Brain Abscess in Adults - Microbiology Full Clinical Guideline

Reference number: CG-ANTI/2023/072

Introduction

- Brain abscesses can be caused by multiple pathogens (polymicrobial infection) or, more commonly, by single pathogens (monomicrobial infectious disease).
- The Gram positive *Staphylococcus aureus* and *Streptococcus* species (e.g. viridans streptococci, including the *Streptococcus anginosus* group [= *Streptococcus anginosus/constellatus/intermedius*]) are the most frequent microbial causes.
- Anaerobes (e.g. *Bacteroides* species) and Gram negatives (e.g. *Enterobacterales* [for example, *Proteus* species]) are other identified bacterial causes.

- The pathogens of brain abscesses are most commonly inoculated through a contiguous mechanism of transmission. Another focus of infection (e.g. dental infection, mastoiditis, otitis media, sinusitis) disseminates locally and invades the brain parenchyma.
- Less commonly, inoculation is via a haematogenous mechanism of transmission. Another focus of infection (e.g. infective endocarditis, lung abscess, pleural empyema) culminates in bacteraemia; the microorganism disseminates via the blood and inoculates the brain parenchyma.
- The pathogens of brain abscesses can also be inoculated directly via surgery or trauma; iatrogenic and traumatic mechanisms of transmission, respectively.

- One of the outcomes of:
    - Microbial invasion of the brain parenchyma; and
    - The subsequent cerebral inflammatory response

  is cerebritis.
- Another of the outcomes is the formation of an encapsulated lesion containing necrotic immune cells and invading pathogens, i.e. a brain abscess.
    - Direct, contiguous spread commonly causes a single brain abscess.
    - Indirect, haematogenous spread commonly causes multiple brain abscesses.
- The brain abscess may manifest with altered mental status, fever, focal neurological deficit, headache, neck stiffness, seizure, and/or vomiting.

Differential diagnosis

- Altered mental status, fever, focal neurological deficit, headache, neck stiffness, seizure, and/or vomiting can be caused by multiple pathologies.
- Other infectious diseases and non-microbial mimickers include cerebral sinus venous thrombosis, encephalitis, intracranial epidural abscess, intracranial tumour (primary and metastatic), meningitis, mycotic aneurysm, and subdural empyema.

Investigation

Radiology

- First line: in general, computed tomography (CT).
- Second line: in general, magnetic resonance imaging (MRI); collaborate with the consultant radiologist.

- NB1 Within the Queen's Hospital Burton (QHB) and the Royal Derby Hospital (RDH), the CT service operates 24 hours per day, 7 days per week.

- NB2 Within the QHB and RDH, the MRI service operates 0900-1700 Mondays to Fridays.
- NB3 In the QHB, there is no MRI service out-of-hours.
- NB4 In the RDH, discussion with the medical consultant and – if the senior physician deems MRI essential – liaison with the on call radiology consultant is required 1700-0900 Mondays to Fridays, and all-day Saturdays and Sundays.

Microbiology

- With the range of microbial pathogens, variations in resistance and susceptibility profiles, variable antimicrobial blood-brain penetration, contraindications, side-effects, and with prolonged durations of weeks-months of antimicrobial chemotherapy, microbiological investigation enables best antibiotic practice:
    - Before starting antimicrobials:
        - Blood cultures × 2.
    - If the neurosurgical team intervenes:
        - Aspirate/Biopsy for microscopy, culture, and susceptibilities.
            - If the differential diagnosis includes tuberculosis, aspirate/biopsy also for acid-alcohol fast bacilli microscopy and *Mycobacterium* culture.

Histology

- With the infectious and non-infectious differential diagnosis including intracranial tumors:
    - If the neurosurgical team intervenes:
        - Biopsy for neurohistopathology.

Blood sciences

- Full blood count (FBC), C reactive protein (CRP), lactate, urea and electrolytes (U&Es), and liver function tests (LFTs).

Treatment

Surgical intervention

- Neurosurgical intervention with:
    - Needle aspiration; or
    - Excision

  may establish the diagnosis and enable drainage of the focus of infection.
- With the variable:
    - Mechanisms of inoculation (contiguous, haematogenous, iatrogenic, and traumatic)
    - Maturity of lesions (early cerebritis, late cerebritis, early capsule formation, late capsule formation)
    - Locations of brain abscesses (parietal, occipital, temporal, frontal, cerebellar)
    - Number(s) of brain abscesses (single or multiple)
    - Neurologic sequelae associated with neurosurgical intervention

  ensure collaboration with the neurosurgery registrar/consultant on call in Nottingham.

Empiric, intravenous antibiotics

	First line	Second line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy
If there is: (i) no past medical history of acute or chronic otitis media; and (ii) if there are no symptoms, no signs, and no radiological findings of middle ear infectious disease	Metronidazole 500 mg 8 hourly; **and** Ceftriaxone 2 g 12 hourly	Chloramphenicol 25 mg/kg 6 hourly (NB maximums of 2 g 6 hourly and of 8 g within 24 hours)
If there is: (i) past medical history of acute or chronic otitis media; and/or (ii) symptoms, signs, or radiological findings of middle ear infectious disease	Meropenem 2 g 8 hourly	Metronidazole 500 mg 8 hourly; **and** Ciprofloxacin 400 mg 8 hourly; **and** Linezolid* 600 mg 12 hourly
If history of penetrating traumatic injury to the brain or post-operative (neurosurgery) brain abscess	Meropenem 2 g 8 hourly; **and** Linezolid* 600 mg 12 hourly	Metronidazole 500 mg 8 hourly; **and** Ciprofloxacin 400 mg 8 hourly; **and** Linezolid* 600 mg 12 hourly
* If linezolid is contraindicated, vancomycin (dose as per hospital guidelines), target pre dose level 15-20 mg/l		

NB Empiric, intravenous antibiotics: chloramphenicol

Treatment regimens in adults	Central nervous system infection: chloramphenicol 12.5-25 mg/kg 6 hourly (NB maximums of 2 g 6 hourly and of 8 g within 24 hours)
Cautions	BNF: "With intravenous use avoid repeated courses and prolonged treatment"
Interactions	Please review the BNF for an up-to-date and comprehensive list of interactions
Rare or very rare side-effects	BNF: "With parenteral use **aplastic anaemia** (reversible or irreversible, with reports of resulting leukaemia)"
Renal impairment • GFR 25-50 ml/min • GFR 10-25 ml/min • GFR < 10 ml/min	 Dose as in normal renal function Dose as in normal renal function Dose as in normal renal function
Hepatic impairment	BNF: "With intravenous use… manufacturer advises caution (increased risk of bone-marrow depression) – monitor plasma-chloramphenicol concentration… manufacturer advises consider dose reduction"
Therapeutic drug monitoring (TDM) • Recommended • First TDM • Sample • Level • Repeat	 Yes, in discussion with the microbiology consultant Before and after 3rd or 4th dose 1-2 ml serum, pre and post (2 hours) dose Pre dose < 10 mg/l; post dose 10-25 mg/l 5-7 days

Directed, intravenous antibiotics (with susceptibilities)

- Brain abscesses can be caused by single or multiple pathogens. Specific bacteria can be associated with polymicrobial infectious disease. Therefore, microbiologists may recommend directed, intravenous antibiotics with spectrums of activity that extend beyond the cultured bacteria.
- Case by case discussion between neurosurgery and microbiology is recommended.
- *Streptococcus* species, according to susceptibilities:
    - First line: benzylpenicillin 2.4 g 4 hourly ± metronidazole 500 mg 8 hourly (e.g. if culture of *Streptococcus anginosus*, *Streptococcus constellatus*, or *Streptococcus intermedius*).
    - Second line, if non-immediate without systemic involvement penicillin allergy: ceftriaxone 2 g 12 hourly ± metronidazole 500 mg 8 hourly (e.g. if culture of *Streptococcus anginosus*, *Streptococcus constellatus*, or *Streptococcus intermedius*).
- Anaerobes (e.g. *Bacteroides* species), according to susceptibilities:
    - First line: metronidazole 500 mg 8 hourly and ceftriaxone 2 g 12 hourly.
    - Second line: meropenem 2 g 8 hourly.
- *Enterobacterales* (e.g. *Proteus* species) species, according to susceptibilities:
    - First line: ceftriaxone 2 g 12 hourly.
    - Second line: ciprofloxacin 400 mg 8 hourly.
- *Staphylococcus aureus*, according to susceptibilities:
    - First line: flucloxacillin 2 g 4 hourly.
    - Second line: linezolid 600 mg 12 hourly.
- Other bacteria, fungi, and parasites:
    - Collaborate with the microbiology team.

Intravenous to per oral step down, or outpatient parenteral antimicrobial therapy

- After 10-14 days of intravenous antimicrobial chemotherapy, if the patient is afebrile, observations stable, and inflammatory markers downward trending, collaborate with the neurosurgeon and microbiologist regarding (1) per oral step down, or (2) outpatient parenteral antimicrobial therapy (OPAT).
- After 10-14 days of intravenous antimicrobial chemotherapy, if the patient is febrile, observations unstable, and/or inflammatory markers upward trending, collaborate with the neurosurgeon, radiologist, and microbiologist regarding re-imaging, further surgical intervention, and continue intravenous therapy.

Directed, per oral antibiotics (with susceptibilities)

- Brain abscesses can be caused by single or multiple pathogens. Specific bacteria can be associated with polymicrobial infectious disease. Therefore, microbiologists may recommend directed, per oral antibiotics with spectrums of activity that extend beyond the cultured bacteria.
- Please note, opinions vary regarding brain abscesses and per oral antibiotics. Variations from microbiologist to microbiologist reflect pharmacokinetic and pharmacodynamics principles (Appendix: pathophysiology and antibiotics) and the relative weighting of these parameters. One microbiologist may recommend OPAT for the patient in question; another microbiologist per orals.
- Case by case discussion between neurosurgery and microbiology is recommended. Please liaise with the neurosurgeon first and the microbiologist second.

- *Streptococcus* species, according to susceptibilities:
    - Microbiology may recommend: amoxicillin 1 g 8 hourly ± metronidazole 400 mg 8 hourly (e.g. if culture of *Streptococcus anginosus*, *Streptococcus constellatus*, or *Streptococcus intermedius*).
- Anaerobes (e.g. *Bacteroides* species), according to susceptibilities:
    - Microbiology may recommend: metronidazole 400 mg 8 hourly and amoxicillin 1 g 8 hourly.
- *Enterobacterales* (e.g. *Proteus* species) species, according to susceptibilities:
    - Microbiology may recommend: ciprofloxacin 500-750 mg 12 hourly or co-trimoxazole 960 mg 12 hourly.
- *Staphylococcus aureus*, according to susceptibilities:
    - Microbiology may recommend: linezolid 600 mg 12 hourly.
- Other bacteria, fungi, and parasites:
    - Collaborate with the microbiology team.

Directed, outpatient parenteral antimicrobial therapy

- Collaborate with the OPAT consultant.

Empiric, per oral or outpatient parenteral antimicrobial therapy

- If symptoms/signs/radiology features of brain abscess, and the microbiology is negative, collaborate with a microbiologist regarding empiric options.

Duration of antibiotics

- Before discharge to the community, neurosurgery to collaborate with radiology regarding the timeframe for follow-up CT imaging.
- If for per oral step down or OPAT, monitor bloods (FBC, CRP, U&Es, and LFTs) weekly-fortnightly.

- Courses of antibiotics 4-8 weeks:
    - If surgical drainage and if the patient is afebrile, observations stable, inflammatory marker resolution, and follow-up CT satisfactory:
        - 4-6 weeks.
    - If no surgical intervention:
        - 6-8 weeks.

Management

Clinical concerns re brain abscess (altered mental status, fever, focal neurological deficit, headache, neck stiffness, seizure, vomiting, etc.)

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Investigation
- Radiology:
  - CT head
- Microbiology:
  - Blood cultures × 2
- Blood sciences:
  - FBC, CRP, lactate, U&Es, and LFTs

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Collaborate with the neurosurgical registrar/consultant on call in Nottingham

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Treatment
- Empiric, intravenous antibiotics (please note, page 3)

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Treatment
- ± Surgical intervention
  - Needle aspiration or excision
    - ± Biopsy for microbiology and histology

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Treatment
- Directed, intravenous antibiotics (please note, pages 4 and 5)

Appendix: pathophysiology and antibiotics

Blood brain barrier

- In the central nervous system, the pathway from the blood to the brain is: endothelial cells of continuous capillaries → basal lamina → pericytes → astrocytes → interstitial fluid of the brain → tissue of the brain.
- The endothelial cells, through a multitude of junctional complexes, are anchored to one another. The tight junctions prevent the passive diffusion of an array of macromolecules into the brain.

Antibiotic absorption; permissive facets of pathology

- Infection in the brain initiates an inflammatory response. Inflammatory cells are present throughout the early cerebritis-late cerebritis-early capsule formation-late capsule formation stages of brain abscess pathology. Inflammatory mediators are released and the vasculature of the brain transitions from continuous capillaries with tight junctions to capillaries with leaky junctions.
- The breakdown of the blood-brain barrier could enhance antibiotic absorption from the systemic circulation into the brain.

Antibiotic absorption; restrictive facets of pathology

- The nervous system – in contrast to the flora-containing integumentary, respiratory, urinary, gastrointestinal, and reproductive systems – is sterile. The parenchyma of the brain is resistant to colonization and infection. The pathology of brain abscess requires hypoxemia, ischaemia, or necrosis before invasion of the brain tissue. Pre-existing suboptimal vascularity could restrict the delivery of antibiotics.
- Infection in the brain initiates an inflammatory response. The inflammatory response is capable of destruction of uninfected brain tissue surrounding the infection. Damage to the vasculature on the periphery of infection could further impede the delivery of antibiotics.
- In microbial infection with abscess formation, an antibiotic must first traverse the membranes of the endothelium, then diffuse through the interstitium, and then traverse a second membrane, that of the abscess.
    - Infection initiates an inflammatory response; the inflammation renders the interstitial fluid more viscous. The increase in viscosity decreases the amount of antibiotic transferred by diffusion.
    - The abscess is traversed through passive diffusion across the membrane, rather than pores, impairing the delivery of antibiotics. As the abscess forms and matures, the permeation of the membrane decreases, impeding the delivery of antibiotics.
    - In microbial infection with abscess formation, as the abscess matures, bacteria transition from the planktonic to the sessile state. The planktonic state of bacteria is preferable for antibiotics; active bacterial metabolism is integral to the mechanism of action for anti-bacterials and bactericide (e.g. turnover of peptidoglycan enables beta-lactam inhibition of transpeptidases to cause bacterial death). The slow growing bacteria of mature abscesses are less susceptible to antibiotics.

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Document control

Development of guidelines:	Dr Chris Durojaiye, Dr Ravi Kothari, Kayleigh Lehal, Dr Peter Slovak
Consultation with:	Infectious Diseases and OPAT Consultant, Lead Antimicrobial Pharmacist, Microbiology Consultant, Radiology Consultant
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Key contacts:	Dr Peter Slovak, Microbiology Consultant p.slovak@nhs.net Kayleigh Lehal, Lead Antimicrobial Pharmacist kayleigh.lehal@nhs.net