Infections of the Central Nervous System (CNS)

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Disclosures

- I have no financial relationships to disclose
- I will not discuss off-label use and/or investigational use in my presentation
- Slides provided by various sources including IDSA and Mandell Textbook of Infectious Diseases

Learning Objectives

1. Describe 3 common syndromes associated with infections of the Central Nervous System (CNS)

2. Discuss the clinical presentations, diagnosis including Cerebrospinal Fluid (CSF) analysis, and management of common CNS infections

3. Identify risk factors associated with the development of invasive fungal infections of the CNS

Infections of the CNS

- The central nervous system (CNS) may be infected by viruses, bacteria, fungi, protozoa, and helminths

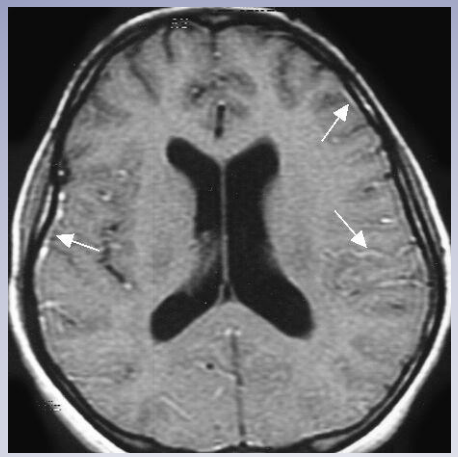
- The clinical presentation of a CNS infection may be acute, subacute, or chronic, depending on the virulence of the infecting agent and the location of the infection

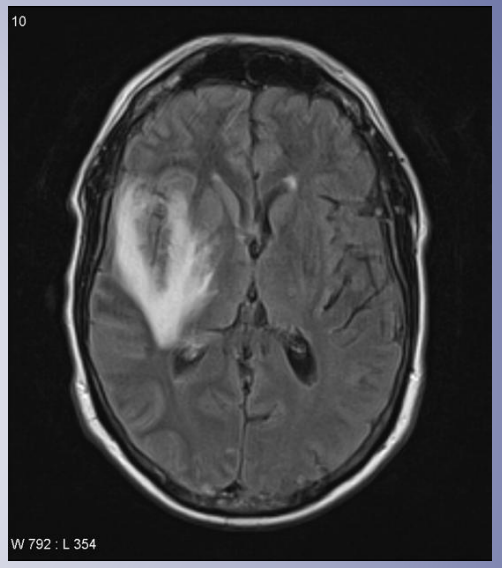
Clinical Presentation

- Key Factors
  - Pathogenesis of spread of the infection to the CNS
  - Virulence of the etiologic agent
  - Area of CNS involvement
- Common manifestations
  - Fever
  - Headache
  - Altered mental status
  - Focal neurologic deficits

Syndromes

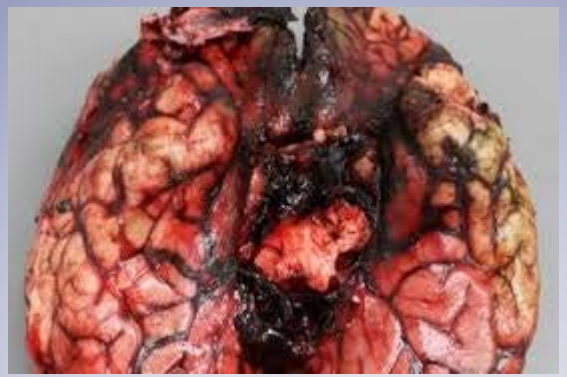
- Meningitis
  - Acute
  - Subacute/Chronic
- Encephalitis
- Focal CNS Infections
  - Brain abscess
  - Subdural empyema
  - Epidural abscess



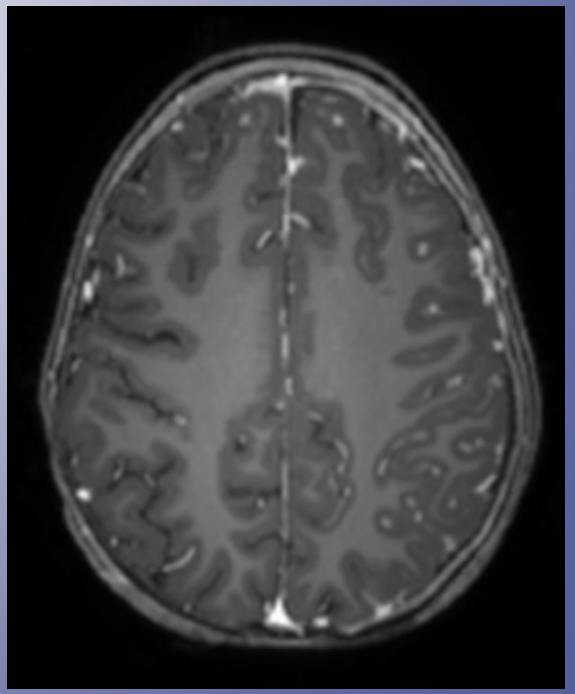


“ My Head is About to Explode”

- A 35 year old healthy woman c/o severe headache for 3 days, associated with fever, nausea, and vomiting
- Self-diagnosed “sinus infection” but did NOT take any antibiotics
- Her family called EMS when she became disoriented



Meningitis



A continuum of syndromes

- Meningitis
  - Acute: Fever, headache, +/- altered mental status
  - Chronic: More gradual, less severe
- Encephalitis
  - Mental status change may occur early and may progress to obtundation or coma
  - Behavioral and speech disturbances

Predisposing factor	Common bacterial pathogens
Age	
<1 month	*Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes, Klebsiella* species
1–23 months	*Streptococcus pneumoniae, Neisseria meningitidis, S. agalactiae, Haemophilus influenzae, E. coli*
2–50 years	*N . meningitidis, S. pneumoniae*
>50 years	*S. pneumoniae, N. meningitidis, L. monocytogenes,* aerobic gram-negative bacilli
Head trauma	
Basilar skull fracture	*S. pneumoniae, H. influenzae,* group A β-hemolytic streptococci
Penetrating trauma	*Staphylococcus aureus,* coagulase-negative staphylococci (especially *Staphylococcus epidermidis),* aerobic gram-negative bacilli (including *Pseudomonas aeruginosa)*
Postneurosurgery	Aerobic gram-negative bacilli (including *P. aeruginosa), S . aureus,* coagulase-negative staphylococci (especially *S. epidermidis)*
CSF shunt	Coagulase-negative staphylococci (especially *S. epidermidis), S. aureus,* aerobic gram-negative bacilli (including *P. aeruginosa), Propionibacterium acnes*

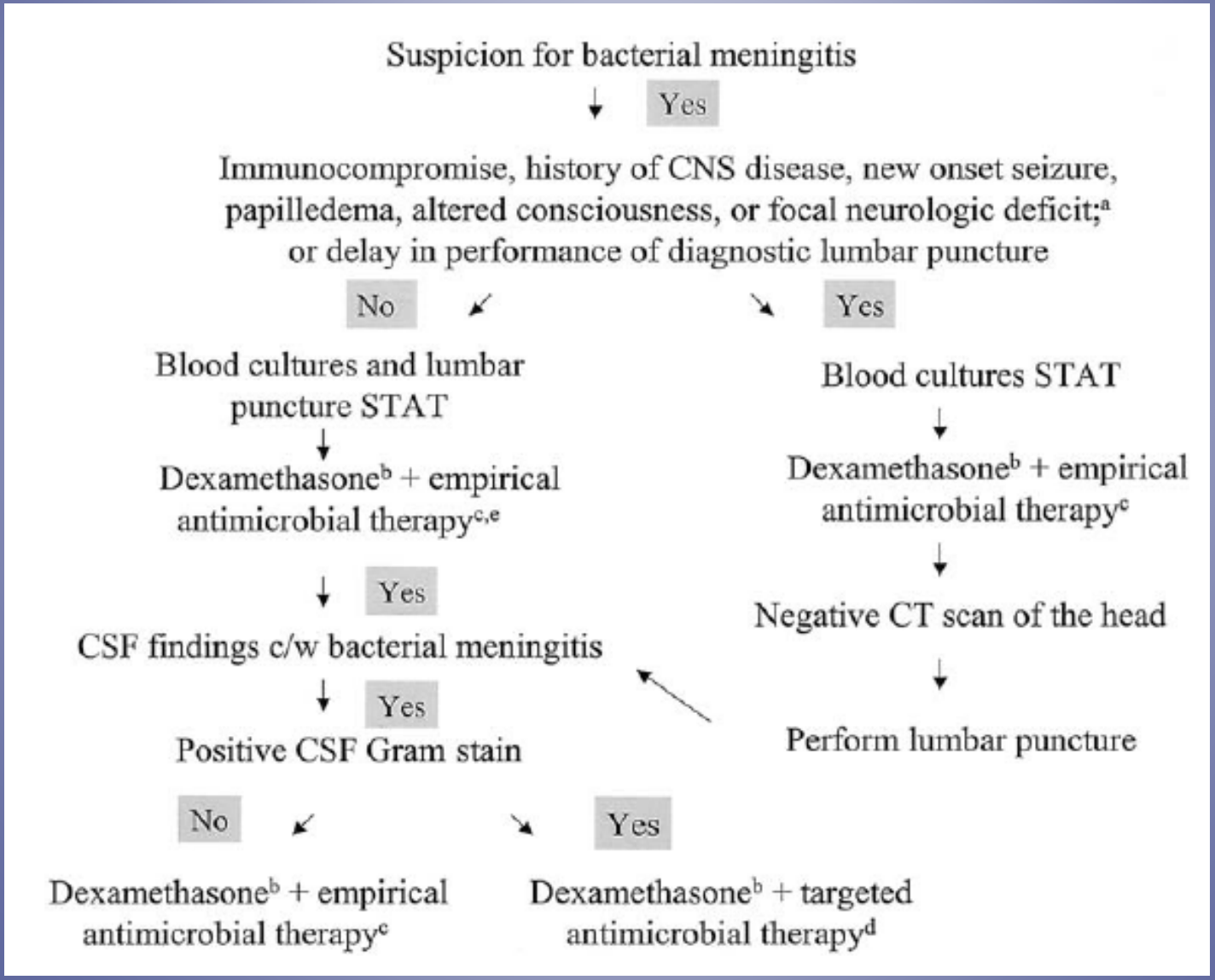
Chronic Meningitis

Mycoses
Cryptococcus (cryptococcosis)
Coccidioides (coccidioidomycosis)
Histoplasma (histoplasmosis)
Candida (candidiasis)
Sporothrix (sporotrichosis [rare])
Blastomyces (blastomycosis [rare])
Other molds (rare): *Scedosporium, Aspergillus, Cladophialophora* and other dark-walled molds
Bacteria
Mycobacterium tuberculosis (tuberculosis)
Treponema pallidum (syphilis)
Borrelia burgdorferi (Lyme disease)
Tropheryma whipplei (Whipple's disease)
Actinomyces (actinomycosis [parameningeal, rare])
Nocardia (nocardiosis [with brain abscess])
Brucella (brucellosis [rare])
Parasites
Acanthamoeba (acanthamebiasis)
Taenia solium (cysticercosis)
Angiostrongylus cantonensis (angiostrongyliasis)

CSF Analysis and the Differential Diagnosis

50-100 WBC 90% mononuclear Normal glucose Mildly elevated protein	Viral or "Aseptic" Neurosyphilis	Enteroviral PCR West Nile IgM HSV PCR VDRL
1000+ WBC 90% neutrophils Glucose < 10 Elevated protein	Bacterial	Gram stain and culture Blood cultures DNA testing
20-200 WBC 90% mononuclear Glucose < 40 Elevated protein	Fungal Tuberculosis	Fungal culture Cryptococcal Ag Coccidioides CF Coccidioides Ag AFB culture/PCR

Management


Suspicion for bacterial meningitis
Yes
Immunocompromise, history of CNS disease, new onset seizure, papilledema, altered consciousness, or focal neurologic deficit;[a] or delay in performance of diagnostic lumbar puncture
No
Yes
Blood cultures and lumbar puncture STAT
Dexamethasone[b] + empirical antimicrobial therapy[c,e]
Yes
CSF findings c/w bacterial meningitis
Yes
Positive CSF Gram stain
No
Yes
Dexamethasone[b] + empirical antimicrobial therapy[c]
Dexamethasone[b] + targeted antimicrobial therapy[d]
Blood cultures STAT
Dexamethasone[b] + empirical antimicrobial therapy[c]
Negative CT scan of the head
Perform lumbar puncture

Streptococcus pneumoniae

- Increased risk with HIV/AIDS,

  Sickle Cell Disease,

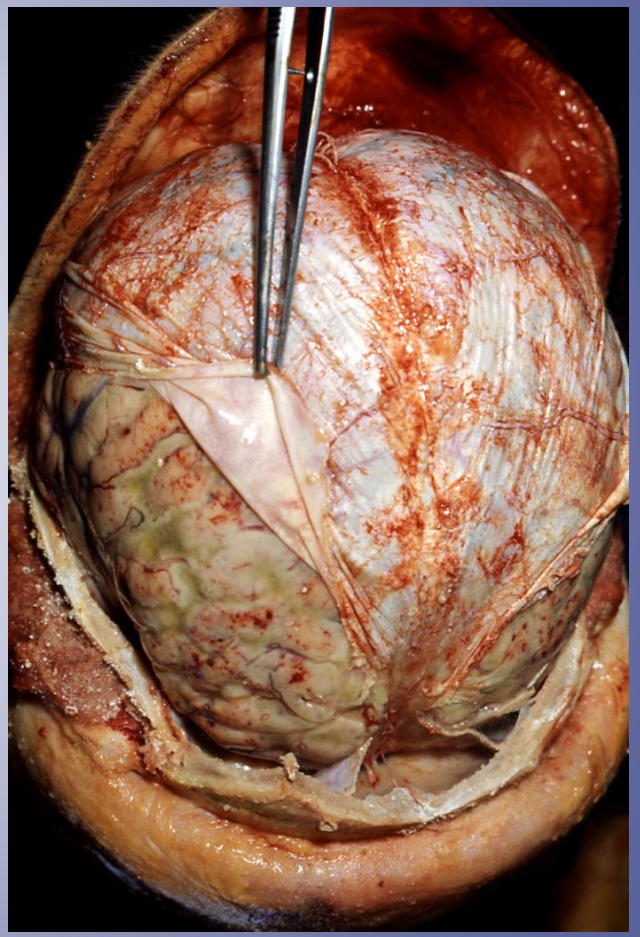
  Transplantation,

  Hypogammaglobulinemia

- Concurrent bacteremia,

  pneumonia (20%), otitis (30%).

  Mortality up to 30%



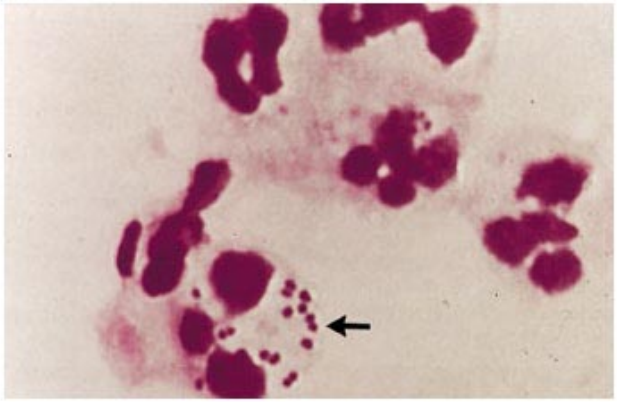
Treatment of *S. pneumoniae*

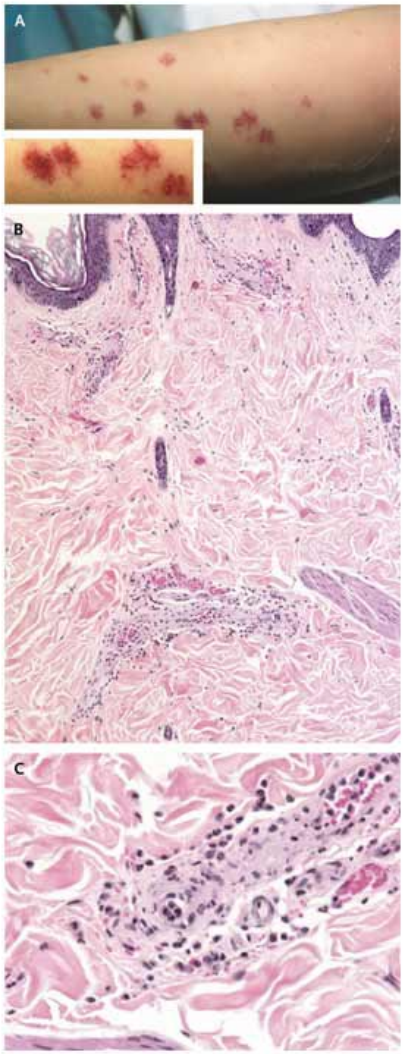
- Treatment includes a combination of Ceftriaxone and Vancomycin initially
- Antibiotic levels in CSF reach only 2-10% of serum levels
- PCN CSF breakpoints:
  - <0.1 ug/ml
  - 0.1 – 1.0 ug/ml
  - ≥ 2.0 ug/ml

IDSA Guidelines 2005

Neisseria meningitidis

- 10% case-fatality
- Host Risk factors:
  - Asplenia
  - Complement deficiency
  - Hypogammaglobulinemia
- Sequelae in 11-19% of cases
- Asymptomatic colonization





Warren H et al. N Engl J Med 2003;349:2341-2349

Treatment of *N. meningitidis*

- Most strains are penicillin-susceptible but reduced susceptibility is common in Africa, Europe, regional in U.S.
- Susceptible to 3rd generation cephalosporins
- Droplet Transmission: Up to 24 hours after antibiotic therapy is started
- Chemoprophylaxis: Rifampin, ceftriaxone, and ciprofloxacin

- A 70 year old man is brought in by EMS with fever, headache, vomiting, and diarrhea lasting about 4 days

- This was followed by the abrupt onset of asymmetrical cranial nerve deficits, cerebellar signs, and hemiparesis

- Nuchal rigidity is present and CSF findings are only mildly abnormal with a positive CSF culture

Which bacteria is most likely causing this infection?

A. *Strep pneuomoniae*
B. *Neisseria meningitidis*
C. *Haemophilus influenzae*
D. *L. monocytogenes*
E. *Treponema pallidum*

Which bacteria is most likely causing this infection?

A. *Strep pneuomoniae*

B. *Neisseria meningitidis*

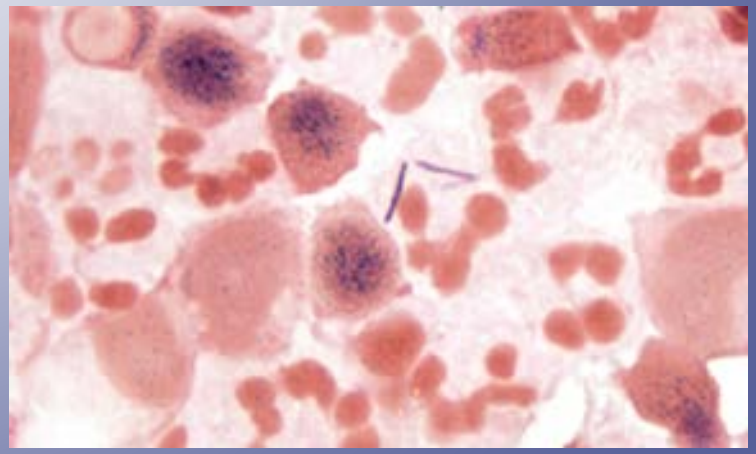
C. *Haemophilus influenzae*

D. *L. monocytogenes*

E. *Treponema pallidum*

Listeria monocytogenes

- Foodborne
- Highest risk in infants, adults > 50 years, pregnancy, HIV/AIDS, hematologic malignancy, transplantation
- Brainstem Encephalitis (Rhombencephalitis)
- Meningoencephalitis
- Parenchymal infection



Treatment

Microorganism	Recommended therapy	Alternative therapies
Streptococcus pneumoniae	Vancomycin plus a third-generation cephalosporin[a,b]	Meropenem (C-III), fluoroquinolone[c] (B-II)
Neisseria meningitidis	Third-generation cephalosporin[a]	Penicillin G, ampicillin, chloramphenicol, fluoroquinolone, aztreonam
Listeria monocytogenes	Ampicillin[d] or penicillin G[d]	Trimethoprim-sulfamethoxazole, meropenem (B-III)
Streptococcus agalactiae	Ampicillin[d] or penicillin G[d]	Third-generation cephalosporin[a] (B-III)
Haemophilus influenzae	Third-generation cephalosporin[a] (A-I)	Chloramphenicol, cefepime (A-I), meropenem (A-I), fluoroquinolone
Escherichia coli	Third-generation cephalosporin[a] (A-II)	Cefepime, meropenem, aztreonam, fluoroquinolone, trimethoprim-sulfamethoxazole

Treatment

Microorganism	Duration of therapy, days
Neisseria meningitidis	7
Haemophilus influenzae	7
Streptococcus pneumoniae	10–14
Streptococcus agalactiae	14–21
Aerobic gram-negative bacilli[a]	21
Listeria monocytogenes	⩾21

Red Herring

- An 82 year old man presented to the clinic with fever, fatigue, urinary incontinence, confusion, and was reported to have been walking naked in the house

- Urinalysis showed bacteriuria and pyuria

- He was diagnosed with a urinary tract infection and was prescribed Levofloxacin

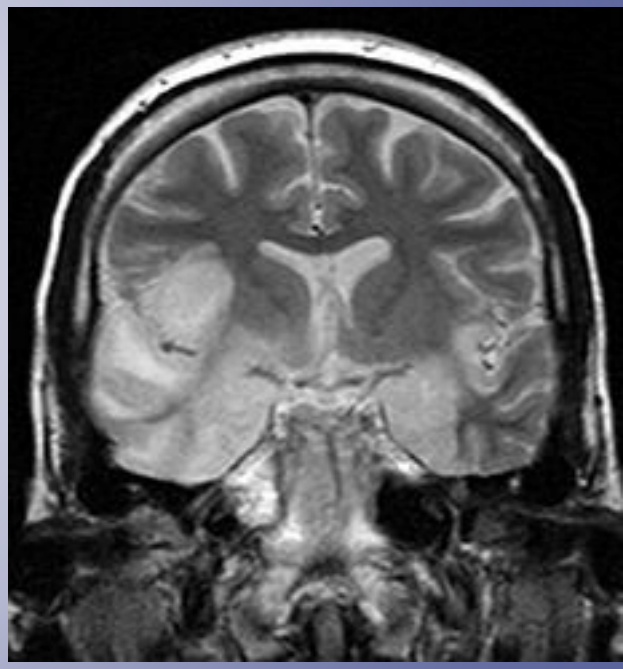
Red Herring

- The following day he continued to have fever and worsening confusion

- He was transferred to the ED that evening with reports of having developed aphasia, ataxia, and an episode of seizure

HSV Encephalitis

- Pathogenesis: Reactivation of virus in cranial nerve ganglia and retrograde spread along axons



- Focal involvement of temporal lobe

- Personality changes, obtundation, seizures, focal neurologic findings

Herpes simplex in the CNS

Meningitis

HSV 2 >> 1

Associated with primary infection

Normal mental status

Can be recurrent (Mollaret)

Usually benign

Encephalitis

HSV 1 >> 2

Usually not primary in adults

Abnormal mental status, seizures

Usually no oral lesions

Acyclovir decreases mortality

Whitley et al JAMA 1982:247:317

Encephalitis: Epidemiology and Risk Factors

- Travel
- Insect Contact
- Animal Contact
- Human Contact
- Season
- Recreational Activities/Ingestions
- Occupation
- Age and Immune Status

Infectious Causes of Encephalitis

Viral

- HIV
- Influenza
- Herpes
- Rabies
- Tick borne encephalitis
- Arboviruses
- Herpes B (monkeys)
- West Nile Virus

Other

- ADEM
- *Mycoplasma*
- *Coxiella burnetii*
- *Bartonella henselae*
- *Listeria*
- Syphilis
- Toxoplasmosis
- *R. rickettsii*

PPID 7th Ed Table 87-3

ADEM: Acute Disseminated Encephalomyelitis

Viral meningoencephalitis: Diagnosis

- **Enteroviral**
  - PCR: best, 94-96% sensitive
  - Viral culture: 60-70% sensitive, takes 4-8 days
- **West Nile**
  - IgM in CSF most sensitive
  - Can cross react with other flaviviruses
- **HSV1/2**, other herpes viruses (3 – 8)
  - PCR in CSF
  - Serum antibodies not useful

Therapy of viral CNS infection

- Few specific antiviral medications exist
- Acyclovir for herpes encephalitis
- Supportive: Treat fever, headaches, seizures

Fungal Meningitis

- *Coccidioides* spp: Everyone in the endemic region
- *Cryptococcus neoformans*: Deficiencies in cell mediated immunity and normal hosts
- *Histoplasma capsulatum:* Ohio and Mississippi river valleys
- *Aspergillus, Candida, and Mucor* (Immunosuppressed)

Coccidioidomycosis of the CNS

- Dimorphic fungi, *Coccidioidomycosis immitis* (California) and *posadasii*, also known as the *San Joaquin Valley fever*

- During 1998–2011, a total of 111,717 cases were reported: 66% from Arizona, 31% from California, 1% from other endemic states, and <1% from non-endemic states

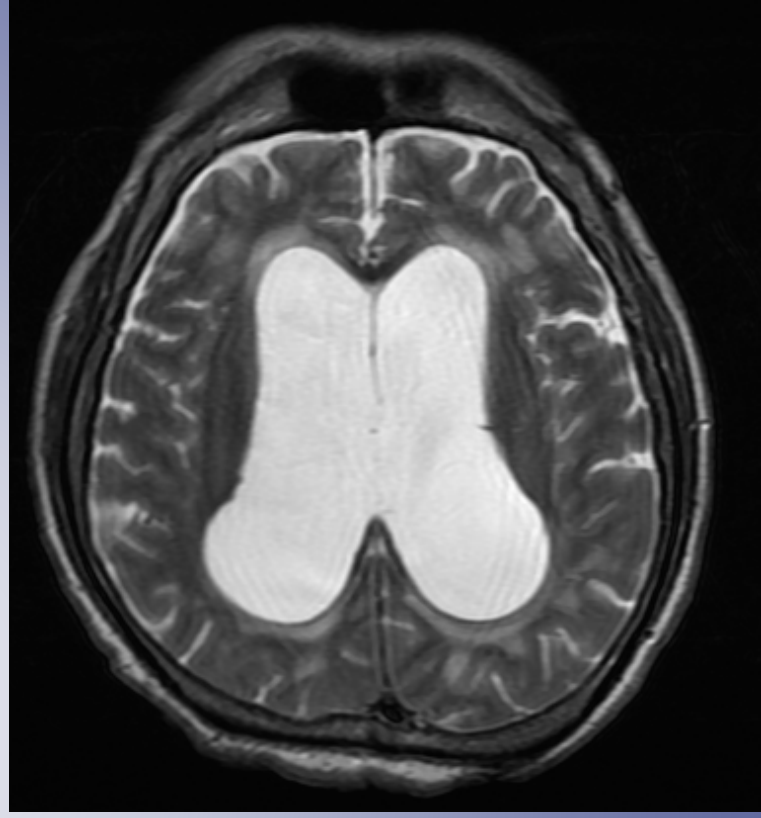
- Coccidioidomycosis involving the CNS was initially reported in the early 1900s and is one of the most devastating forms of dissemination, reported in 1/3 to 1/2 of patients

Clinical Manifestations

- Headache (77%)
- Nuchal rigidity (23%)
- Mental status changes (39%) including confusion, lethargy, memory loss, general malaise, and poor recognition
- Focal neurologic manifestations (33%) including ataxia due to hydrocephalus

CNS Dissemination

- The main areas of involvement are the basilar meninges
- Hydrocephalus the most common complication (49%)
- Vasculitis and focal intracerebral coccidioidal abscesses as less frequent complications



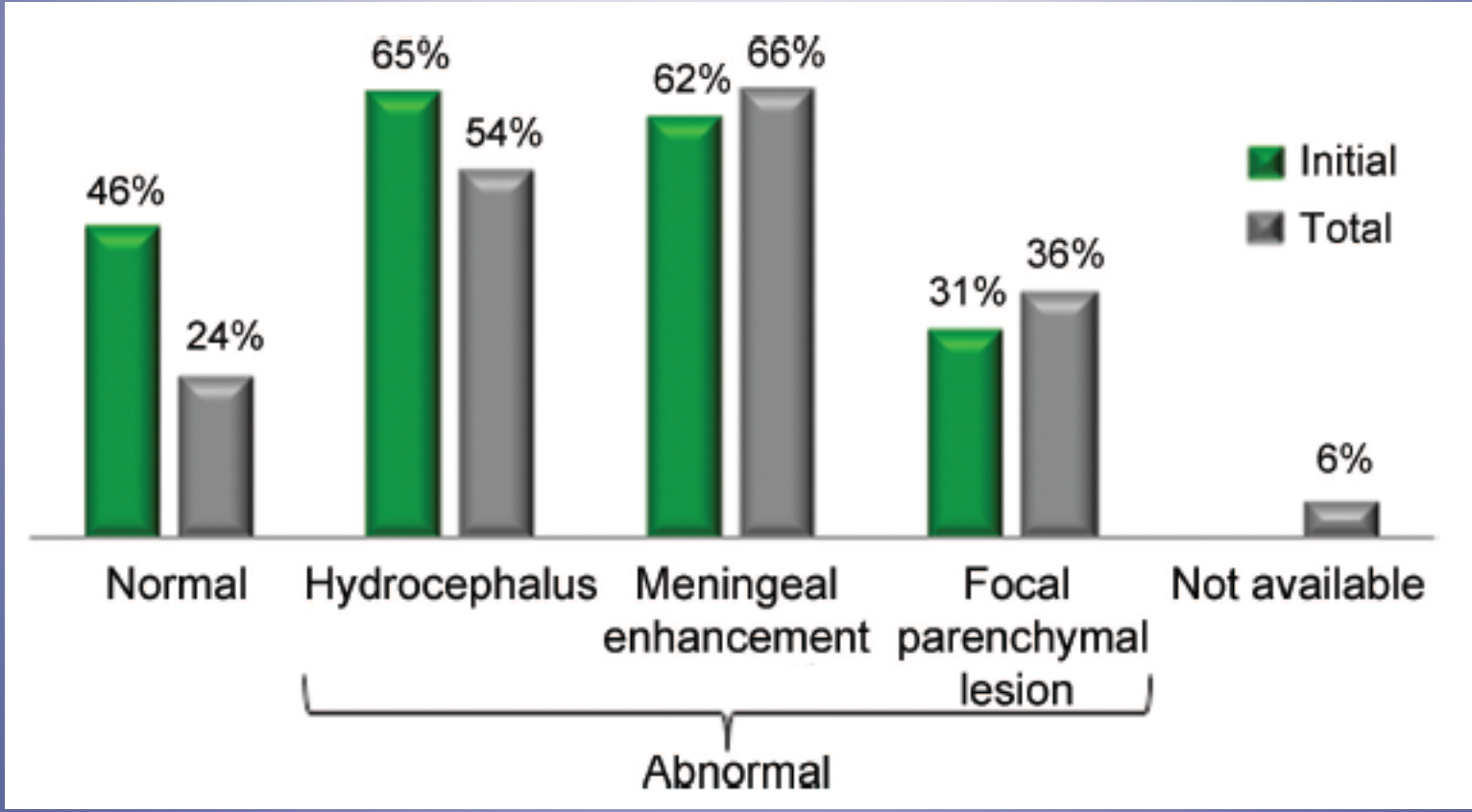
Mischel PS, Vinters HV. *CID*. 1995;20:400-405.

Coccidioidal meningitis and brain abscesses

Analysis of 71 cases at a referral center

Kendra W. Drake, MD
Rodney D. Adam, MD

Neurology® 2009;73:1780-1786



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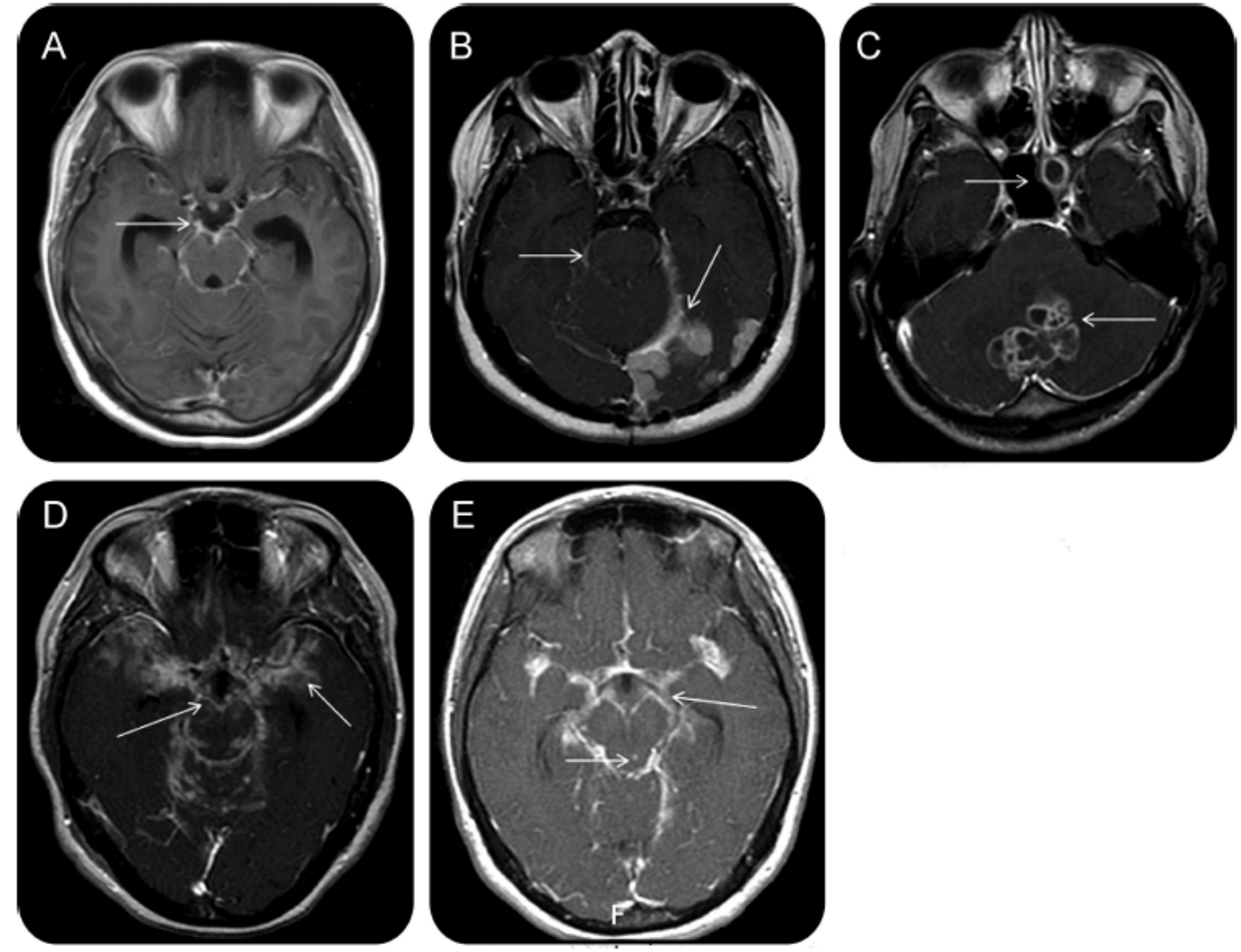
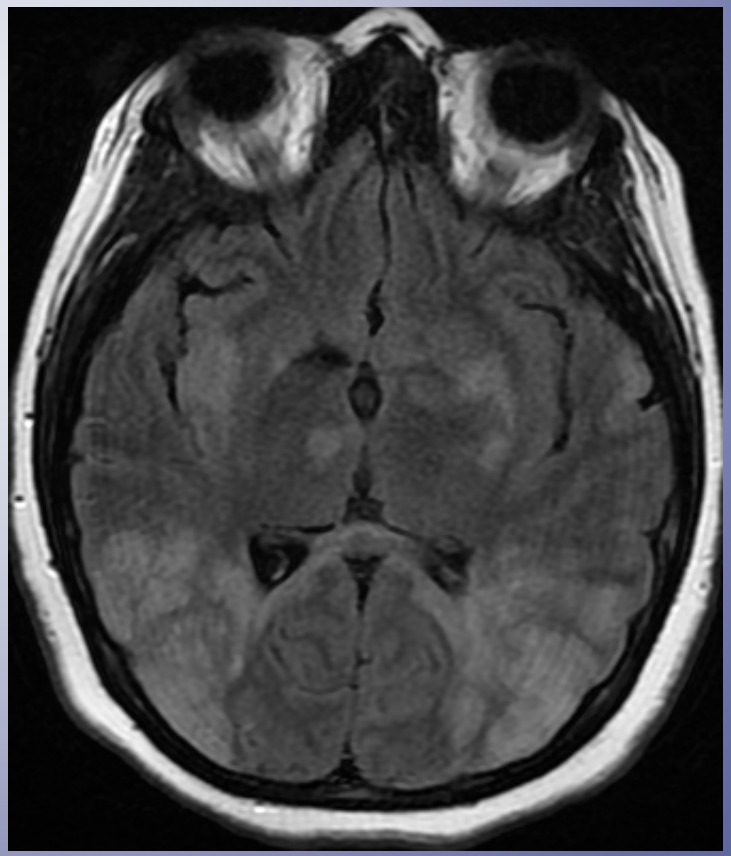
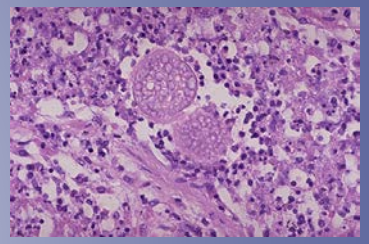


Vasculitis Secondary to Coccidioidal Meningitis

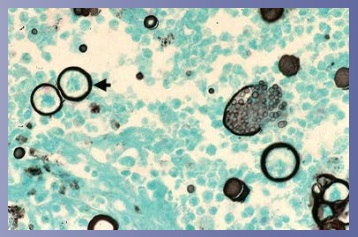


Diagnostics

- Detected by hematoxylin and eosin (H&E) stains, silver (GMS) and/or by culture in serum/blood, cerebrospinal fluid, or other body fluids/tissues



- Immunodiffusion: Tube precipitin (IDTP) and complement-fixing tests (IDCF) and titers



- Enzyme-Linked Immunoassays (EIA): Specific detection of IgM or IgG antibodies

- Antigen is detected in serum, urine, or CSF

Galgiani J., Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th Edition, 2014

Diagnostics

- CSF Coccidioides antigen (CAg) has a sensitivity and specificity of 93% and 100%

- Binnicker *et al.* applied real-time PCR to 266 respiratory specimens

- Analysis demonstrated 100% sensitivity and 98% specificity for Coccidioides when compared with culture

Management

- Treatment with intrathecal amphotericin B was the standard of care until the availability of azoles in the 1980s
- Fluconazole replaced amphotericin after its efficacy was reported in a retrospective study in 1988 and a prospective study in 1993
- Other antifungal agents used successfully in CNS infections include, voriconazole, posaconazole, isavuconazole, and intravenous liposomal amphotericin B
- Hydrocephalus nearly always requires a shunt for decompression

IDSA GUIDELINE

2016 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Treatment of Coccidioidomycosis

John N. Galgiani,[1] Neil M. Ampel,[2] Janis E. Blair,[3] Antonino Catanzaro,[4] Francesca Geertsma,[5] Susan E. Hoover,[6] Royce H. Johnson,[7] Shimon Kusne,[3] Jeffrey Lisse,[8] Joel D. MacDonald,[9] Shari L. Meyerson,[10] Patricia B. Raksin,[11] John Siever,[12] David A. Stevens,[13] Rebecca Sunenshine,[14,15] and Nicholas Theodore[16]

Brain Abscess

PREDISPOSING CONDITION	USUAL MICROBIAL ISOLATES
Otitis media or mastoiditis	Streptococci (anaerobic or aerobic), *Bacteroides* and *Prevotella* spp., Enterobacteriaceae
Sinusitis (frontoethmoid or sphenoid)	Streptococci, *Bacteroides* spp., Enterobacteriaceae, *Staphylococcus aureus*, *Haemophilus* spp.
Dental infection	Mixed *Fusobacterium*, *Prevotella*, *Actinomyces*, and *Bacteroides* spp., streptococci
Penetrating trauma or postneurosurgical	*S. aureus*, streptococci, Enterobacteriaceae, *Clostridium* spp.
Lung abscess, empyema, bronchiectasis	*Fusobacterium*, *Actinomyces*, *Bacteroides*, and *Prevotella* spp., streptococci, *Nocardia* spp.
Bacterial endocarditis	*S. aureus*, streptococci
Congenital heart disease	Streptococci, *Haemophilus* spp.
Neutropenia	Aerobic gram-negative bacilli, *Aspergillus* spp., Mucorales, *Candida* spp., *Scedosporium* spp.
Transplantation	*Aspergillus* spp., *Candida* spp., Mucorales, *Scedosporium* spp., Enterobacteriaceae, *Nocardia* spp., *Toxoplasma gondii*, *Mycobacterium tuberculosis*
Human immunodeficiency virus infection	*T. gondii*, *Nocardia* spp., *Mycobacterium* spp., *Listeria monocytogenes*, *Cryptococcus neoformans*

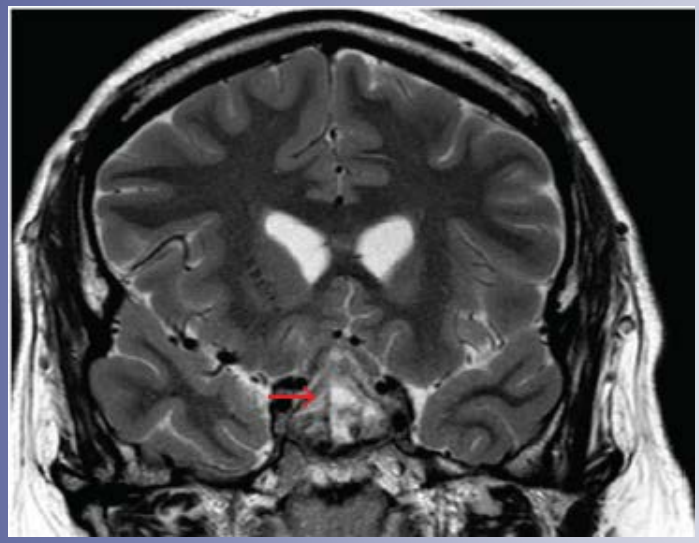
Brain Abscess: Clinical Presentation

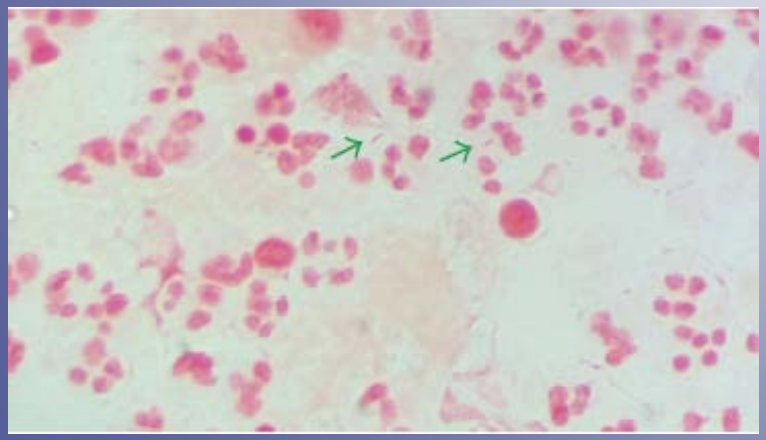
SYMPTOM OR SIGN	FREQUENCY (%)
Headache	49-97
Mental status changes	28-91
Focal neurologic deficits	20-66
Fever	32-79
Triad of headache, fever, and focal deficit	<50
Seizures	13-35
Nausea and vomiting	27-85
Nuchal rigidity	5-52
Papilledema	9-51

Polymicrobial Pituitary Abscess Predominately Involving *Escherichia coli* in the Setting of an Apoplectic Pituitary Prolactinoma

Norman Beatty, Luis Medina-Garcia, Mayar Al Mohajer, and Tirdad T. Zangeneh

Division of Infectious Diseases, Department of Medicine, University of Arizona College of Medicine, Banner-University Medical Center, 1501 N. Campbell Avenue, Tucson, AZ 85724, USA

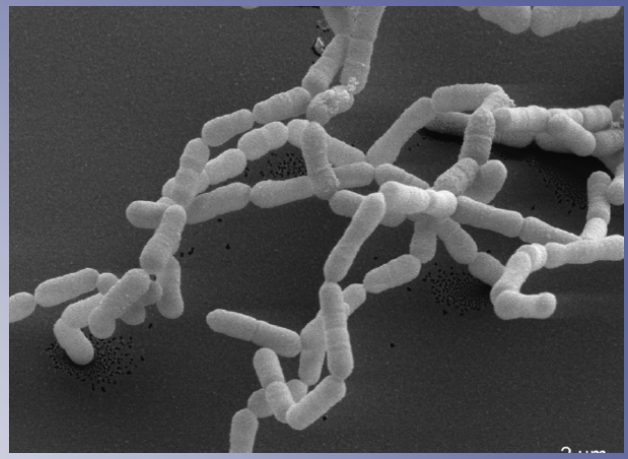


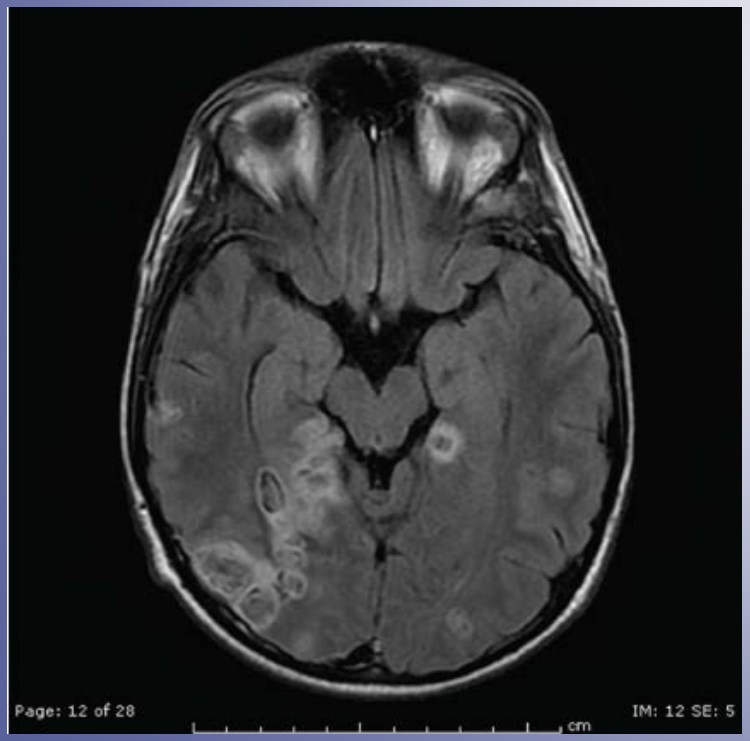


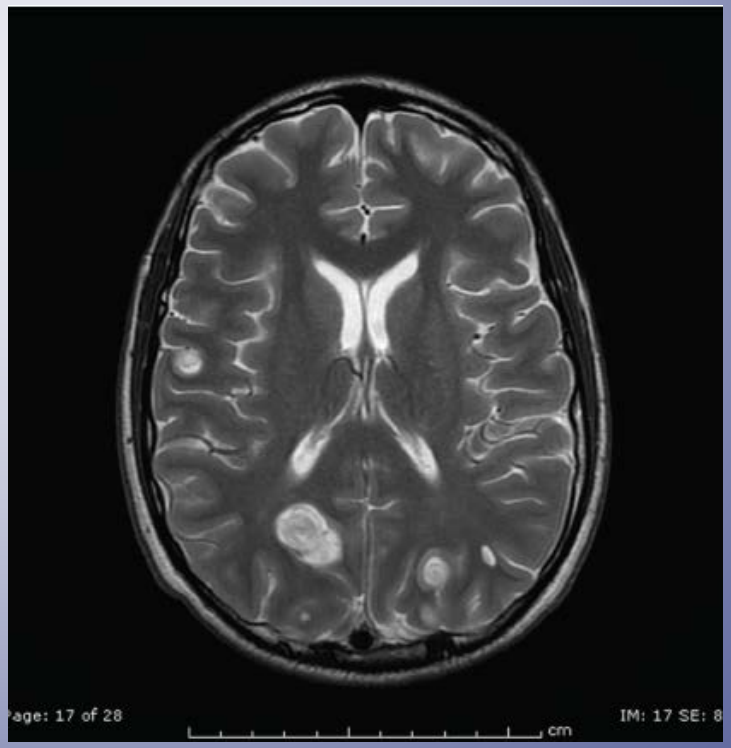
Disseminated Infection Caused by *Eggerthella lenta* in a Previously Healthy Young Man: A Case Report

Ahmad Salameh,[1] Stephen A. Klotz,[2] and Tirdad T. Zangeneh[2]

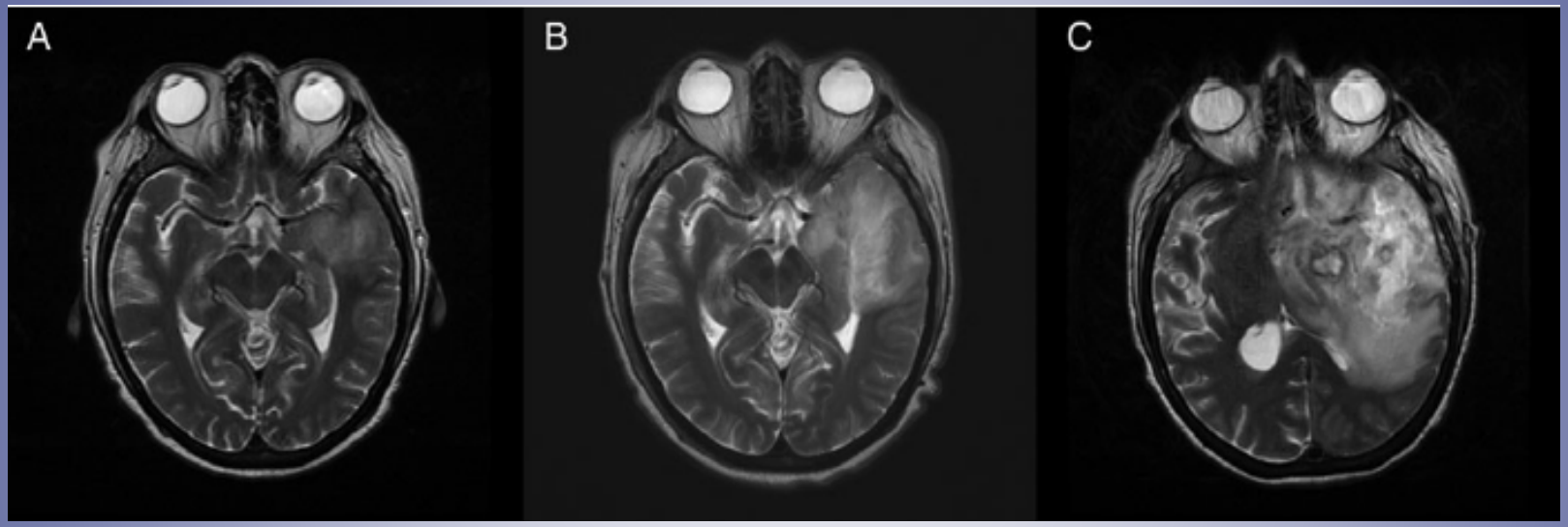
[1] *Department of Medicine, The University of Arizona Medical Center, University of Arizona, Tucson, AZ 85724, USA*
[2] *Division of Infectious Diseases, Department of Medicine, The University of Arizona Medical Center, University of Arizona, Tucson, AZ 85724, USA*

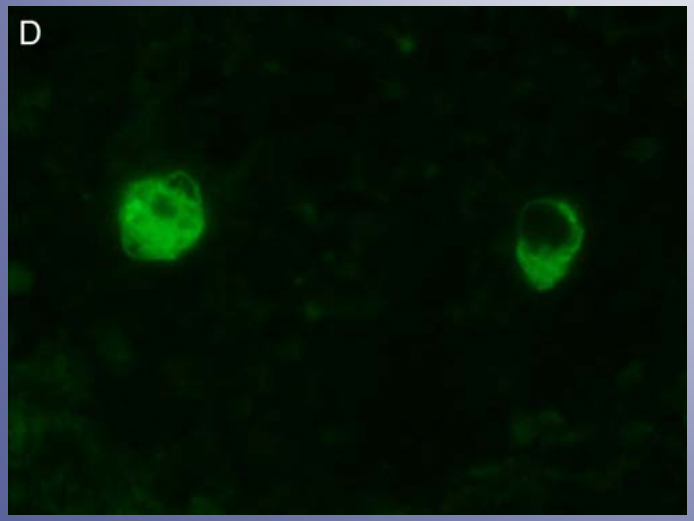


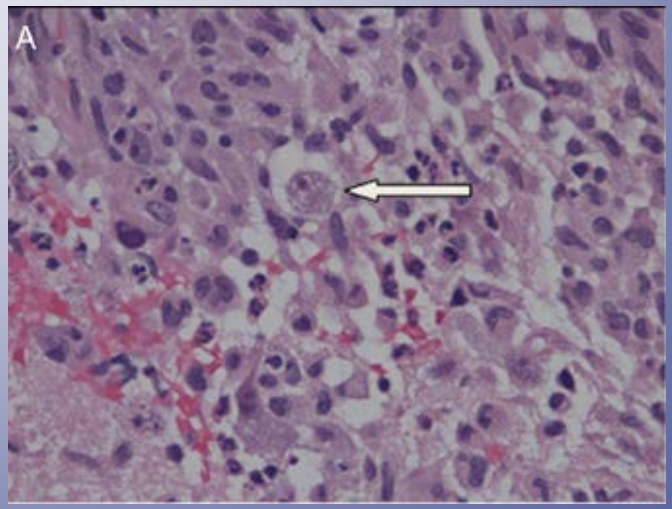




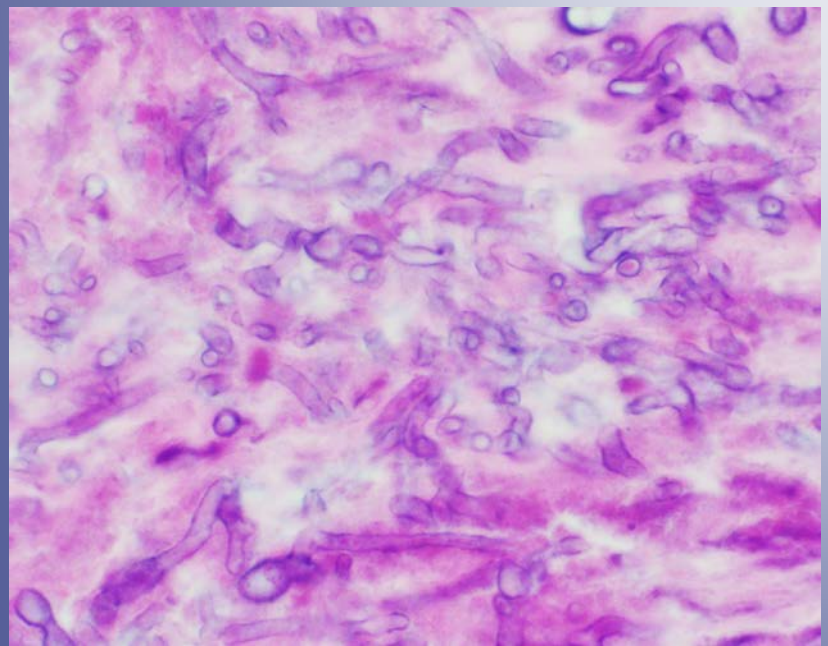
Fatal Granulomatous Amoebic Encephalitis Caused by *Acanthamoeba* in a Patient With Kidney Transplant: A Case Report





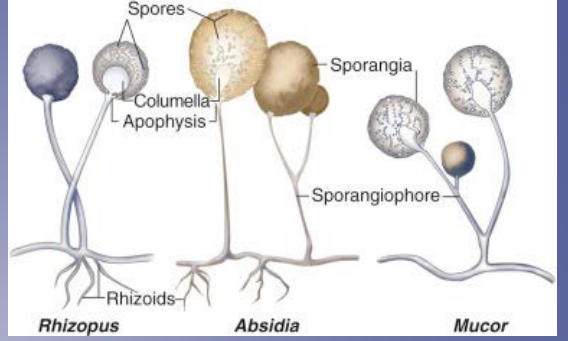


Fatal *Aspergillus fumisynneamatus* Sinusitis with CNS invasion in a healthy 36 year old man



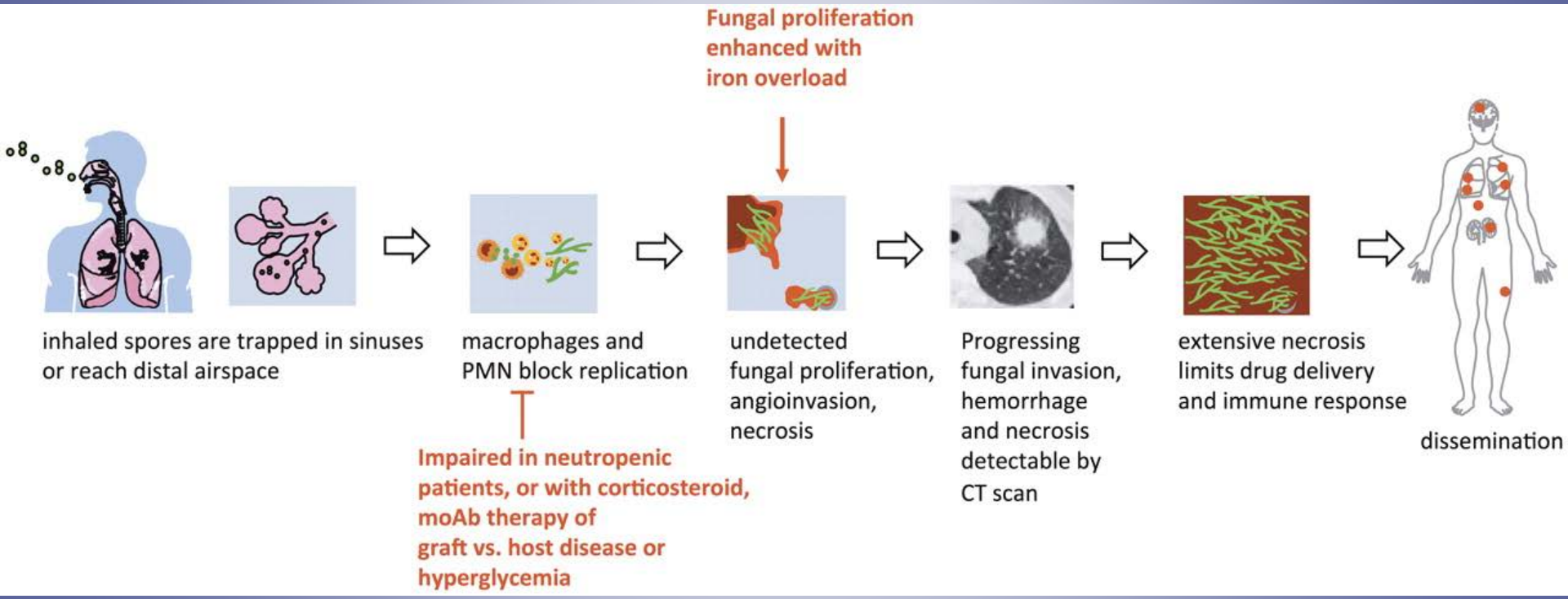
Fatal Invasive Orbitorhinocerebral Mucormycosis in a 54 year old woman with uncontrolled diabetes

Mucormycosis



- *Rhizopus* species are the most common genera followed by:
  - *Mucor species* (19%)
  - *Rhizomucor* species (7%)
  - *Cunninghamella* species (9%)
- Ubiquitous in nature and can be found on decaying vegetation and in the soil
- Mortality rate ranging from 68 to 100%

Pathogenesis



Role in Diabetic Ketoacidosis: Diminished capacity of transferrin to bind to and sequester free iron at a pH of <7.4

Risk Factors

Table 2 Factors predisposing patients to zygomycosis

Diabetes mellitus
Diabetic ketoacidosis
Poorly controlled diabetes mellitus
Chronic metabolic acidosis
Renal failure
Chronic salicylate poisoning
Deferoxamine therapy
Iron overload
Immunosuppression
Neutropenia (due to malignancies or chemotherapy)
Corticosteroid therapy
Organ or hematopoietic cell transplantation
HIV infection
Skin or soft tissue breakdown
Burn
Trauma
Surgical wound
Miscellaneous
Intravenous illicit drug use
Neonatal prematurity
Malnourishment
Prolonged use of broad-spectrum antimocrobial agents

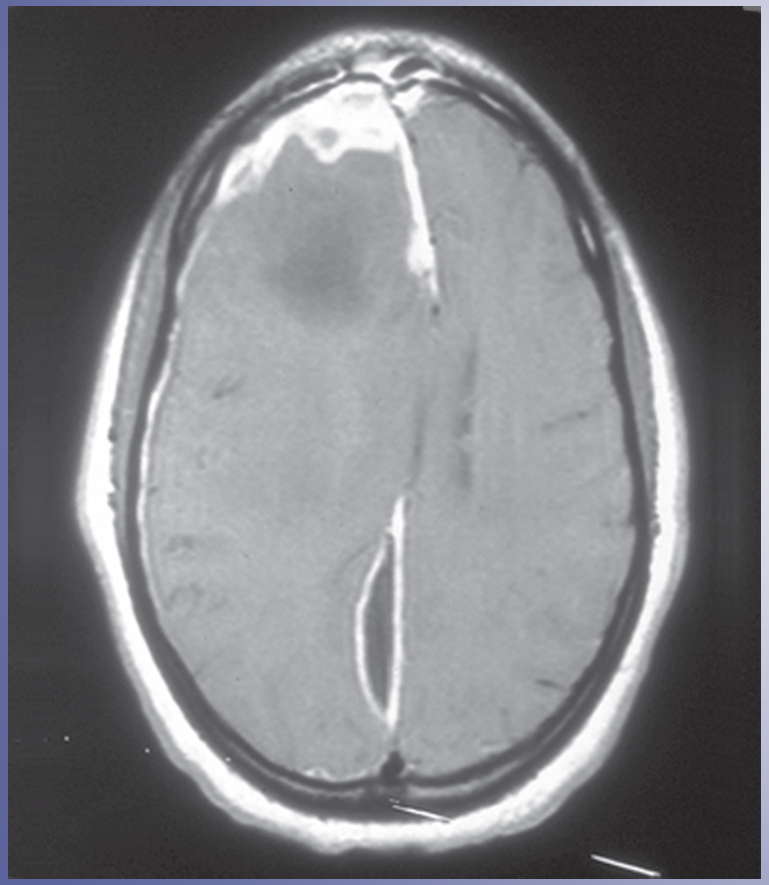
Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3)

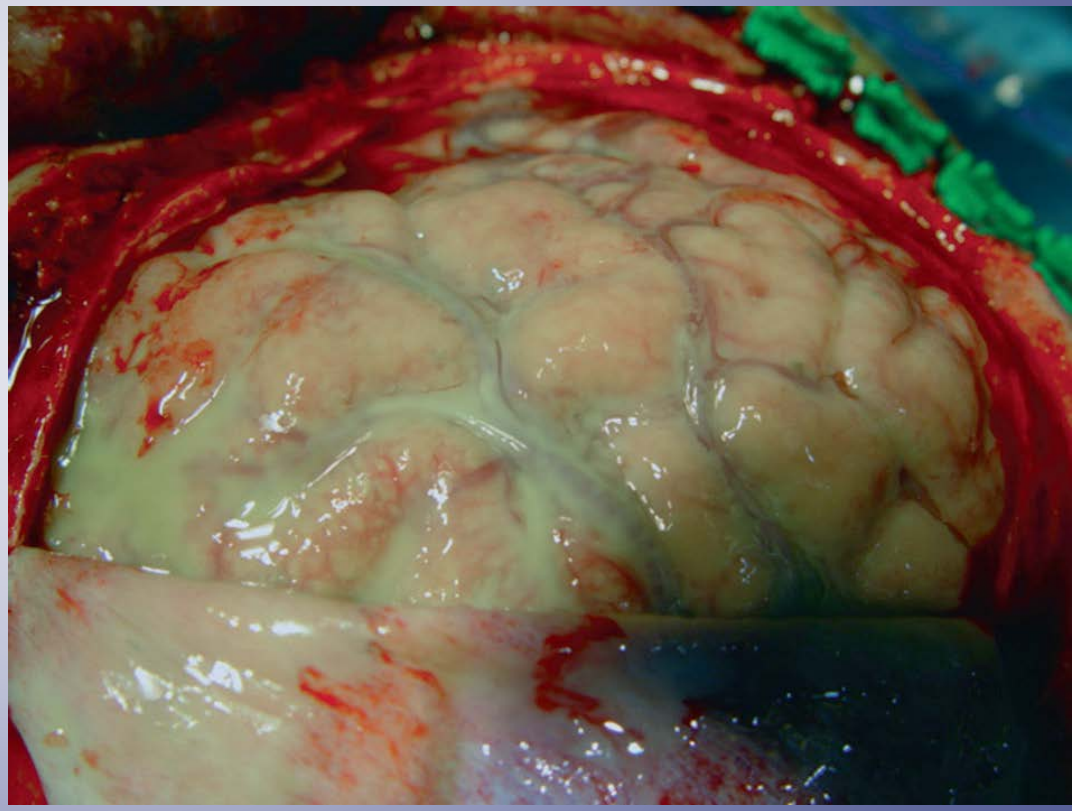
Anna Skiada,[1] Fanny Lanternier,[2] Andreas H. Groll,[3] Livio Pagano,[4] Stephan Zimmerli,[5] Raoul Herbrecht,[6] Olivier Lortholary,[7] and George L. Petrikkos[8] on behalf of the third European Conference on Infections in Leukemia*

Management should include antifungal therapy, control of underlying conditions and surgery	AII
Antifungal therapy	
AmB deoxycholate[4,29,30]	CII
Liposomal AmB[16,29-34], 5-10 mg/kg[35,36]	BII[1]
ABLC[37,29], 5-7.5 mg/kg[35]	BII1
ABCD[42,45]	CII
Posaconazole[16,17] 400 mg bid	CIII[2]
Combination therapy[39]	CIII
Control of underlying condition[5,42,43]	AII[3]
Surgery	
-rhino-orbito-cerebral[44-47]	AII
-soft tissue[48,49]	AII
-localized pulmonary lesion[50,51]	BII
-disseminated[22]	CIII[4]
Hyperbaric oxygen	CIII

Haematologica.
2013 Apr;98(4):492-504

Subdural Empyema





Subdural Empyema

- Subdural empyema refers to a collection of pus between the dura and arachnoid

- Predisposing factors include otorhinologic infections which are affected in 40% to 80% of cases

- Caused by aerobic streptococci, staphylococci, aerobic gram-negative bacilli, and anaerobic streptococci, and other anaerobes

Subdural Empyema

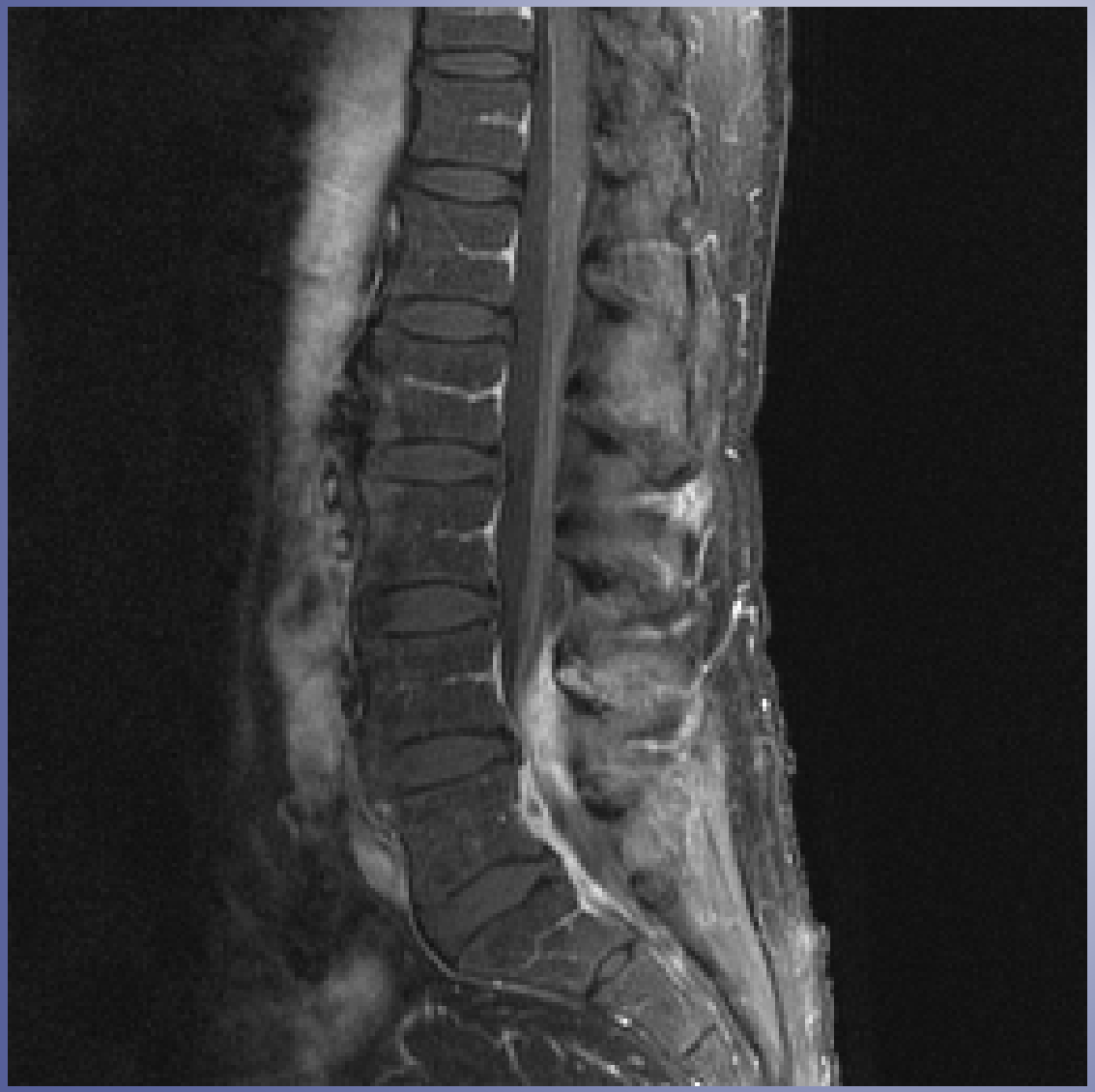
- Magnetic resonance imaging (MRI) is the diagnostic procedure of choice in patients with subdural empyema
- Subdural empyema is a medical and surgical emergency
- The goals of surgery are to achieve adequate decompression and evacuation of empyema with craniotomy being the surgical procedure of choice

“My back is killing me”

- A 24 y/o man presents to the ED with c/o fever, severe back pain described as "shooting” and stabbing in nature, lower extremity weakness with decreased sensation, difficulty walking, and bladder dysfunction

- He reports injecting heroin for the past 3 months

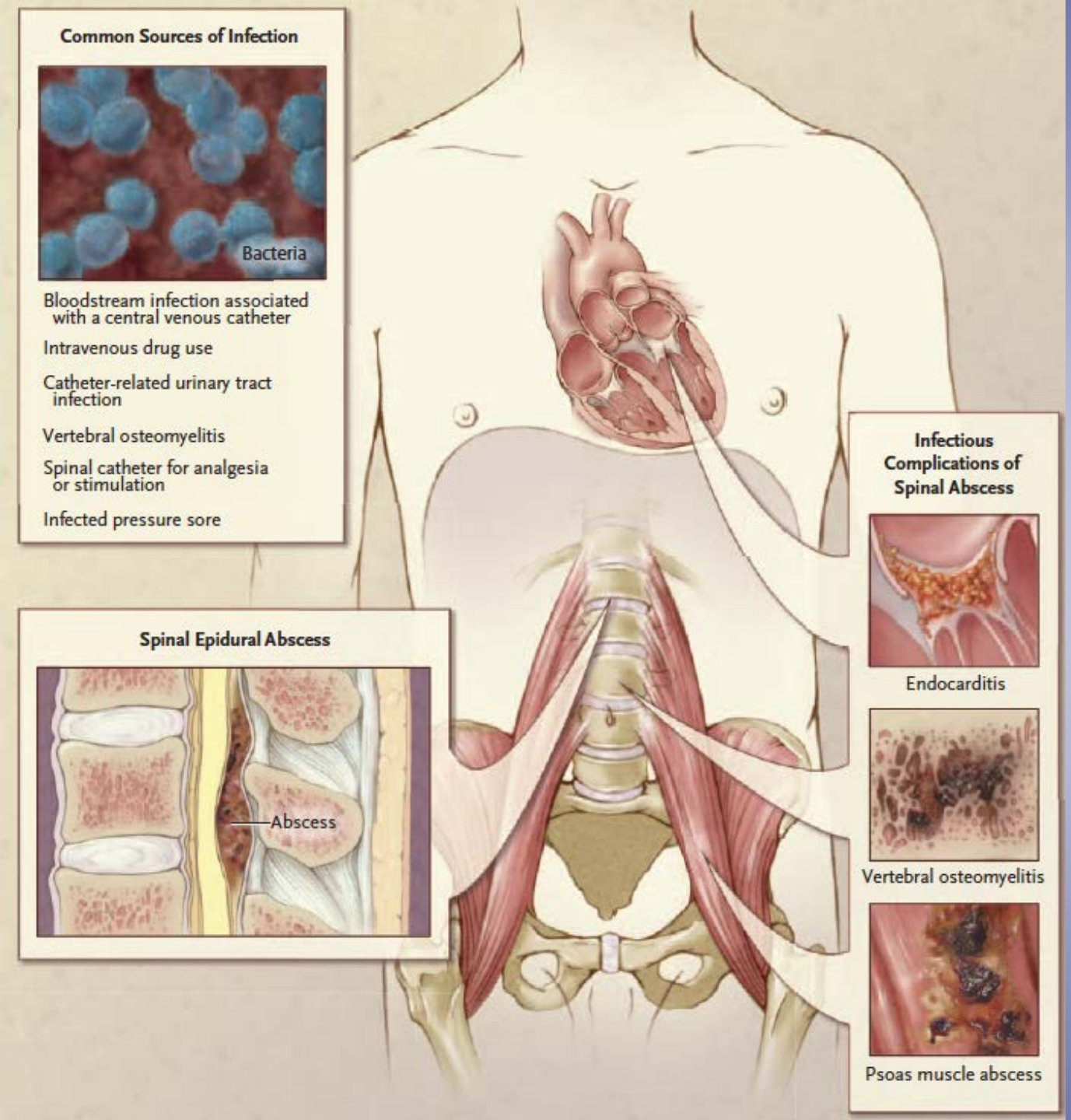
Imaging



- Epidural abscess extending from the L4-S1 levels causing severe thecal sac stenosis with cauda equina impingement

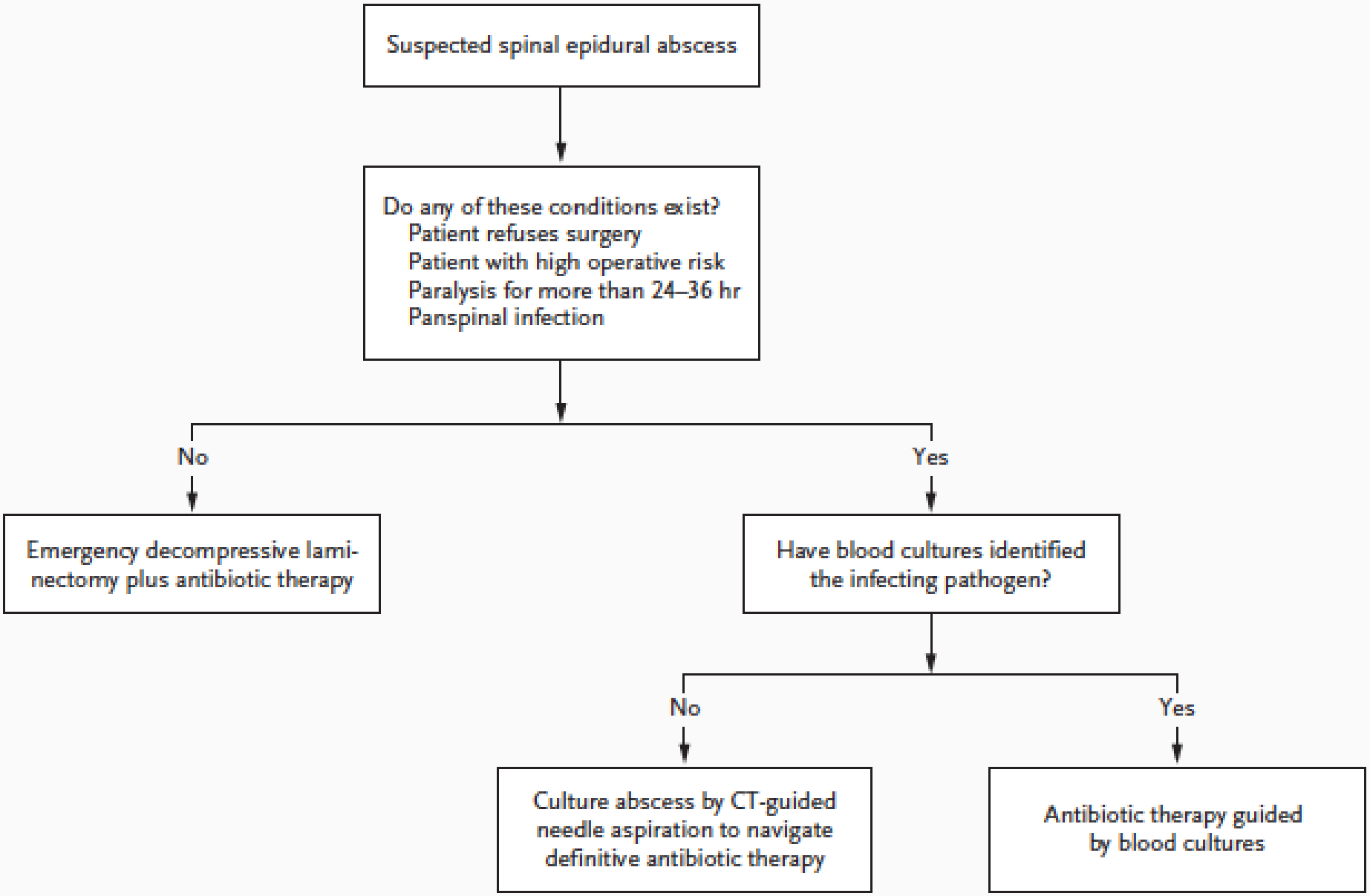
Microbiology

- *S. aureus* (Over 60% of cases)
- Gram-negative bacilli
- Streptococci
- Coagulase-negative staphylococci
- Anaerobes
- Others (fungi, tuberculosis, parasites)



Abscesses are more likely to develop in larger epidural spaces that contain infection-prone fat

Management of Spinal Epidural Abscess

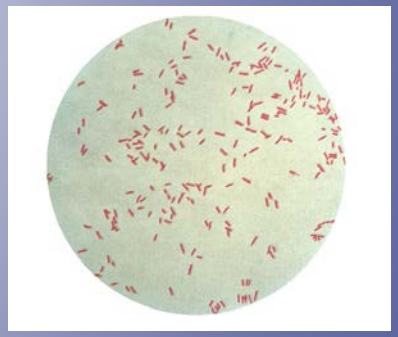


Infective Endocarditis (IE)

- Infection of the endocardium that involves the cardiac valves and adjacent structures
- Bacterial (most common), fungal, rickettsia
- Acute and subacute course

Microbiology

- *S. aureus* — 31 percent
- *Viridans* group streptococci — 17 percent
- *Enterococci* — 11 percent
- *Coagulase-negative staph*ylococci — 11 percent
- *Streptococcus bovis* — 7 percent
- Non-HACEK gram-negative bacteria — 2 percent
- Fungi — 2 percent
- HACEK — 2 percent

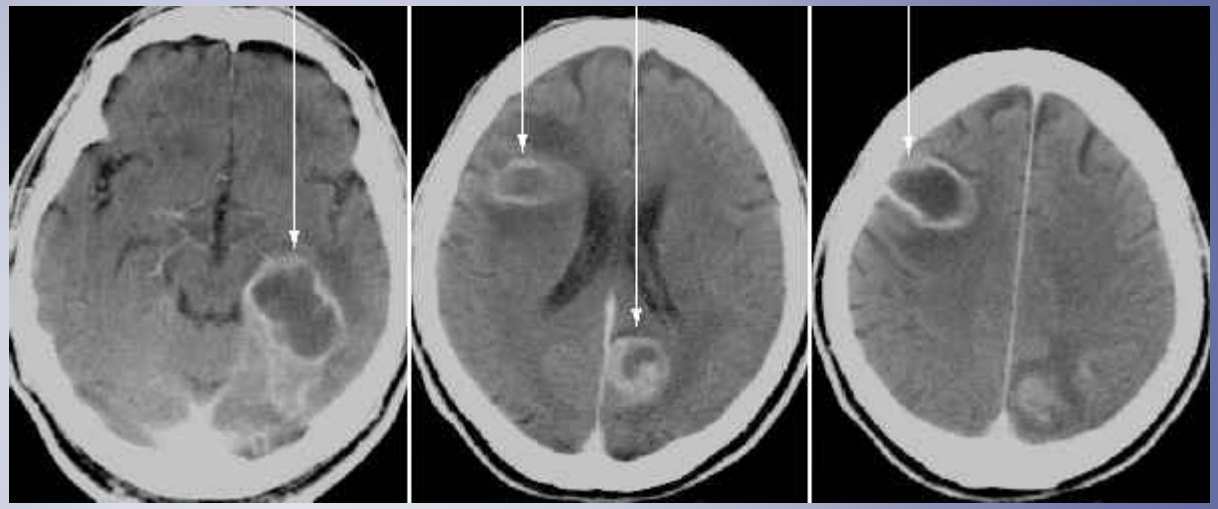


**Haemophilus spp*
Aggregatibacter [formerly *Actinobacillus* spp.]
Cardiobacterium hominis
Eikenella corrodens
Kingella kingae

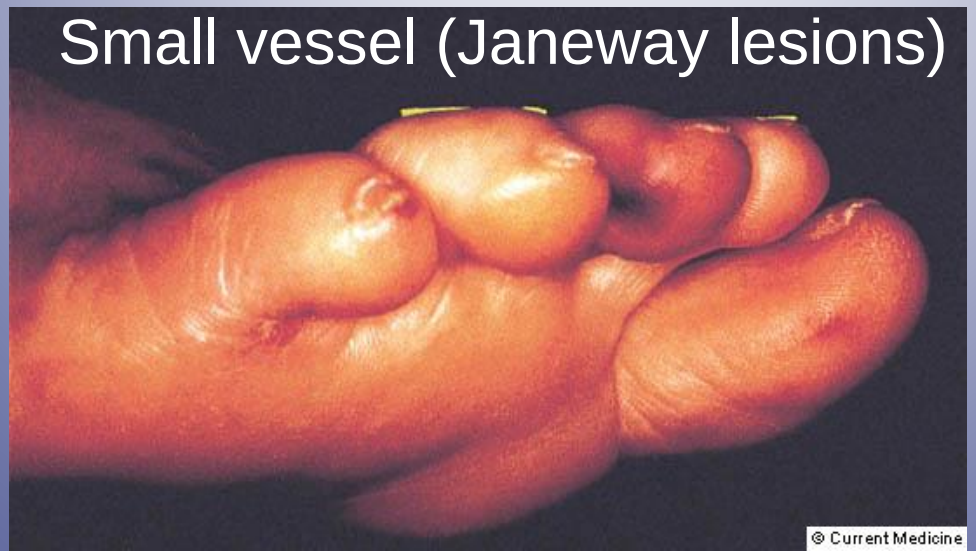
Consequences of Septic Emboli

Mitral or aortic valve → Left ventricle → Aorta

Large vessel



Small vessel (Janeway lesions)



CNS Involvement

- Patients with left-sided IE were prospectively evaluated with cerebral MRI regardless of neurologic symptoms
- The total cerebrovascular complication rate was 65%, including 35% (symptomatic) and 30% (clinically silent)
- Middle cerebral artery and its branches are involved commonly
- Hemorrhagic transformation of septic emboli commonly results in fatal intracerebral hemorrhage

Martin et al. *Clin Infect Dis*. 2008; 47:23

Conclusion

- Infections involving the CNS are caused by a variety of organisms
- The clinical presentations depend on the virulence of the organism, host immunity, and the involved location
- A delay in diagnosis is often associated with a high morbidity and mortality

TIME LOST IS BRAIN LOST