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Consensus document on controversial issues for the treatment of infections of the central nervous system: bacterial brain abscesses

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SUMMARY

Background: Bacterial brain abscesses remain a serious central nervous system problem despite advances in neurosurgical, neuroimaging, and microbiological techniques and the availability of new antibiotics. The successful treatment of brain abscesses requires surgery, appropriate antibiotic therapy, and eradication of the primary source; nevertheless many controversial issues on the management of this serious infection remain unresolved.

Controversial issues: The aim of this GISIG (Gruppo Italiano di Studio sulle Infezioni Gravi) working group – a panel of multidisciplinary experts – was to define recommendations for some controversial issues using an evidence-based and analytical approach. The controversial issues were: (1) Which patients with bacterial brain abscesses can be managed safely using medical treatment alone? (1a) What is the efficacy in terms of outcome, tolerability, cost/efficacy, and quality of life of the different antibiotic regimens used to treat bacterial cerebral abscesses? (1b) Which antibiotics have the best pharmacokinetics and/or tissue penetration of brain and/or brain abscess? 2) What is the best surgical approach in terms of outcome in managing bacterial brain abscesses? Results are presented and discussed in detail.

Methods: A systematic literature search using the MEDLINE database for the period 1988 to 2008 of randomized controlled trials and/or non-randomized studies was performed. A matrix was created to extract evidence from original studies using the CONSORT method to evaluate randomized clinical trials and the Newcastle–Ottawa Quality Assessment Scale for case–control studies, longitudinal cohorts, and retrospective studies. The GRADE method for grading quality of evidence and strength of recommendation was applied.

1. Introduction

Brain abscesses are focal suppurative processes in the brain parenchyma. They begin as localized areas of cerebritis and develop into a collection of pus surrounded by a well-vascularized capsule within approximately 14 days.[1]

Brain abscesses may have 'exogenous origins' when lesions are caused by skull trauma or surgery or 'endogenous origins' when they originate from infections of the continuous structures (e.g., otitis media, sinusitis, mastoiditis, dental infections), meningitis, or as a

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result of hematogenous spread from a remote site (e.g., infective endocarditis, cyanotic congenital heart diseases, pulmonary infections). Sometimes the origin of the abscess is not found and it remains of 'unknown origin'. Clinical signs of brain abscesses depend on their origin and location. The most frequent symptoms include headache, nausea and vomiting, focal neurological deficits, mental alteration, and fever. The symptoms of infections are not obvious and fever is not always present, occurring in 24–70% of cases.[2,3]

Despite modern neuro-imaging and neurosurgical techniques, including stereotactic brain biopsy and aspiration, better culture techniques, and new antibiotics, brain abscesses remain a serious central nervous system (CNS) problem, which can cause severe disability or even death, especially if misdiagnosed or managed improperly.[4–6] The successful treatment of brain abscesses requires surgery, appropriate antibiotic therapy, and eradication of the primary source. Surgical management aims to quickly reduce increased intracranial pressure, confirm diagnosis, and obtain pus for microbiological diagnosis in order to enhance the efficacy of antibiotic therapy and to avoid iatrogenic spread of the infection into the ventricles.[7]

However, total recovery using medical treatment alone is possible in selected patients with brain abscesses,[2,6,8] and this option is very attractive in many cases. Antibiotics are always necessary to manage cerebral abscesses, either alone or associated with surgical intervention. In most cases, antibiotics will be commenced before the infecting organism(s) and their sensitivities are known, and are continued either empirically or on the basis of the sensitivity profile of the infecting organism for a long period of time.

Therefore, an 'ideal' antibiotic regimen should include antibiotics active against the suspected or proven infecting flora, which can penetrate the brain tissue and intracranial pus with a good long-term safety profile and be administrable both intravenously and orally.

There are presently no guidelines for the management of cerebral abscesses and many controversial issues remain unresolved, including the selection of patients who can be treated conservatively, the best surgical approach, the most appropriate antibiotic regimens in terms of drug choice, route and time of administration, the role of new antibiotics, the efficacy of local administration of antibiotics, the role of antibiotic prophylaxis, and the appropriate use of corticosteroid therapy.

From these controversial issues, we have tried to formulate specific research questions regarding patients who can be treated solely with medical treatment, the choice of the most effective antibiotic regimens in terms of activity and penetration of the brain tissue, and the best choice of surgery.

2. Objectives

To find the effects (both detrimental and beneficial), from the best available evidence, of different management strategies in patients with cerebral abscesses.

3. Methods

3.1. Controversial issues

The Gruppo Italiano di Studio sulle Infezioni Gravi (GISIG) is a nationwide group of Italian experts on the diagnostic and therapeutic management of patients affected by serious healthcare-associated infections. Six experts were selected on the basis of their personal curricula to take part in the GISIG working group on central nervous system (CNS) infections. Among CNS infections the panel chose to consider the brain abscess. Subsequently, during two workshop meetings held in Milan, Italy, the panel restricted its work to the four following controversial issues:

Question 1: Which patients with bacterial brain abscesses can be managed safely using only medical treatment?
Question 1a: What is the efficacy in terms of outcome, tolerability, cost/efficiency, and quality of life of the different antibiotic regimens used to treat bacterial cerebral abscesses?
Question 1b: Which antibiotics have the best pharmacokinetics and/or tissue penetration of brain tissue and/or brain abscess?
Question 2: What is the best surgical approach in terms of outcome in managing bacterial brain abscesses?

3.2. Literature search and study selection

A MEDLINE/EMBASE search was made.

3.3. Research strategy question 1

'Brain abscess/therapy' [MAJR] AND 'anti-bacterial agents' [MAJR] AND (('1' [PDat]: '2008/06/30' [PDat])): retrieved 114, of which 11 were reviews. 'Brain abscess/drug therapy' [MeSH] AND 'brain abscess/surgery' [MeSH] NOT tuberculosis (no limits): retrieved 194, of which 28 were reviews. 'Brain abscess/drug therapy' [MAJR] AND 'brain abscess/surgery' [MAJR] NOT tuberculosis: retrieved 17, of which five were reviews. This was limited to the last 30 years and written in English.

3.4. Inclusion criteria question 1

Patients of all ages, with non-tuberculosis bacterial cerebral abscesses of any origin (spontaneous or post-surgical), singular or multiple, of any size, occurring in the last 30 years were included.

- Operations: any treatment to cure bacterial cerebral abscess.
- Comparison: any comparison between antibiotic regimes vs. any surgical approach used to treat bacterial cerebral abscess.
- Outcome: survival, follow-up results, quality of life, time for the reduction of abscesses, frequency of recurrence.
- Design: publications in English, randomized controlled trials (RCTs), and any comparative designs declared to be so or which are shown from research within the last 30 years (Fig. 1).

3.5. Research strategy question 1a

'Brain abscess/therapy' [MAJR] AND 'anti-bacterial agents' [MAJR] NOT tuberculosis (chronological limit: from 01/01/1978 to 31/08/2008): retrieved 95, of which nine were reviews. (('Brain' OR 'intra-cerebral' OR 'intracranial' OR 'cerebral') AND 'abscess') AND 'therapy' AND 'anti-bacterial agents' NOT tuberculosis (within the last 30 years in English): retrieved 342, of which 74 were reviews; linezolid and brain abscess 15; linezolid and ventriculitis

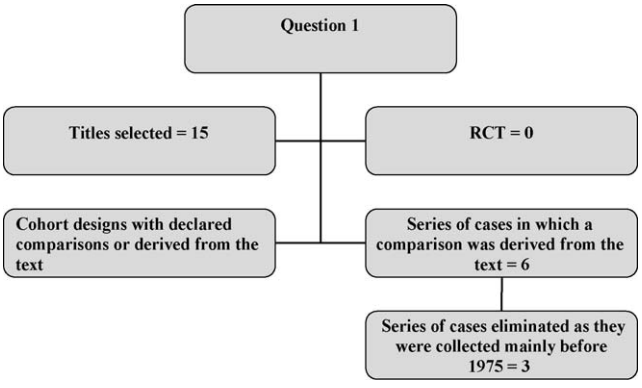

Figure 1. Studies included in the final analysis.

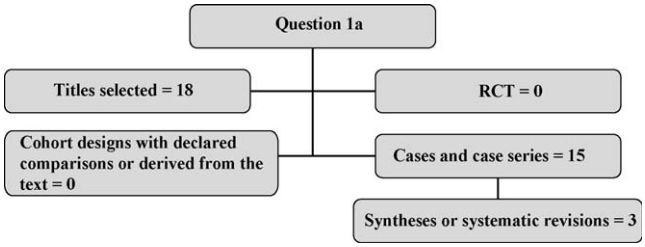

Figure 2. Studies included in the final analysis.

11, of which one was a review; daptomycin and brain abscess 0; daptomycin and ventriculitis 3; tigecycline and brain abscess 0.

3.6. Inclusion criteria question 1a

Patients of any age with non-tuberculosis bacterial cerebral abscesses of any origin (spontaneous or post-surgical), singular or multiple, of any size, occurring in the last 30 years were included.

- Operations: any treatment to cure bacterial cerebral abscess.
- Comparison: any comparison between antibiotic regimes vs. any surgical approach used to treat bacterial cerebral abscess.
- Outcome: survival, follow-up results, quality of life, time for the reduction of abscesses, frequency of recurrence.
- Design: publications in English, RCTs, and any comparative designs declared to be so or which are shown from research within the last 30 years (Fig. 2).

3.7. Research strategy question 1b

'Anti-bacterial agents' AND 'pharmacokinetics' AND ('cerebrospinal fluid' OR 'brain abscess') NOT tuberculosis (within the last 30 years and in English): retrieved 95, of which nine were reviews. ('brain abscess' [MeSH Terms]) AND ('antibiotic penetration'): retrieved 23, of which seven were reviews.

3.8. Inclusion criteria question 1b

Patients of any age with non-tuberculosis bacterial cerebral abscess of any origin (spontaneous or post-surgical), singular or multiple, of any size, occurring in the last 30 years were included.

- Operations: any treatment to cure bacterial cerebral abscess.
- Comparison: any comparison between pharmacokinetics of any antibiotics on brain tissue or cerebral abscess.
- Outcome: therapeutic concentration evaluated on cerebral tissue or cerebral abscess.
- Design: publications in English, RCTs, and any comparative designs declared to be so or which are shown from research (Fig. 3).

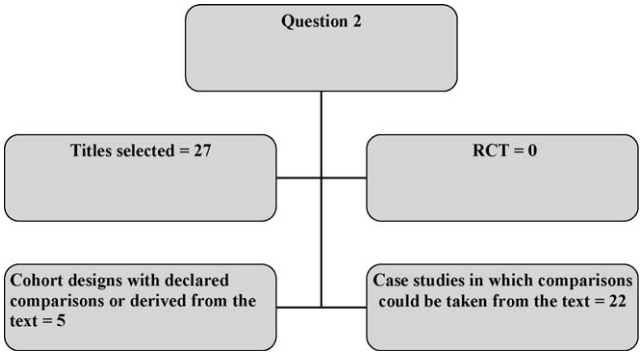

Figure 4. Studies included in the final analysis.

3.9. Research strategy question 2

'Brain abscess/surgery' [MAJR] AND (('1' [PDat]: '2008/06/30' [PDat])): retrieved 392, of which 35 were reviews. 'Brain abscess' AND 'surgery' AND (('2008/07/01' [PDat]: '2008/09/20' [PDat])): retrieved nine, of which two were reviews. 'Brain abscess/surgery' [MAJR] NOT tuberculosis: retrieved 199, of which 29 were reviews. (('Brain' OR 'intra-cerebral' OR 'intracranial' OR 'cerebral') AND 'abscess') AND ('surgical treatment' OR 'operative surgical procedures') NOT tuberculosis: retrieved seven.

3.10. Inclusion criteria question 2

Patients of any age with non-tuberculosis bacterial cerebral abscess of any origin (spontaneous or post-surgical), singular or multiple, of any size, occurring in the last 30 years were included.

- Operations: any surgical treatment to cure bacterial cerebral abscess.
- Comparison: any comparison between any surgical approach used to treat cerebral abscess.
- Outcome: survival, follow-up results, quality of life, time for the reduction of abscesses, frequency of recurrence.
- Design: publications in English, RCTs, and any comparative designs declared to be so or which are shown from research within the last 30 years (Fig. 4).

3.11. Classification and evaluation of selected evidence

No RCTs were found. For questions 1 (antibiotic therapy compared with surgical therapy) and 2 (comparisons between different surgical approaches), data were present only in retrospective cohort studies or descriptive case series planned to underline the clinical characteristics of people with cerebral abscess and to determine factors related to the outcome. A matrix

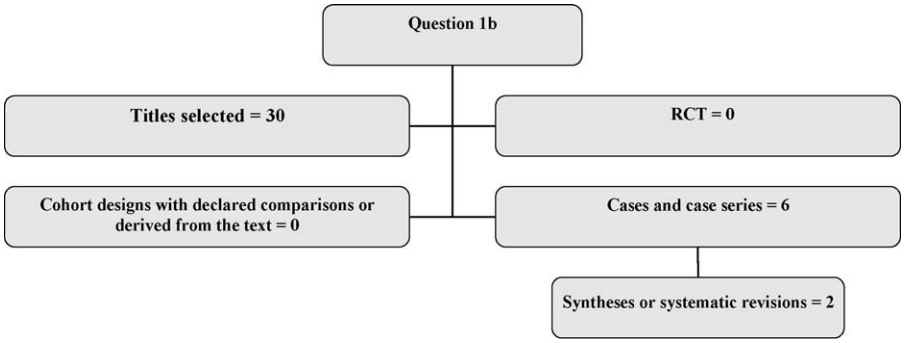

Figure 3. Studies included in the final analysis.

was made to extract evidence from individual original studies using the Newcastle–Ottawa Quality Assessment Scale for case-control studies and longitudinal cohorts and retrospective studies with comparative evaluations. The original data from case studies were made homogeneous using a predefined format, both for cases reports and series of reported cases. For questions 1a (comparison between different antibiotic regimens) and 1b (comparison between pharmacokinetics/pharmacodynamics of different antibiotics), no comparative studies were found. For the first question, we chose to consider papers where the antibiotic regimens were reported and the impact on outcome was clear. For the second question, we looked at papers where the antibiotic penetration into the brain tissue or brain pus was investigated.

We were not able to precisely separate research for each of these categories given that none of the categories were treated prospectively or in a controlled manner. We only had retrospective cohorts of case series, and any information on individual cases was within these case studies. Therefore, these publications were often used to answer different types of questions.

In the discussion section, to assign the strength to the level of the recommendations, a methodology adapted from GRADE Working Group was applied. The details of the methodology are reported in this supplement.[9]

4. Results

4.1. Question 1: Which patients with bacterial brain abscesses can be managed safely using only medical treatment?

Bacterial brain abscess is essentially a surgical pathology and most cases arise from neurosurgery.

In many of these case series, a variable number of patients were treated successfully with medical therapy alone. Xiao et al.[6] retrospectively analyzed the medical records of patients with brain abscess treated over a period of 17 years (1986–2002) to determine the factors related to outcome. One hundred and fifteen patients (65%) underwent surgical decompression of the abscess, while 63 (35%) received only medical treatment (38 had relatively small lesions and 25 had a larger abscess, with significant surgical risk). Unfavorable outcomes included death (25%), vegetative status (5%), and responding but remaining totally dependent during daily life (8%). In the surgically treated patients, 27–38% of patients had an unfavorable outcome, depending on the type of surgical approach, whereas 41% ($n = 26$) of medically treated patients died. Considering patients with small lesions, 24/38 (65%) patients had favorable outcomes compared with only 3/25 (12%) patients at significant surgical risk. Multivariate analysis showed that the factors predictive of outcome were: initial Glasgow Coma Score (GCS), immunodeficiency, and absence of underlying diseases, but not type of treatment.

Tseng and Tseng[10] retrospectively analyzed the medical records of 142 patients with intracranial abscess observed between 1986 and 2004 to identify clinical, biological, and therapeutic characteristics important for outcome. The cases had the same structure as the previous study and the time-scale was largely similar. The authors found no association between outcome and treatment type. Six out of 20 (30%) medically treated patients had an unfavorable outcome compared with 31/122 (25.4%) surgically treated patients. Multivariate logistic regression confirmed that being male, having a GCS >12, and being sepsis-free were the main factors for a favorable outcome.

Hakan et al.[11] reviewed 96 consecutive cases treated over 13 years (1988–2001) in order to determine the current characteristics and the other factors important for the outcome of brain abscess. Surgery was performed in 90% of patients (lesions were aspirated in 84% and excised in 16%), whereas 10 patients (10%) were treated non-surgically. The choice of treatment was based on the size of the abscess (8–29 mm in the group treated with medical therapy alone compared with 20–35 mm in the excision group and 30–69 mm in the aspiration group). The recovery ratios were 90%, 85%, and 47%, respectively. The initial neurological grade (GCS < 12), the size of the abscess, meningismus, high fever ($>38.5\ ^\circ C$), and leukocytosis ($>20 \times 10^9$/l), were the factors mostly influencing mortality and sequelae.

In documenting changes in the characteristics and management of brain abscesses, Mampalan and Rosemblum[12] reviewed 107 consecutive cases at the University of California, San Francisco over 17 years (1970–1986). Ninety-six of these patients were treated: 79 surgically (46 excision, 33 aspiration) and 17 with medical therapy alone. The mortality and reoperation rates in the three treatment groups were not significantly different. The duration of intravenous (iv) antibiotic therapy was shorter in the excision group than in the aspiration and non-surgical groups. Factors influencing outcome were the initial neurological grade and the size of the abscess. The average diameter of non-surgically treated abscesses was 2 cm (range 0.75–4.5 cm). Both patients who failed medical therapy had abscesses larger than 3 cm in diameter.

Over a period of 4 years (1984–1987), Leys et al.[8] selected a population of consecutively treated patients with similar initial prognoses in order to compare the results of the three procedures: medical treatment alone, aspiration, and excision. The choice of treatment was at the discretion of the neurologist or neurosurgeon in charge of the patient and based on perceived best procedure. From the initial 79 cases, patients with multiple focal intracranial infections (21 cases), focal infections located in the posterior fossa (six cases), and lesions smaller than 1 cm or larger than 5 cm (four patients) were withdrawn; 56 cases with a single hemisphere focal intracranial infection of 1–5 cm were retained. There were no statistical differences in number of deaths (after months 1, 3, and 12) or in social outcome among the three groups. Sequelae (seizures and focal deficits) were more severe in surgically treated patients, and in these patients the causative organism was more often isolated and the hospital stay was shorter.

Qureshi et al.[13] selected 66 patients with brain abscess treated over 12 years (1987–1998) to clarify the clinical status of brain abscess and to assess predictors of mortality in these patients. Management was conservative in 27 (42%) patients and surgical in 38 (58%). Logistic regression identified a distant metastatic focus as the sole independent predictor of mortality. Conservative treatment, coma at presentation, duration of symptoms <2 weeks, multiple abscesses, steroid therapy, age, and sex were not predictive factors.

In order to report their experience of managing brain abscesses in Taiwan, Wong et al.[3] considered 83 patients of different ages, ranging from neonates to those aged 15 years. Fifteen (18.1%) patients were treated with medical therapy alone, whereas 68 (81.9%) were treated with antibiotics and surgery. Deaths were 40% and 14.7%, respectively, and patients lost to follow-up 33.3% and 19.1%, respectively; however no statistical analysis of the differences was made.

Carpenter et al.[2] reported 49 cases of cerebral abscess; all except five were treated surgically. Surgical intervention was considered unnecessary (criteria not reported) in these five patients, all of whom recovered well.

To compare clinical, electroencephalographic, and computed tomography (CT) results of different therapeutic approaches (excision, puncture, and medical treatment), over a period of 3 years Russeaux et al.[14] selected 31 cases of hemispheric brain abscess. The patients were divided into three groups according to their treatment, and on the basis of their initial neurological status were divided into four stages of increasing gravity. No apparent

differences were observed in the initial clinical condition of the three groups. Only 1/15 patients in the non-surgically treated group died; the survivors completely recovered or had moderate disabilities. There were no deaths among the four patients treated by puncture and antibiotic therapy and all patients totally recovered, whereas among the patients treated by excision, 2/12 died and two had important neurological deficits. The differences in terms of outcome were more definite between the groups treated medically and by puncture, but no statistical analysis was made to compare these differences. The medically treated patients were in poor initial neurological condition, but the abscesses were smaller. The criteria for the choice of the different therapeutic approaches were not clear.

Schliamser et al.[15] reviewed 54 consecutive adult patients with cerebral abscess. Thirty-three patients was treated by surgery plus antibiotics and 14 by medical treatment alone; seven patients died as a result of missed diagnosis, the abscess was found at autopsy. Indications for conservative therapy were multiple abscesses, the site in a high-risk region of the brain, and concomitant endocarditis. Twenty-three of the 33 (69.6%) patients who underwent surgery died or had severe sequelae vs. 6/14 (42.8%) of patients treated with medical therapy alone. No statistical analysis for the different therapies was made.

Ferriero et al.[16] reviewed 17 patients, aged 4 months to 18 years, of whom eight were treated medically and nine received surgery. All but one patient treated with medical therapy alone fully recovered (one patient died of causes not related to the cerebral abscess), whereas of the patients treated surgically, one died and four had neurological deficits. The authors concluded that antibiotic therapy without surgical intervention is the treatment of choice for patients with positive identification of organisms. Nevertheless, medically treated patients were in better initial condition, the criteria for the choice of the different therapeutic approaches were not reported, and a statistical analysis of the differences was not made.

Chun et al.[17] reviewed 45 consecutive patients admitted to eight hospitals in Louisville, to evaluate the efficacy of various diagnostic and therapeutic approaches. Forty-one patients were treated for brain abscess, of whom 31 (75.6%) received both surgical and antimicrobial therapy and 10 (24.4%) antimicrobial therapy alone. Of the surgically treated patients, 10/31 (32.2%) died and 11/31 (35.4%) had moderate or severe neurological sequelae compared with 4/10 (40%) and 1/10 (10%) patients treated with antibiotics alone. The higher mortality was significantly associated with older age, male sex, altered sensorium on admission, and a pulmonary source as a predisposing factor, but not with surgical operation, the type of surgery, or the appropriateness of antibiotic treatment in terms of dosage, route of administration and sensitivity of the organism. The patients received a total of 27 different antibiotics, and although patient characteristics on admission were similar, the rationale for treating with antibiotics alone was not clearly stated.

4.2. Question 1a: What is the efficacy in terms of outcome, tolerability, cost/efficiency, and quality of life of the different antibiotic regimens used in the treatment of bacterial cerebral abscesses?

Often antibiotic therapy is started empirically, before a possible surgical operation and in cases of medical treatment alone, without a microbiological diagnosis, and is also continued empirically. The first element to consider in the choice of antibiotic regimen is therefore the etiology of the bacterial cerebral abscess.

4.3. Bacteriology of the cerebral abscess

The bacterial etiology of cerebral abscess is largely dependent on the origin of the abscess itself. Many series of cases measure the frequency of bacterial isolation, but not all correlate the isolation with the origin of the abscess. Generally, the most frequent isolated microorganisms are Gram-positive cocci (e.g., streptococci and staphylococci) and anaerobes, even if Gram-negative bacteria are also present. Often there is mixed bacterial flora (Table 1). In particular, post-traumatic and post-surgical abscesses frequently have a staphylococcal etiology, although Gram-negative aerobic bacilli have also been reported.[18,19]

Dashti et al.[18] retrospectively reviewed the cases of post-operative infection after cranial surgery over 10 years (1997–2007) focusing on patients who required a re-operation to control the infection, to determine the rate of these infections. They considered 16 540 cranial operations performed by 25 neurosurgeons, including 82 (0.5%) corresponding to 50 patients, performed to treat a post-operative infection. Brain abscesses accounted for 10 (20%) of these infections. The most common organism was *Staphylococcus spp* (10 methicillin-susceptible *Staphylococcus aureus* (MSSA), two methicillin-resistant *Staphylococcus aureus* (MRSA), six coagulase-negative staphylococci (CoNS)), isolated from 18 (36%) patients.

McLelland and Hall[20] wanted to definitively establish the incidence of post-operative CNS infections in patients undergoing neurosurgical procedures and the potential risk factors. They analyzed 2111 elective procedures performed by a single surgeon between February 1991 and December 2005. Of the 1587 cranial operations, 14 (0.8%) were complicated by infection. The most common causative organism was *S. aureus* (six cases, 42.9%); none of these strains were methicillin-resistant.

Tekkök and Erbengy[21] cultured four *S. aureus* isolates from 11 post-traumatic brain abscesses.

In a case series of 96 children with cerebral abscess, Domingo and Peter[22] reported 26 cases of implantation abscesses secondary to trauma where the most common organism isolated was *S. aureus*.

Schliamser et al.[15] isolated 19 staphylococci (12 *S. aureus*, seven *S. epidermidis*) from 24 adults with post-traumatic cerebral abscesses.

Sichizya et al.[19] reviewed 121 patients treated at the Groote-Schuur Hospital (Cape Town, South Africa) of whom 49% had abscesses associated with implantation by trauma. *S. aureus*, CoNS and β-hemolytic streptococci were the three most prevalent pathogens. The periodontal/sinusitis origin of abscess was frequently associated with *Streptococcus milleri*.[19,22]

Otogenic abscesses almost invariably yield a mixed flora, including anaerobes and various streptococci, but also *Enterobacteriaceae* (especially *Proteus mirabilis*) and/or *Pseudomonas aeruginosa*.[7,19,20,23,24]

The organisms predominantly associated with metastatic or cryptogenic abscesses are *Streptococcus spp*. In these cases, abscesses frequently complicate episodes of septicemia, in which etiological agents can be isolated from blood cultures.[2,7,12,13,23]

Table 1 lists the principle microorganisms isolated from cerebral abscesses in the different case series.

In 2007 The Cochrane Collaboration[25] published a review to evaluate the effectiveness of antibiotic regimens for treating brain abscess in people with cyanotic congenital heart disease. The studies included were all RCTs that reported clinically meaningful outcomes and presented results on intention to treat, irrespective of blinding, publication status, and language. There were no studies that met the inclusion criteria.

In 2000, the 'Infection in Neurosurgery Working Party' of the British Society of Antimicrobial Chemotherapy (BSAC)[7] published a review providing recommendations on the management of bacterial brain abscesses based on information from the review process together with the experience and knowledge of its members. The recommendations suggested a combination of

Table 1
Frequency of the principle microorganisms isolated from cerebral abscess from different case series

Microorganism	Hirsh 1983[69]	Schliamser 1988[15]	Jansson 2004[26]	Wong 1989[3]	Seydoux 1992[50]	Tekkök 1992[21]	Lunardi 1993[48]	Domingo 1994[23]
Gram-positive bacteria				13				
Streptococci	6	10	19	9	18	5	40	12
Staphylococcus aureus	1	19	1	2	3	19	16	17
CoNS	1	9	2	2	1			
Other		Enterococci 5						
Gram-negative bacilli				12				
Proteus spp	2					5		12
Klebsiella spp		1				1	3	
Enterobacter spp		1				1		
Escherichia coli		4						
Serratia spp								
Pseudomonas spp						1	5	
Anaerobes				2				
Peptostreptococcus	1	11	4	2	3	5		3
Bacteroides spp			1		7		14	6
Fusobacterium spp		3			14			
Clostridium spp	1							
Bacillus fragilis		3			5			

Microorganism	Kao 2003[70]	Sichizya 2005[19]	Xiao 2005[6]	Hakan 2006[11]	Menhaz 2006[49]	Tseng 2006[10]	Carpenter 2007[2]	Cavuşoglu 2008[4]
Gram-positive bacteria						27		
Streptococci	7	46	14	18	11		12	8
Staphylococcus aureus	2	24	5	17			8	6 MRSA
CoNS		14	1		1			3 MRSE
Other		Enterococci 6						7 *S. pneumoniae*
Gram-negative bacilli						21		
Proteus spp	4	13	2	12				
Klebsiella spp	1	4	3	2				1
Enterobacter spp		7	2	2				1
Escherichia coli		6	1		1			
Serratia spp	1		2					
Pseudomonas spp		3	1	3	1			2
Anaerobes						24	8	
Peptostreptococcus	2	4	5	10	1			2
Bacteroides spp	2	7	4	4				
Fusobacterium spp	1		1	2				
Clostridium spp		8	1					
Propionibacterium spp		4						3

CoNS, coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*.

third-generation cephalosporin and metronidazole as first-line empirical therapy for patients with sinugenic or odontogenic brain abscesses, a combination of ampicillin, metronidazole and either ceftazidime or gentamicin for those with otogenic abscesses, flucloxacillin or third-generation cephalosporin for abscesses secondary to trauma and, depending on the presumptive source, benzylpenicillin or third-generation cephalosporin ± metronidazole for patients with metastatic abscesses.

Jansson et al.[26] retrospectively evaluated 66 patients treated with cefotaxime over a period of 10 years using a prospectively designed protocol. Sixty-two of these patients received additional metronidazole and 53 underwent surgery. The dose of cefotaxime and metronidazole recommended for adults with normal renal function was 3 g three times daily and 1 g once daily, respectively, after a loading dose of 4 g and 1.5 g, respectively. The duration of treatment was left to the discretion of the physician. Reversible adverse reactions, which occurred in 57% of patients, were the most common reasons for withdrawing the cefotaxime. The median duration of parenteral antibiotic treatment was 36 days in patients treated with total excision, 36.5 days in those treated with sub-total excision, 41 days in aspiration, 22 days in evacuation of subdural empyema, and 46 days in patients treated with antibiotics alone. The total durations of antibiotic treatment, including oral administration performed in 71% of patients, were 46, 114, 84.5, 49, and 84 days, respectively. In 25 cultures from patients treated for ≤3 days there was growth in 21 (84%) compared with 7/22 (32%) from patients treated for >3 days ($p < 0.001$).

Sjölin et al.[27] studied 15 consecutive patients with cerebral abscess over a period of 3 years (1986–1989), treated with cefotaxime (3 g three times daily) plus metronidazole (0.5 g three times daily) and surgical excision, to prospectively study clinical and bacteriological outcomes. All patients survived and there was no recurrence within 1 year. The duration of cefotaxime plus metronidazole therapy was 22 ± 6 days. Eleven of 15 patients received subsequent oral regimens, which was mainly trimethoprim–sulfamethoxazole-based. Adverse reversible side effects leading to the discontinuation of therapy were observed in nine (60%) patients. Cultures of specimens from three of nine patients treated for >24 h were positive compared with positive cultures for all six specimens obtained from patients treated for <24 h ($p = 0.017$); anaerobic bacteria were isolated from two of three patients given two doses of metronidazole or fewer compared with none of 12 patients given three doses or more.

Kowlessar et al.[23] described 22 patients observed over a period of 8 years (1996–2004) in order to evaluate the efficacy of cefotaxime in the management of brain abscess caused by *S. milleri*. The patients were divided into two groups: group A (15 patients with GCS >12) received 2 g cefotaxime 4 times daily plus metronidazole 1.5 mg 3 times daily iv for 4 weeks. Intravenous benzylpenicillin was added in four patients and in five patients the therapy with oral antibiotics was prolonged based on neurological deterioration and incomplete resolution on imaging. Group B (four patients with GCS <12 and three patients with GCS = 14, but considered at risk of clinical deterioration) received cefotaxime six times a day plus metronidazole and rifampin 600 mg twice daily

orally for 4–6 weeks. Three patients in this group had additional iv benzylpenicillin and three had additional switch therapy. All patients underwent surgery. Eighteen patients (82%) had a good outcome after 6 months, resuming normal life or having minor deficits. There were no significant differences in terms of outcome between the two groups.

Akova et al.[28] examined the efficacy and safety of sulbactam/ampicillin (50 and 100 mg/kg/day, respectively in four divided doses) in 21 patients with a diagnosis of cerebral abscess enrolled over a period of 4 years (1987–1991). Sixteen patients underwent surgery (drainage by burr hole in 12 patients and exploration by craniotomy in four patients), whereas five patients were treated with antibiotics alone. Three patients died due to causes not related to their infections. The overall success rate was 81% and did not differ in patients treated with or without surgery. The mean duration of antibiotic therapy was 48 ± 10 days, and four patients (19%) experienced mild reversible side effects that recovered after temporary cessation of the antibiotic.

Rau et al.[29] reviewed 33 cases that occurred over a period of 14 years (1986–1999) of which 23 were community-acquired and 10 were hospital-acquired (mainly post-neurosurgical) to improve the therapeutic strategies available for the management of brain abscesses caused by aerobic Gram-negative bacilli. The most prevalent pathogen isolated was *Klebsiella pneumoniae* followed by *P. aeruginosa, Escherichia coli* and *Proteus spp*, all isolated bacteria were susceptible to third-generation cephalosporins and chloramphenicol. Twenty-six patients were treated surgically and with antibiotic therapy, while seven received antibiotics alone. Seven patients died with an overall mortality of 21%, 6/16 patients treated with penicillin plus chloramphenicol and one medicated with piperacillin died compared to none of the 16 patients treated with various cephalosporins.

To compare aspiration, excision, and antibiotic treatment alone, Leys et al.[8] treated patients with ceftriaxone (2–3 g iv), pefloxacin (800 mg intramuscularly) and metronidazole (1.5 g iv), except when these antibiotics failed to be effective in vitro against the causative organisms. In these cases, thiophenicol (3–4.5 g iv) or ampicillin (8–12 g iv) or trimethoprim–sulfamethoxazole (320–1600 mg) were used.

In a review of 121 patients with surgically treated cerebral abscesses observed before 1996, Sichizya et al.[19] reported the use of empirical antibiotic regimens including benzylpenicillin, chloramphenicol, and metronidazole, replaced by third-generation cephalosporins with cloxacillin and metronidazole following the advent of third-generation cephalosporins. These regimens were changed according to bacterial isolation and sensitivity test results. The patients in the study received an average of 15 and 19 days of parenteral antibiotics for excision and aspiration, respectively. The duration of antibiotic therapy was determined by the decrease in level of the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), the diameter of the abscess on follow-up CT scans, and the temperature charts of the patient, but specific indicators were not reported.

In more recently treated cases, Tayfun (2006)[30] principally reported the use of third-generation cephalosporins and anti-anaerobic antibiotics. In cases of MRSA, vancomycin was used.

Carpenter et al.[2] reported cefotaxime and metronidazole as the most commonly used antibiotics in 37/49 (73%) patients, sometimes with the addition of benzylpenicillin, vancomycin, flucloxacillin, or gentamicin.

Javad et al.[31] reported a case of multiple brain abscesses in a renal transplant recipient that developed two days after a nephrectomy of the left transplanted kidney. No aspiration of the abscess was performed due to the patient's poor clinical condition. *P. aeruginosa* resistant to ciprofloxacin was isolated from the pleural effusion and assumed to be the cause of the brain abscess. Although sensitivity testing was not performed for cefepime, imipenem, and piperacillin/tazobactam, the patient was successfully treated with piperacillin/tazobactam 2.25 mg three times daily continued for 2 months.

Ntziora and Falagas[32] reviewed 42 cases where linezolid was used for the treatment of patients with CNS infections, of whom 11 (26%) had cerebral abscesses (excluding three patients with mycobacterial abscesses and one with aspergillosis, and including one patient with cerebritis). All patients were treated following either failure or toxicity of the first-line therapy. Of these, nine were cured or recovered considerably, one was stable, and one died due to the abscess. Collateral effects were reported in seven of the 42 patients and in two of these the treatment had to be suspended (severe anemia and myelosuppression).

Malacarne et al.[33] reported two cases of CNS infection due to methicillin-resistant *S. epidermidis* (MRSE) treated with linezolid. The first case, a woman with ventriculitis with a ventricular catheter, was successfully treated with linezolid concentrations in the cerebrospinal fluid (CSF) higher than the minimum inhibitory concentration (MIC), agreeing with other reports.[34] In the second case, a man with post-traumatic cerebral abscess, despite the high serum peak level of linezolid, it was not found in the CSF after 5 days, or in cerebral tissue removed 14 days after therapy. Unexplainably, the drug was measured in the CSF at a concentration greater than the MIC value for MRSE at day 15 and the patient clearly improved clinically.

4.4. Question 1b: Which antibiotics have the best pharmacokinetics and/or tissue penetration of brain and/or brain abscess?

Sjölin et al.[35] assessed the penetration of cefotaxime and of its active metabolite desacetyl cefotaxime in brain abscesses in eight patients. After an initial 4 g loading dose of cefotaxime, a maintenance dose of 3 g every 8 h (q8 h) was administered. After a variable number of drug doses (one to seven), brain abscess samples were collected 4–9 h after the last drug administration before surgery. Mean ± standard deviation (SD) cefotaxime and desacetyl cefotaxime concentrations in brain tissue were higher than in plasma (2.1 ± 1.6 mg/l vs. 2.0 ± 1.0 mg/l and 4.0 ± 2.2 mg/l vs. 3.9 ± 1.8 mg/l, respectively). These values, which were higher than the MIC of the bacterial isolates (range 0.02–2.0 mg/l), led the authors to suggest that both cefotaxime and its active metabolite may well penetrate the brain abscess.

Green et al.[36] investigated the penetration of ceftazidime into intra-cranial abscesses in nine patients. Variable daily drug dosages were used (0.5–2 g q8 h); the number of drug doses before tissue sampling was not indicated. Brain abscess samples were collected 1–9 h after the last drug administration before surgery. Ceftazidime concentrations in brain tissue ranged between 2.7 and 27.0 mg/l. Since no comparison with simultaneously collected plasma samples was performed, no definitive conclusion on the tissue penetration rate was reported. These values, which were higher than the MIC_{50} of most microorganisms commonly involved, led the authors to suggest that ceftazidime may penetrate brain abscesses.

In a small clinical series of 15 brain abscess patients treated with imipenem 1 g every 6–8 h, drug levels were determined in three patients who underwent abscess aspiration.[37] Brain pus trough levels ranged between 0.1 and 0.4 mg/l with a brain pus-to-plasma trough concentration ratio ranging between 0.05 and 0.13. These values were considered above the MIC_{90} of several Gram-positive and anaerobic bacterial isolates.

Mindermann et al.[38] assessed the penetration of fusidic acid into human brain tumors and/or into the perifocal cortex in six neurosurgical patients after a single 500 mg iv dose. Brain tissue samples were collected 50–135 min after drug administration

before surgery. Fusidic acid concentrations in brain tissue ranged between <0.25 and 9.04 mg/l with a brain tissue-to-plasma concentration ratio of 0.01–0.1. These values were on average several-fold higher than the MIC of staphylococci, so that the authors suggested that fusidic acid may well penetrate brain tissue.

4.5. Question 2: What is the best surgical approach in terms of outcome in managing bacterial brain abscess?

Mampalan and Rosemblum[12] in their review of 102 cases over a period of 17 years, grouped patients according to treatment. Forty-six underwent craniotomy and the excision of the brain abscess and 33 underwent aspiration of a single lesion through a craniotomy or burr hole; however the reasons for the different approaches were not reported. Mortality (8.7% in the excision group and 6.1% in the aspiration group) and reoperation rates (8.7% and 15.2%, respectively) in the two groups were not statistically different. Long-term follow-up was available for 48 patients. Seizures occurred in 10% of patients without significant differences between the treatment groups.

Xiao et al. [6] retrospectively analyzing 178 patients over a period of 17 years, reported surgical decompression of the abscess in 115 patients (65%). The initial procedures included drainage in 73 patients, aspiration in 13 (who underwent stereotactic techniques because the abscess was either deep or small), and excision in 29. Thirteen patients required one or more reoperations, 10 of whom were in the drainage group. There were no significant differences in percentage of favorable outcome in the three groups: 73%, 72%, and 62%, respectively. However, the mortality rate was lowest in patients undergoing excision (3.4%), followed by drainage (18%) and aspiration (31%).

Tseng and Tseng[10] retrospectively considered 142 patients of whom 122 (85.9%) underwent surgical treatment. 74 had drainages by craniotomy, 14 had excision and 34 had stereotactic aspirations. The drainage or excision by craniotomy was performed for larger (> 2.5 cm) or superficial brain abscesses. The stereotactic aspirations were performed in patients with a brain stem abscess, a small and deep seated abscess, or multiple small abscesses. There was no association between favorable outcome and treatment modalities.

Padney et al.,[39] to investigate whether cerebral abscesses are better managed by excision or aspiration, evaluated the management of cerebral abscesses in 82 children over a period of 10 years (1995–2004). Primary excision was performed in 66 patients (60%) and aspiration in 16 patients (40%). The indications for primary aspiration included a poorly formed abscess wall, a poor GCS at presentation, rapid neurological deterioration, and severe anemia requiring preoperative correction. In five patients who underwent aspiration as first treatment, the residual abscess was electively excised. There were no deaths among patients who underwent excision (four in the aspiration group; $p = 0.001$), fewer recurrences (12.6% vs. 54.5%; $p = 0.003$), and less need of repeated procedures (9.8% vs. 45.4%; $p = 0.008$). However, patients who underwent primary aspiration were in a poorer condition at presentation.

Renier et al.,[40] to correlate clinical, bacteriological, radiological, and therapeutic features of neonatal brain abscesses in order to identify possible prognostic criteria, considered 30 newborn infants with cerebral abscesses treated over a period of 12 years (1975–1987). The abscesses were treated with aspiration and antibiotics in 25 cases and by antibiotics alone in five. The indications for the different approaches were not reported. A series of 36 older children with brain abscess treated in the same institution over the same period was considered to detect differences in prognostic factors between the two groups. Early aspiration (100% survival rate in children aspirated before day 30 of life vs. 70% in children aspirated later than day 30 of life) of the abscess was the only significant factor influencing survival in this series. Early aspiration together with the absence of initial seizures, sterile CSF, and normal ventricles on CT scan, appeared to be factors leading to a better prognosis in terms of epilepsy and mental sequelae.

Mamelak et al. [41] developed an algorithmic rationale and a course of treatment for patients with multiple brain abscesses, analyzing 16 patients with multiple brain abscesses from a total of 131 patients with brain abscess over 16 years (1976–1992). All abscesses >2.5 cm in diameter or causing significant mass effect were excised or stereotactically aspirated. The choice of surgical approach was not critical, even though the stereotactic approach may have been useful for deep-seated lesions or multiple hemispheric abscesses, while aspiration by craniotomy or excision in cases of posterior fossa abscesses. Abscesses in the cerebritis phase could be approached with medical treatment alone. When a surgical approach was chosen, antibiotics were started after withdrawal of pus and were continued for a minimum of 6 weeks (typically 8 weeks). Using this systematic approach, the mortality rate was 6%, while the morbidity of further and multiple procedures was not observed.

Kocherry et al.,[42] to evaluate the efficacy of stereotactic aspiration in managing deep-seated and/or intracranial abscesses in the eloquent region, reported 22 cases treated over a period of 6 years (1995–2001). All patients received iv antibiotics for a minimum of 4 weeks or longer, and in cases of multiple abscesses (five patients) the larger ones were treated with stereotactic aspiration while the smaller ones were medically treated. There were no deaths; early recurrence requiring repeated aspiration was diagnosed in five patients, minor hemorrhages were noted in three patients, and one patient developed ventriculitis requiring a shunt insertion, but there were no late recurrences.

Moss et al.[43] reviewed 54 consecutive cases observed between 1958 and 1987 to compare changes in surgical treatment and outcome of cerebral abscesses in children. Forty-eight children had surgical operations (12 aspirations, 14 open evacuations, and 22 resections). The mortality rate in the aspiration group was twice that of the evacuation or resection group (17.7% and 9%, respectively), but no indications for the different approaches were reported and no stratification of groups or statistical analyses was made.

Erşain et al.[44] reviewed 44 consecutive patients aged between 1 month and 16 years. Total excision was accomplished in 22 patients, three patients underwent needle aspiration, and drainage was performed in 13, but indications for choosing the different surgical approaches were not reported. The mortality rates associated with the different modes of surgical treatment were not significantly different from each other.

Cavuşoglu et al.,[4] in their review of 51 patients, reported completed excision for 10 patients, stereotactic aspiration for nine, and aspiration from a single burr hole for the remaining 32 patients. Indications for stereotactic aspiration were multiple or deep-seated abscesses or abscesses located in the eloquent areas of the brain. Post-traumatic, cerebral, post-operative, or poor response to repetitive aspiration abscesses underwent complete excision. No comparisons were made between the different surgical approaches, but the choice of surgical approach was considered not critical and should be dictated by surgeon preference and the ability of the patient to tolerate each type of surgical procedure.

Srinivasan et al.[45] reported 37 cases of capsulated brain abscess treated with elective aspiration through a burr hole and intracavity application of antibiotics on alternative days until two consecutive negative aspirations were obtained. A combination of

furosemide and systemic antibiotics was also given. The population was in good initial neurological condition with 30 cases (81.1%) having a GCS of 12–15; the mortality rate was 2.7% and no new neurological deficits occurred after surgery.

Gupta et al.[46] reviewed 80 cases of brain abscess of which 74 were treated surgically: 28 underwent aspiration followed by excision, 25 were treated by aspiration(s) alone, and 21 by direct excision. Only one patient who underwent excision died compared with eight and three managed with repeated aspiration and medical treatment alone, respectively. Nevertheless, no indications for the different approaches and no stratifications for GCS level at presentation into the different groups of treatment were reported.

Barlas et al.[47] reported 21 patients who underwent stereotactic surgical drainage and an 8-week iv antibiotic regimen. Eleven of these 21 patients had multiple (from two to nine) abscesses, all deep-seated. Four patients had an abscess >2.5 cm in diameter, the largest being 4.4 cm. Except for three patients who had residual mild hemiparesis and one patient recovering from ataxia, all patients irrespective of small or large size, solitary or multiple, superficial or deep-seated abscesses, made a complete neurological recovery.

Huda et al. [24] reported 40 patients with Gram-negative bacillary brain abscesses managed by total excision ($n = 31$), aspiration ($n = 5$), and aspiration followed by excision ($n = 4$), but no comparison in terms of outcome was made between groups.

Domingo and Peter[22] reported the presentation, treatment, and outcome of 98 children with cerebral abscesses. Ninety-eight percent of patients were treated surgically, of whom 92% underwent burr hole aspiration, while 8% with cerebellar abscesses underwent surgical excision. A further 12% had a secondary excision because of the failure of aspiration. The mortality rate was correlated to initial GCS (70% for patients with GCS <8) supporting the importance of early diagnosis, but no differences in outcome were correlated with the different surgical approaches.

Lunardi et al.[48] considered 80 patients with surgically managed cerebral abscesses observed from 1953 to 1989. Twenty-one patients underwent aspiration (10 either CT- or ultrasound-guided). Twenty percent of patients died within 30 days of operation and in 16.2% of patients, death was attributable to surgical complications. During follow-up, another 22.2% of patients died and in all cases death was due to progression of the primary illness. The mortality rate was related to clinical grading on admission, but not to the type of surgical approach (20% of deaths in the excision group compared to 19.9% in the aspiration group). No deaths occurred in patients treated stereotactically.

Menhaz et al.,[49] investigating the clinical profile, microbiology, and outcome of children with cerebral abscess with underlying congenital heart disease compared with other predisposing conditions, reported 30 children, 37% of whom had congenital heart disease, who underwent surgical treatment of their cerebral abscess. All patients were initially managed by drainage via burr hole, but six were subsequently excised. Five (16%) children died soon after abscess drainage. The overall bad prognostic features included deranged sensorium, midline shift, and cerebral edema; the latter two were found to complicate children with congenital heart disease more than the non-cardiac group.

Seydoux and Francioli[50] reviewed 36 of 39 patients with cerebral abscess managed surgically. In 26 patients the lesions were excised, while in 10 they were aspirated. The surgical technique used did not depend on the location, but on the length of the lesions. Excision was attempted for superficial lesions and stereotactic aspiration for the deeper ones. Twelve out of 39 patients died or had severe sequelae, but apart from the patient's initial clinical impairment, none of the factors analyzed, including the type of surgery performed, influenced the outcome.

Brindon and Hardwidge[51] reported 15 patients with cerebral abscesses, seven of whom underwent aspiration as the primary procedure, while eight had total or partial excision. No significant differences between the two groups could be found comparing mortality rate, number of complications, and residual symptoms.

Tekkök and Erbengy,[21] in their retrospective review of 130 cases of cerebral abscesses in children over a period of 21 years, reported a mortality rate of 14.5% in patients who underwent aspiration and 16.2% in patients who had total or partial excision. The difference was not statistically significant. No statistically significant contribution to mortality rate was found either for location or number of abscesses and underlying congenital heart disease.

Aydin et al.[52] aiming to determine factors affecting the prognosis, reviewed 42 patients with cerebral abscesses treated over a period of 8 years (1979–1987). Twenty-four patients underwent drainage, while 18 were managed by excision, but no indications were reported for choosing the different surgical techniques. No statistically significant differences were found in mortality for age, sex, and different surgical approach, whereas mortality was influenced by the duration of the complaints and preoperative conditions.

Bhand[53] reviewed 82 patients with cerebral abscess treated over a period of 5 years (1998–2003). Surgical management consisted of aspiration in 38% of cases, while aspiration along with excision was carried out in the remaining 62% of patients. Indications for aspiration alone were deep-seated, less developed capsular formation of the abscess and cyanotic heart disease origin. Excisional removal of brain abscess was done in cases where the abscess was superficial and with well-developed capsule formation, or where the etiology was of traumatic or otogenic origin. The overall mortality rate was 22% (18 cases), 12 in the excision group (related to ventriculitis (six cases), septicemia (three cases), and postoperative hemorrhage (three cases)) and six patients in the aspiration group. Patients who underwent excision fared well on GCS, but there was no stratifications of cases for clinical seriousness at presentation.

Yildizhan et al.[1] retrospectively investigated 41 cases of cerebral abscesses. Seventeen patients underwent aspiration, while 24 patients were managed by excision, but the criteria for choosing the different surgical approaches were not reported. The overall mortality rate was 36.5%, with 58.8% in the aspiration group and 20.8% in the excision group. The mortality rate was highly related to the preoperative level of consciousness, with all deaths in patients who had a GCS <10, but no differences were reported in the number of patients with poor GCS between the two groups managed by different surgical techniques.

5. From the evidence to the recommendations

5.1. Question 1: Which patients with bacterial brain abscess can be managed safely using only medical treatment?

5.1.1. Discussion

The studies considered were all retrospective, not randomized, and not designed to detect differences. The case studies often included long periods of time with possible changes in risk factors, sensitivity and diagnostic methods, the sensitivity of microorganisms, and availability and choice of antibiotics. The antibiotic therapy was often not indicated and the choice of therapeutic approach in most cases was not made on clear and explicit grounds. There were therefore no references that would allow us to choose patients with cerebral abscess for medical treatment alone, even if a variable number of patients were treated successfully, thus avoiding surgery.

So, without certain criteria, the choice of the treatment should consider the advantages and disadvantages of each of the separate

choices. What makes a solely medical approach attractive is the reduced morbidity linked to surgical operations (particularly cerebral edema,[47,49] hemorrhage complications,[5,42,47–49] and the possible spread of the infection[17,41,48]). The reduction in late sequelae mentioned by certain authors[14] (GRADE score 1) needs to be confirmed in wider case studies with an adequate follow-up.

However, we need to consider that surgery is not only a therapeutic option, but also allows confirmation of the diagnosis and the sampling of material for microbiological diagnosis, and, for excision in particular, often reduces the duration of antibiotic treatment[3,12,14,16] (GRADE scores 1, 2, 1, 1, respectively), reducing the toxicity risk[26,27,53–55] (GRADE score 1, 2, 1, 1, 1, respectively), the hospitalization rate, and the frequency of controls[8] (GRADE score 2).

Common data in most of the case studies examined were the factors that most influenced the final outcome, being the initial neurological state and the size of the abscess[6,10,11,12,13,26,41] (GRADE score 1, 1, 1, 2, 1, 2, 2, respectively), although other factors such as gender[10,17] (GRADE score 1 for both), etiology, diagnosis of sepsis[10,11] (GRADE score 1 for both), and origin of the abscess[13] (GRADE score 1) have also been reported.

Recommendations

The best candidates for medical treatment appear to be those with a small abscess (<2.5 cm), in good initial clinical condition (GCS >12), and for whom the etiology is well-known (microorganism isolated from material other than the abscess pus) [C].

Medical treatment can also be used in the therapy of multiple abscesses, after surgery of abscesses >2.5 cm or surgery of abscesses that cause a mass effect, or in patients at serious risk of operation even if in these, the final decision must consider that the prognosis is often bad in any case [D].

In agreement with the algorithms proposed by Mamelak et al.[41] and Xiao et al.,[6] in patients treated solely medically, surgery should be reconsidered when the clinical condition is worsening or without clinical and radiological improvements within 1–2 weeks [C].

The choice of patients for a medical approach must be made on an individual basis, considering the patient's characteristics and the experience and consideration of the surgeon, and trying to find a balance between the risk of the surgical approach and the risk of not achieving a microbiological diagnosis, increasing the hospitalization time and the duration of antibiotic treatment, with related toxicity [D].

5.2. Question 1a: What is the efficacy in terms of outcome, tolerability, cost/efficiency, and quality of life of the different antibiotic regimens used to treat bacterial cerebral abscesses?

5.2.1. Discussion

There have been no RCTs that have evaluated the efficacy of different antibiotic therapies. There has also been no comparison of different antibiotic treatments. In many series of cases, the antibiotic therapy was not shown or was incomplete for the molecule used, the type of administration, and the administration time. Few case studies have looked at the toxicity of antibiotic treatment.

Recommendations on initial empirical therapy made by the BSAC[7] (GRADE score 2), include the microbiology of the abscess, the data concerning penetration of the various antibiotics into the CNS, and some clinical data and experience of the members of the working group.

Since the publication of these recommendations (2000), the most common association of antibiotics has been metronidazole + third-generation cephalosporin, particularly cefotaxime, but also ceftriaxone. Metronidazole + cefotaxime has been seen to be efficient in empirical treatment and that aimed at cerebral abscesses, but is also highly toxic, mainly causing rashes with or without itching, leucopenia, high temperatures, and increased transaminase[26,27] (GRADE score 2 and 1, respectively). Undesired effects appear after the first week of therapy or later and often lead to the discontinuation of treatment. This, also considering that data on the toxicity of antibiotic treatment is often not shown, should be kept in consideration when the therapeutic approach is chosen, given that surgery, particularly excision, could considerably reduce the overall exposure time to antibiotics[3,12,14,17] (GRADE score 1, 2, 1, 1, respectively).

Other iv antibiotics used in treating cerebral abscesses, often within different associations, include: penicillin[2,12,13,17,19,23] (GRADE score 1, 2, 1, 1, 1, 1, respectively), chloramphenicol[12,13,17,19,29] (GRADE score 2, 1, 1, 1, 1, respectively), ampicillin[8,12,17] (GRADE score 2, 2, 1, respectively), ampicillin/sulbactam[28] (GRADE score 1), pefloxacin[8] (GRADE score 2), nafcillin[12] (GRADE score 2), cloxacillin[19] (GRADE score 1), flucloxacillin[2] (GRADE score 1), vancomycin[2,11,12] (GRADE score 1, 1, 2, respectively), aminoglycoside[2,12] (GRADE score 1, 2, respectively), piperacillin and tazobactam[31] (GRADE score 1), and linezolid[31] (GRADE score 1). However, there are no concrete data comparing their efficacy and tolerability.

In particular the use of linezolid for therapy of CNS infections has been reported. There are, however, few reports on the successful treatment of meningitis and ventriculitis from difficult Gram-positive bacteria[56,57] (GRADE score 1 for both) even in neonates[58] (GRADE score 1) or cerebral abscesses secondary to meningitis[54,55] (GRADE score 1 for both). In cerebral abscesses of other origins where there is even less experience, alongside therapeutic success[32] (GRADE score 1), other more contradictory, but unexplainable results have also been reported[54] (GRADE score 1).

5.3. Question 1b: Which antibiotics have the best pharmacokinetics and/or tissue penetration of brain tissue and/or brain abscess?

5.3.1. Discussion

The infrequency of intracranial infection has precluded comparative pharmacokinetic studies of antimicrobials, and only in a minority of cases has the penetration of antimicrobials into brain abscess and/or brain tissue been assessed. This is mainly related to methodological issues in tissue sampling; direct measurement of drug concentrations at this body site is usually very difficult to perform.

Since in all of these pharmacokinetic studies, drug concentrations of antimicrobials in brain abscess and/or brain tissue were simply assessed in a single tissue sample at variable times from drug administration without a complete pharmacokinetic profile, as a general rule, it is almost impossible to draw any definitive conclusions on penetration rates of antimicrobials due to the hysteresis phenomenon. Accordingly, from a pharmacokinetic point of view, in the absence of any definitive evidence about which antibiotics have the best pharmacokinetics in brain tissue and/or brain abscess, it could be helpful to consider some general rules when choosing a drug to treat brain abscess[35,59] (GRADE score 1 for both).

Drug penetration into brain tissue may be impaired by the anatomical integrity of the blood–brain barrier. It is expected that this impairment may be greater for hydrophilic compounds, namely β-lactams and aminoglycosides, but especially for glycopeptides, which have a very high molecular weight. Accordingly, larger than standard doses of antibiotics are

frequently used to increase the availability of drugs to cross the barriers in these cases[59] (GRADE score 1), even if drug diffusion across the blood–brain barrier could be enhanced in the brain areas affected by inflammation[60] (GRADE score 1).

Conversely, lipophilic compounds, namely fluoroquinolones, rifampin, metronidazole, and oxazolidinones are expected to achieve much higher penetration rates even in the presence of undamaged barriers. Although the physiological properties of the blood–brain barrier and the blood–CSF barrier are distinct, additional pharmacokinetic information about the penetration of antimicrobials into the CNS could be extrapolated from studies carried out in neurosurgical patients with external ventriculostomy who are unaffected by meningitis. Indeed, in these situations, penetration of systemically administered antimicrobials into the CSF could be similar, since it may occur only through undamaged barriers[61] (GRADE score 1).

Various studies have documented that optimal exposure in the CSF with lipophilic agents such as rifampin[62] (GRADE score 1), linezolid[34] (GRADE score 1), levofloxacin[63] (GRADE score 1), and moxifloxacin[64] (GRADE score 1), may also be achieved with standard dosages. However, for hydrophilic antimicrobials such as third-generation cephalosporins[65] (GRADE score 1), meropenem[66] (GRADE score 1), and vancomycin[67,68] (GRADE score 1 and 2, respectively), larger than standard dosages may be necessary.

5.4. Antibiotic therapy of cerebral abscess

5.4.1. Start of the antibiotic therapy

Frequently, given the possible critical nature of the patients, the antibiotic therapy is started before surgery, when this occurs. Data on sterilization of cerebral abscesses are both fragmented and not controlled, however the probability of identifying the pathogen in the pus culture decreases with the administration time of the antibiotics. For metronidazole associated with third-generation cephalosporin, the probability of having a positive culture from the pus taken surgically reduces considerably during the first three days of therapy[26,27] (GRADE score 2 and 1, respectively).[27]

Recommendations

The sample from the abscess should be made without antibiotic therapy or, at least within not more than 3 days of the start of therapy [D].

5.4.2. Choice of the drug

Theoretically, the ideal antibiotic to treat cerebral abscess should be that active in the microbial flora, with the best penetration of the abscess pus and with the best safety profile especially in long-term administration, possibly administrated orally.

In post-trauma and post-surgical abscesses, the empirical therapy should consider the possible presence of staphylococci and Gram-negative rods. In post-surgical ones in particular, there is the possibility of methicillin resistance for staphylococci and variable resistance according to the ecology of Gram-negative rods. Therefore, particularly in post-surgical forms, the possibility of using new molecules seems to be attractive, both given their spectrum of action and their ease of administration (e.g., linezolid, daptomycin, tigecycline). There has been no clinical experience with tigecycline and daptomycin, while for linezolid there have been some clinical evaluations of efficacy[32,54] (GRADE score 1 for both), nevertheless with unexplainable conflicting results in one case[33] (GRADE score 1), and demonstration of good kinetics[34] (GRADE score 1). Experience is scarce and activity data should be validated in wider studies. However, linezolid could be a valid alternative in cases of allergy to β-lactam antibiotics or to sulfonamides or in the case of failure of a previously administered treatment. It should be considered in the front line against difficult Gram-positive bacteria, considering the high dosages of glycopeptides, especially vancomycin[67,68] (GRADE score 2 and 1, respectively), needed for efficient concentrations in CNS infections. Obviously there are no concrete data on the toxicity of linezolid in this pathology, but this is common practice for all molecules with these indications. Where toxicity data are shown (e.g., cefotaxime), these underline the high risk of collateral effects that could lead to the suspension of treatment[26,27] (GRADE score 2 and 1, respectively).

Recommendations

There is insufficient evidence to make specific recommendations for antibacterial treatment of cerebral abscess. However, on the basis of the limited clinical data and of pharmacokinetic/pharmacodynamic (PK/PD) considerations, some drug choices and schedule regimens may be suggested (Table 2) [D].

5.4.3. Duration of treatment

No study has comparatively evaluated how the duration of the iv treatment and/or the overall duration of antibiotic therapy influence outcome. Often, these parameters are not shown, or are simply described without evaluating the correlation with the final outcome. The duration of the antibiotic treatment has therefore been considered a largely empirical choice. Where therapy time of intravenously administered antibiotics is shown, it is usually not less than 4 weeks[4,12,23,26–28,41,42,47,53] (GRADE score 1, 2, 1, 1, 2, 1, 2, 1, 1, 1, respectively). Where shorter times are reported,[19] (GRADE score 1) reference is made to other parameters such as the reduction of CRP (C-reactive protein), the size of the abscess, and the thermal curve. However, quantitative indicators are not mentioned (the amount of CRP reduction and the size of the abscess that permits the iv therapy to be stopped safely).

Without parameters that can safely evaluate the endovenous therapy time, we agree with the BSAC recommendations[7] (GRADE score 2).

Recommendations

An advised overall period of 4–6 weeks is considered prudent for surgically treated abscesses. Six to eight weeks is advised for iv treatment of abscesses treated solely medically and in the case of multiple abscesses when larger ones are treated surgically [C].

5.4.4. Oral therapy

Often, antibiotic treatment is prolonged orally after the initial iv treatment[19,27] (GRADE score 1 for both), but in these cases the drug/s used are not reported. Many of the recommended iv drugs (e.g., third-generation cephalosporin, oxacillin, vancomycin, carbapenem, and piperacillin/tazobactam) do not have indications for oral use or dosages needed for cerebral abscesses cannot be reached using this method. Therefore, the choice to change to an orally administered treatment appears often to be arbitrary and the outcome difficult to quantify.

Drugs that could be used orally include: trimethoprim–sulfamethoxazole, fluoroquinolone, amoxicillin/clavulanic acid,

Table 2
Suggested drug choices and scheduled regimens.

Post-trauma abscess	Post-surgical abscess	Abscesses from paranasal sinuses, middle ear and of dental origin	Metastatic or cryptogenic abscesses[b]
Cefotaxime 2 g q6h + metronidazole 500 q8h ± rifampin 10 mg/kg q24h	Linezolid 600 mg q12h or vancomycin 40–60 mg/kg/24-hourly as a continuous infusion (adjusted for creatinine clearance) after a 15 mg/kg loading dose or 10–15 mg/kg q6h aiming for serum levels of 15–25 mg/l plus rifampin 10 mg/kg q24h + meropenem 1.5 g q6h or 2 g q8h or piperacillin/tazobactam 4.5 g q6h	Metronidazole 500 mg q8h + cefotaxime 2 g q6h or piperacillin/tazobactam 4.5 g q6h[a]	Cefotaxime 2 g q6h ± metronidazole 500 mg q8h or ampicillin/sulbactam 100/50 mg/kg q6h

[a] If *Pseudomonas aeruginosa* is suspected.
[b] In the case of a positive blood culture in the presence of endocarditis, use therapy suggested for endocarditis.

metronidazole, linezolid, and rifampin. Oral antibiotics with reported indications in published research include ampicillin/sulbactam[28] (GRADE score 1), metronidazole[27] (GRADE score 1), trimethoprim–sulfamethoxazole[27,44] (GRADE score 1 for both), rifampin[23] (GRADE score 1), and linezolid[58] (GRADE score 1).

Recommendations

We do not believe there is sufficient information to give recommendations for orally administered antibiotics. However, the choice of completing treatment using this method should to reserved for those cases where the bacteria have been isolated and there is a sensitivity profile, using drugs with good penetration into the infection site [D].

5.5. Question 2: What is the best surgical approach in terms of outcome in managing bacterial brain abscess?

5.5.1. Discussion

Surgical options in cerebral abscess management include complete or partial excision of the abscess or drainage. The latter can be carried out with a burr hole or craniotomy or using stereotactic aspiration.

In very general terms, we can say that the advantages of stereotactic aspiration are as follows: the simplicity of the operation, the possibility of using the technique during cerebritis[39,41] (GRADE score 1 and 2, respectively), the small degree of trauma involved, and the possibility of not resorting to narcosis. The principle disadvantages are however the frequent need for multiple operations[6,39,46] (GRADE score 1 for each) and the possibility of failure requiring rectification with excision, which has a higher degree of complete success[4,19,39,49] (GRADE score 1 for each).

There have been no controlled prospective studies comparing the various surgical approaches in homogeneous populations of patients with cerebral abscesses, neither in terms of efficacy nor in terms of morbidity. The compared data come from studies of retrospective cohorts or descriptive series of cases, which are certainly not suitable for measuring any differences.

Often, indications that lead to different types of surgery are not shown and the follow-up periods are different in the different studies or even within the same case series. Outcome is often considered only in terms of mortality, while long-term outcome is either not shown or only partially so. The case series are often over a long period of time and are collected in very different geographical areas with different epidemiologies and different diagnostic support and technologies.

Apart from these comments:

- Outcome principally in terms of mortality, but also long-term outcome, is affected above all by the initial conditions of the patient rather than the type of surgery[1,22,48,49,50] (GRADE score 1 for each).
- When evaluated[40] (GRADE score 1), even if in a special population such as neonates and compared with a different population, the speed with which the operation is made, rather than the type of operation, is the factor that most affects the final condition of these patients.
- Recurrent indications for aspiration by stereotactic approach are as follows: deep-seated or small abscesses of those located in eloquent areas, multiple hemispheric abscesses, patients who are poor candidates for general anesthesia[4,5,39,41,42,47,53] (GRADE score 1 for each).
- Drainage by craniotomy or craniectomy or excision is used more often in superficial abscesses and those found in the posterior cranial fossa[4,10,22,39,41,50] (GRADE score 1, 1, 1, 1, 2, 1, respectively). Furthermore, excision is often used in post-traumatic, postoperative patients and those with a poor response to repetitive aspiration[4,22,53] (GRADE score 1, 1, 1, respectively).

Recommendations

The choice of the type of surgical approach does not appear to be critical in determining outcome and should take into account the preference and the ability of the surgeon, as well as the ability of the patient to tolerate each procedure. The initial clinical condition of the patient and the speed of the therapeutic operation, including surgery, appear to be the more decisive factors for the final outcome [D].

Recurrent indications for aspiration by stereotactic approach are as follows: deep-seated or small abscesses or those located in eloquent areas, multiple hemispheric abscesses, patients who are poor candidates for general anesthesia [D].

Drainage by craniotomy or craniectomy or excision are used more often in superficial abscesses and those found in the posterior cranial fossa [D]. Furthermore, excision is often used in post-traumatic, postoperative patients and those with a poor response to repetitive aspiration [D].

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Conflict of interest

All members of the faculty of GISIG – M. Arlotti, G. Carosi, P. Grossi, G. Ippolito, F.N. Lauria, M. Moroni, E. Nicastri, F. Pea, G. Di Perri, F.G. De Rosa, G. Tomei, and V. Vullo – report no other potential conflict of interest except as reported in the specific section.

The members of the working group have no specific conflict of interest to report.

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Additional conflict of interest

M. Arlotti has received paid expert opinion fees from BMS. P. Grossi has received honoraria for speaking at congresses from Novartis and Pfizer. G. Ippolito and F.N. Lauria have received expert opinion fees from Pfizer. E. Nicastri has received paid expert opinion from MSD and Pfizer. F. Pea has been a consultant for Astellas, has been a consultant for and on the spreakers' bureau for Pfizer and sanofi-aventis and Schering Plough, and has also been on the spreakers' bureau for Abbott, Gilead, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, and Wyeth. F.G. De Rosa has received speaker fees from Pfizer, Merck Sharp & Dohme, and Novartis.

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