newly immunocompromised patients, patients with viral meningitis, and even an occasional patient with bacterial meningitis may present to the ED without fever. In an evaluation of 696 patients with community-acquired acute bacterial meningitis, the mean reported temperature was 38.8 °C, and 77 % of patients were febrile. The evaluation did not report the number of patients who were hypothermic [2].

Much like body temperature, peripheral WBC can be elevated or depressed in patients with CNS infection, and frequently with increased immature forms [8].

Depending on body temperature as well as the results of the head CT scan and complete blood count (CBC), the exploration of CNS infection may potentially stop short of LP, and work up of non-infectious causes of headache and altered mental status may begin, with the same caveats regarding temperature mentioned above.

For example, a patient with the initial chief complaint—"I have a fever and a headache"—and vital signs obtained in triage of elevated temperature and tachycardia may, on further evaluation, be deemed to have a very low pre-test

probability of bacterial meningitis, because the patient is well-appearing, does not have neck stiffness, has a normal level of consciousness, and has an unremarkable WBC count. However, the patient may yet have viral meningitis, so LP may still be indicated to establish a diagnosis.

Suspicion of Infection

In patients in whom there is a moderate to high suspicion of CNS infection and LP has not yet been performed, parenteral antimicrobials should not be delayed while waiting for a computed CT scan. With the most sensitive organisms, cerebrospinal fluid (CSF) sterilization occurs only after 4–6 h following initiation of antimicrobials.

As described in the Temperature, CBC and CT section above, head CT prior to LP should be performed in the patient with suspected CNS infection when any of the following are present: papilledema or loss of venous pulsations on fundoscopic examination; focal neurological signs; immunocompromised patients; or known mass lesions.

In patients who do not present with these signs, have normal mental status, and have no focal neurologic deficits, a head CT is not always required prior to LP. However, in most patients who have a clinical presentation consistent with acute bacterial meningitis or encephalitis, there will be enough diagnostic uncertainty that CT is advisable prior to LP.

In a study of the need for head CT prior to LP among 301 patients with suspected bacterial meningitis, 78 % of patients had a head CT performed prior to LP [9]. Of these patients, 24 % had an abnormality on the CT reading, and 5 % had evidence of mass effect. The extensive clinical data collected showed that the following clinical variables were associated with an abnormal CT finding: age >60 years; immunocompromised state; history of CNS disease; altered level of consciousness; and focal neurologic deficits.

A normal head CT does not preclude the development of a herniation syndrome. Meningitis can be rapidly progressive, characterized by inflammation of the meninges and brain swelling, and patients can herniate after LP because of disease progression, not as a result of the diagnostic intervention. The above study is limited by the low percentage (28 %) of patients with meningitis in the cohort. Of those, only 22 % had identification of an organism in the CSF. However, the decision to obtain a CT before LP was made in study patients not suspected of having meningitis, reflecting the real-world dilemmas facing clinicians involved in the initial management of these patients. As the study concluded: "Our findings indicate that adults with suspected meningitis who have none of the significant baseline features that we identified are good candidates for immediate LP, since they have a low risk of brain herniation as a result of LP. The use of this approach in our cohort would have decreased the frequency of CT by 41 %" [9].

Known or suspected immunocompromised patients may present with less classic signs of meningitis or encephalitis. For such patients, the clinician should lower his or her pretest probability for these diagnoses and err on the side of a more complete work-up, including emergent brain imaging and LP.

If the head CT shows a mass lesion or another condition, such as a subarachnoid hemorrhage (SAH), that adequately explains the patient's mental status, then the evaluation of bacterial meningitis can be aborted, and the clinician should proceed to work-up the process discovered on the head CT.

In cases of normal (if performed) head CT yet the presence of fever, abnormal WBC count, headache, and altered mental status, there should be moderate to high suspicion for meningitis or encephalitis (see the section Start Antibiotics). There is evidence for the use of dexamethasone in bacterial meningitis, particularly in CNS infections caused by *Streptococcus pneumoniae*. In situations where it is clearly evident that the suspected organism is something other than *Streptococcus pneumoniae*, then dexamethasone may be withheld. Otherwise, empiric use of dexamethasone until cultures return is reasonable. Patients should be given 10 mg of IV dexamethasone immediately and every 6 h thereafter [10]. Ideally, the steroid should be given prior to or at the start of antibiotic therapy.

Start Antibiotics

Appropriate antimicrobials should be started as soon as possible after a patient with suspected CNS infection presents for medical care. A landmark article demonstrated that in patients with septic shock, for each hour's delay in the administration of appropriate antimicrobials after onset of hypotension, mortality increased on average of 7.6 % per hour. These results were confirmed by another study of 261 patients treated with a protocolized resuscitation strategy [11]. When appropriate antimicrobials were administered within 1 h of triage, mortality was 19.5 %; when they were delayed longer than 1 h after triage, mortality increased to 33.2 %.

The applicability of these findings to patients with bacterial meningitis is limited by the small percentage of patients in each study who had primary CNS infections: 0.9 % in the first study and 2.4 % in the second. Earlier, less rigorous studies demonstrated an association between the interval before antibiotics were administered in patients with bacterial meningitis. For example, in a cohort of 122

patients with documented bacterial meningitis, one study found a mean time from triage to antibiotics of 3 h (interquartile range, or IQR, 1.6–4.3 h) and 90 % of this time occurred after the initial physician encounter [12].

The choice of empiric antimicrobials is based on several factors, including the time course of the suspected CNS infection; the age of the patient; and other infectious risk factors. For suspected CNS infections that evolve over hours, bacterial meningitis, viral meningitis, and, less commonly, viral encephalitis may be considered.

Children and young adults with suspected bacterial meningitis are at risk for *Haemophilus influenzae* (if not vaccinated), *Neisseria meningitidis*, and *Streptococcus pneumoniae*. Middle aged adults are at highest risk for *Streptococcus pneumoniae*. As such, both groups should be started on a third generation cephalosporin and vancomycin at doses appropriate for CNS penetration. The elderly and immunosuppressed patients, including alcoholics, are at risk for *Streptococcus pneumoniae* and *Listeria monocytogenes*. As such, they should be started on ampicillin, a third generation cephalosporin, and vancomycin at doses appropriate for CNS penetration.

Vancomycin and trimethaprim-sulfamethoxazole can be used in patients with a severe penicillin allergy. If there is a high suspicion for viral encephalitis (cortical deficits, lymphocytic predominance in the CSF) treatment should begin with acyclovir at the doses listed below.

For suspected CNS infections that evolve over days, viral encephalitis and, particularly, herpes simplex encephalitis (HSE) should be considered. Treatment should begin with IV acyclovir at 10 mg/kg every 8 h. Hydration should be sufficient to achieve normovolemia, avoiding the complication of acyclovir-associated renal failure.

Other forms of viral encephalitis, such as those caused by the Arboviruses, may also have a sub-acute presentation, much like HSE. There are no pharmacotherapeutic interventions for these encephalitides, but until CSF can be obtained, empiric acyclovir is reasonable. For suspected CNS infections that evolve over days in an immunosuppressed patient, fungal meningitis can be considered. If there is a high index of suspicion for fungal meningitis, such as prior history of the disease or systemic fungal infections, and the patient is progressing rapidly, empiric amphotericin B, can be considered. Otherwise, beginning an anti-fungal agent after LP is typically prudent.

Lumbar Puncture

A LP is essential for both establishing a diagnosis and tailoring therapy. Informed consent should be obtained when possible, and the clinical team should perform a "time-out" prior to starting the procedure.

When possible, the patient should be positioned in the left lateral decubitus position, as an opening pressure (OP) cannot be measured easily if the patient is sitting up. After prepping and draping the patient in the usual, sterile fashion, the OP should be measured with a manometer prior to the collection of CSF.

CSF should be collected in a minimum of four tubes. Tubes 1 and 4 should be sent for red blood cell (RBC) and WBC counts; tube 2 for protein, glucose, and lactic acid; tube 3 for Gram's stain, antigens, and culture (and India ink if fungal infection is suspected). If there is a suspicion for herpes encephalitis, a small amount of CSF from either tube 2 or 3 should be sent for herpes polymerase chain reaction (PCR).

Larger volumes of CSF increase the sensitivity of a Gram's stain and culture. Some laboratories perform bacterial antigen assays, which may be useful in certain circumstances. Additional laboratory tests that may be performed at some centers include bacterial PCR (particularly for Mycobacterium), enterovirus PCR, immunoglobulin M (IgM) for arboviruses, fungal antigens, and viral culture.

If the spinal fluid pressure is found to be greatly elevated (e.g., >400 mm H_2O), the needle stylette should be left in place and consideration should be given to the administration of osmotic agents, such as mannitol. It may be prudent to recheck the pressure after a few minutes to determine that it has declined, before removing the needle.

Normal LP

An LP is considered normal if there are no RBCs, fewer than five WBCs, the CSF glucose/serum glucose ratio >0.67, the CSF protein <50 mg/dl, and no organisms are seen on Gram's stain. If all of the above are true, meningitis is ruled out, as is encephalitis in most cases.

After receiving these CSF results, the clinician should continue to work-up the patient from the perspective of the presence of fever, elevated peripheral WBC count, a normal CT scan, and an LP without evidence of meningitis or encephalitis.

Very High CSF White Cells

The finding of a marked elevation in WBCs, particularly neutrophils, of 100–1,000 or higher without a significant number of RBCs is highly suggestive of bacterial meningitis. In addition, the CSF/serum glucose ratio will usually be significantly <0.67, and the CSF protein is usually markedly elevated and almost always >50 mg/dl. Organisms are seen on Gram's stain in approximately 70 % of cases. When these CSF findings are observed, the patient likely has bacterial meningitis.

Mildly Elevated WBC and No RBCs

A mild elevation in CSF WBCs without RBCs is suggestive of viral meningitis or viral (not herpes) encephalitis. If the CSF analyses demonstrate a normal RBC count, WBCs ranging from 10 to several 100, a normal CSF glucose/serum glucose ratio, a protein <50 mg/dl, and if no organisms are seen on the Gram's stain, then the patient likely has a viral meningitis or viral (not herpes) encephalitis.

Clinical presentation and neuro-imaging are particularly important in these circumstances. Patients with viral meningitis will typically appear uncomfortable and at times toxic, but they will have a relatively normal level of consciousness. Neuro-imaging in the form of either CT or MRI will likely be normal.

Those with an arbovirus encephalitis (West Nile virus, Eastern or Western Equine encephalitis, St. Louis virus encephalitis, and others) may present with a depressed level of consciousness. West Nile virus patients may also have significant neurological disease, including focal deficits, new rest tremors, or neuromuscular weakness, occasionally requiring mechanical ventilation [13]. Seroconversion of HIV is also a consideration in these circumstances.

Although the patients with the above findings are unlikely to have bacterial meningitis, in many cases they will be admitted to the hospital and antibiotics continued until the CSF culture results are negative and clinical improvement is demonstrated.

Elevated WBCs and RBCs

If the CSF demonstrates an elevated RBC count (10–100 or higher), WBCs in the hundreds (typically with a lymphocytic predominance) a CSF glucose/serum glucose ratio >0.67, a protein level that may either be <50 mg/dl or elevated, and if no organisms are seen on Gram's stain, then the patient may have herpes encephalitis. The presence of seizures and findings of uni- or bi-lateral hypodensities in the temporal lobes on brain MRI, and rarely on brain CT scans, are also compatible with this diagnosis.

Elevated RBCs or Xanthrochromia

If the CSF reveals an elevated RBC count (100–1,000 and higher), either a WBC count <5 or fewer than 1 WBC/500 RBC, a CSF glucose/serum glucose ratio >0.67, and a protein <50 mg/dl; no organisms are seen on Gram's stain; and xanthochromia is detected, then the patient likely has a subarachnoid hemorrhage that was not detected on the CT scan. Xanthochromia may be absent if the LP was done within the first few hours of headache onset (when RBCs are typically not seen).

Bacterial Meningitis

In patients with CSF demonstrating bacterial meningitis, clinicians should continue antibiotics, stop acyclovir, and continue dexamethasone. Subsequently, they should adjust antibiotics based on final Gram's stain and culture results and sensitivities.

In addition to antibiotics and dexamethasone, supportive care and management of other organ systems is important in patients with bacterial meningitis. Some patients may have a concomitant bloodstream infection with the offending pathogen and may require early goal-directed therapy for severe sepsis or septic shock.

If the LP demonstrates an elevated intracranial pressure (ICP) when the OP is measured, after the emergency procedures to lower pressure are undertaken, the patient should be monitored closely for signs of increased ICP. However, there is no evidence that ICP monitoring devices are helpful in this patient population, and the risks, including the potential of an additional infection associated with insertion of a foreign body, must be weighed against the potential benefits.

Likewise, no evidence exists as to the appropriate treatment of persistently increased ICP. Hyperventilation should likely be avoided, as these patients may already have some degree of decreased cerebral vessel diameter due to vasculopathy. Mannitol or hypertonic saline may be reasonable alternatives.

Viral Meningitis and Viral Encephalitis

The treatment for herpes encephalitis has been discussed above. The treatment of viral meningitis or non-herpetic viral encephalitis is primarily supportive in nature. Many of these patients will have a significantly depressed level of consciousness, making close observation, and airway management crucial. For West Nile virus, there is risk of respiratory decompensation from neuromuscular weakness secondary to spinal cord involvement. These patients may also have a depressed level of consciousness and so are at significant risk of respiratory failure. Oxygen saturation may fall first due to aspiration, but more likely the patient's pCO_2 will rise as an early indicator of respiratory failure. Admission to the intensive care unit (ICU) for observation is frequently warranted. Once it is clear that these patients do not have HSE as evidenced by negative PCR, and since

Table 2 Checklist for patients with suspected meningitis

Vital signs, history, examination
IV access, draw labs, blood cultures, and lactate
IV fluids, treat shock
Immediate administration of dexamethasone followed by appropriate antibiotics to treat suspected meningitis
Consider acyclovir
Obtain head CT if altered mental status or focal neurological findings
Perform LP (after head CT results available, if CT necessary)
If meningococcus, remember exposure prophylaxis

Table 3 Meningitis and encephalitis communication regarding assessment and referral

Presenting signs, symptoms, and vitals on admission
Pertinent PMH/PSH
Relevant labs: WBC, bicarb, lactate, renal function
Whether CT was obtained, and results if obtained
Antibiotics administered, and time started
IV fluid administered, input/output
Results of LP, including OP
Current vital signs
Ongoing concerns, active issues, outstanding studies/tests
Last physical and neurological exam findings prior to transfer

there is no known pharmacotherapy for the viral, non-herpes infections, antimicrobials including acyclovir can safely be discontinued.

Communication

Transfer of care to the accepting health care team is an important consideration in these severe infections. Most of the patients with bacterial meningitis and viral encephalitis require the oversight and care that an ICU can provide. Careful observation of the patient's respiratory status and close monitoring of his or her neurological exam with attention to decline is critical.

Tables 2 is a checklist of items to be completed in the first hour. Table 3 outlines information that is important to pass along to the accepting health care team. Knowledge of whether the presentation was hyper-acute, acute or sub-acute; the presenting and subsequent signs and symptoms; and the results of the imaging and LP (including OP) are vital pieces of information.

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