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Systematic review and meta-analysis

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ABSTRACT

Objective: To define clinical characteristics, causative organisms, and outcome, and evaluate trends in epidemiology and outcome of brain abscesses over the past 60 years.

Methods: We performed a systematic review and meta-analysis of studies on brain abscesses published between 1970 and March 2013. Studies were included if they reported at least 10 patients with brain abscesses, included less than 50% extra-axial CNS infections (empyema) without brain abscess, and did not solely report on brain abscesses caused by a single pathogen.

Results: We identified 123 studies including 9,699 patients reported between 1935 and 2012. There was a male predominance of 2.4 to 1, and the mean age of patients with brain abscesses was 34 years. The most common causative microorganisms were *Streptococcus* and *Staphylococcus* species, comprising 2,000 (34%) and 1,076 (18%) of 5,894 cultured bacteria. Geographical distribution of causative microorganisms over continents was similar and did not substantially change over the past 60 years. Predisposing conditions were present in 8,134 of 9,484 patients (86%) and mostly consisted of contiguous or metastatic foci of infection. The classic triad of fever, headache, and focal neurologic deficits was present in 131 of 668 (20%) of patients. Case fatality rate decreased from 40% to 10% over the past 5 decades, while the rate of patients with full recovery increased from 33% to 70%.

Conclusions: The prognosis of patients with brain abscesses has gradually improved over the past 60 years. Important changes over time were the modality of cranial imaging, neurosurgical technique, and antimicrobial regimen. *Neurology*® 2014;82:806–813

GLOSSARY

CI = confidence interval; **DWI** = diffusion-weighted imaging; **IQR** = interquartile range; **MRSA** = methicillin-resistant *Staphylococcus aureus*.

Brain abscess is a focal intracerebral infection consisting of an encapsulated collection of pus caused by bacteria, mycobacteria, fungi, protozoa, or helminths.[1–3] The incidence of brain abscesses has been estimated at 0.3 to 1.3 per 100,000 people per year but can be considerably higher in certain risk groups, for example, patients with HIV/AIDS.[3] Over the last 30 years, new diagnostic procedures, such as brain imaging techniques (MRI and CT) and stereotactic biopsy, and the introduction of new antibiotics have considerably changed the management of patients with brain abscess, at least in high-income countries. Whether these advantages in diagnostics and treatment lead to improved outcome of patients with brain abscess is unknown. Studies on brain abscess are mostly single-center retrospective cohorts, and reported data on epidemiologic and clinical characteristics vary considerably among studies.[4–7] We performed a systematic review and meta-analysis of studies on brain abscess to define clinical characteristics, causative organisms, and outcome of brain abscesses.

METHODS We searched the Cochrane Library (The Cochrane Library 2011, issue 1), MEDLINE (1970 to March 2013), and Embase (1974 to March 2013). We used the search terms "brain abscesses" or "cerebral abscesses" and included studies on brain abscess written in English, French, German, Spanish, or Italian. We also searched the reference lists of articles identified by this search strategy and selected those that we judged to be relevant. Studies were included in the meta-analysis if 10 patients or more were described and were published after 1970. Exclusion criteria were extra-axial CNS infection (e.g., subdural empyema) in more than 50% of cases, duplicate publications, and

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studies restricted to brain abscesses caused by one specific microorganism. Data on study design, inclusion criteria, demographics, baseline characteristics, underlying conditions, signs and symptoms, abscess localization, causative microorganisms, therapy, and outcome were extracted by M.B. and J.C. according to a prespecified protocol (data e-1 on the *Neurology*® Web site at www.neurology.org). Because the data description was heterogeneous among studies, all of the data are presented as number for which a characteristic was present out of the total number for which the characteristic was evaluated. Because many studies included both children and adults and did not specify characteristics per age group, we chose to present data for all patients (adults and children) and separately for children included in pediatric studies. Pediatric studies were defined as those reporting on "children," without definition of the age range.

Table 1 Culture results and major groups of causative microorganisms[a]

Characteristic	All patients	Children
Positive culture	4,543/6,663 (68)	631/1,093 (63)
Monomicrobial	3,067 (77)	325 (73)
Polymicrobial	902 (23)	117 (27)
Cultured microorganisms	5,894	724
Streptococcus spp	2,000 (34)	260 (36)
Viridans streptococci	755 (13)	58 (6)
S pneumoniae	139 (2)	27 (4)
Enterococcus	49 (0.8)	2 (0.3)
Other/not specified	1,057 (18)	173 (24)
Staphylococcus spp	1,076 (18)	128 (18)
S aureus	782 (13)	80 (11)
S epidermidis	148 (3)	31 (4)
Not specified	146 (2)	16 (2)
Gram-negative enteric	861 (15)	114 (16)
Proteus spp	417 (7)	60 (8)
Klebsiella pneumoniae	135 (2)	11 (2)
Escherichia coli	126 (2)	18 (2)
Enterobacteriae	101 (2)	9 (1)
Pseudomonas spp	122 (2)	13 (2)
Actinomycetales	148 (3)	16 (2)
Nocardia	57 (1)	0
Corynebacterium	49 (0.8)	7 (1)
Actinomyces	48 (0.8)	8 (1)
Mycobacterium tuberculosis	41 (0.7)	1 (0.2)
Haemophilus spp	124 (2)	41 (6)
Peptostreptococcus spp	165 (3)	45 (6)
Bacteroides spp	370 (6)	33 (5)
Fusobacterium spp	119 (2)	17 (2)
Parasites	5 (0.1)	0
Fungi	83 (1)	8 (1)
Other[a]	821 (13)	49 (7)

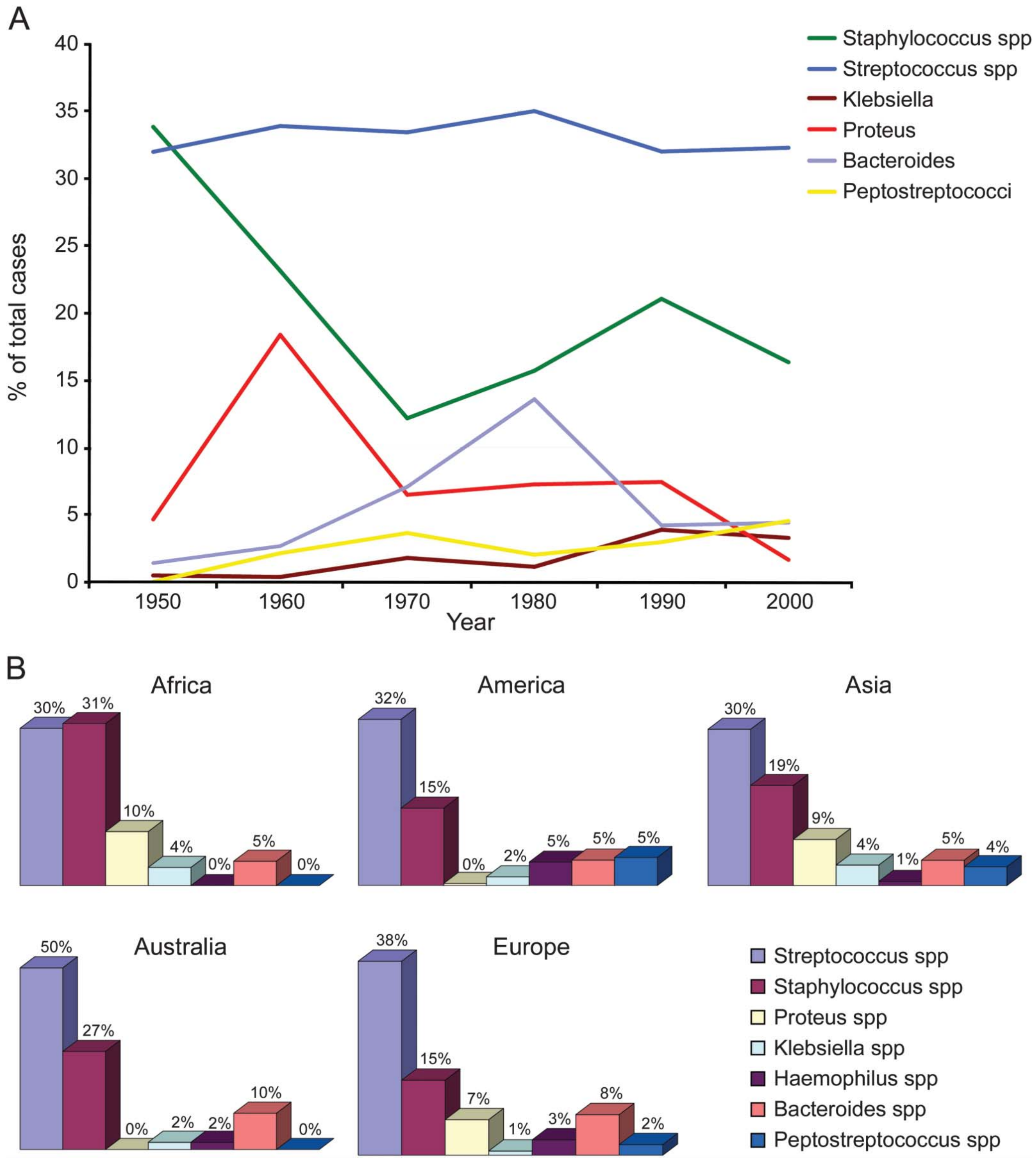
Data are n (%).
[a] List of all pathogen species is given in table e-1.

RESULTS Study characteristics. We retrieved 123 studies including 9,699 patients, presenting data from 1935 to 2012 (figure e-1).[4–40,e1–e84] The number of included patients per study varied between 11 and 973 patients (median 54, interquartile range [IQR] 28–90), and the annual inclusion rate of studies varied between 0.6 and 51.2 patients (median 4.9/year, IQR 2.5–8.3). Described time periods of the studies varied from 1 to 58 years (median 11 years, IQR 7–20). Fifty-three studies described patients of all ages without specific inclusion criteria except for the diagnosis of brain abscess. In the remaining studies, selection criteria for inclusion were brain abscess plus operation for brain abscess in 33 studies, childhood age in 23 studies, and other criteria in 14 studies. The majority of studies (90%) were single-center studies. Only 8 of the 123 studies (6%) were performed prospectively.[4,14,19,e9,e10,e22,e24,e85] Studies were performed in Asia (n = 48), Europe (n = 47), Americas (n = 21), Africa (n = 4), and Australia (n = 3).

Epidemiology. Data on bacterial cultures was reported for 7,340 of 9,699 included patients (76%); cultures were not performed in 677 patients (9%). The source of cultures was specified in 89 studies and was peroperatively obtained pus or an abscess swab in 73 patients (82%). Pathogens were also cultured from blood, CSF, or another primary infection site in 16 studies. Of the 6,663 patients in whom cultures were performed, 4,543 cultures were positive (68%, 95% confidence interval [CI] 67%–69%; table 1) and yielded a total of 5,894 pathogens. Cultures were negative in 2,120 patients (32%, 95% CI 31%–33%). Multiple bacteria were cultured in 902 patients (14% of all cases [95% CI 13%–15%]; 23% of culture-positive cases [95% CI 22%–25%]). A total of 85 different causative microorganisms were reported (table e-1).

The most frequently cultured microorganisms belonged to the *Streptococcus* species (2,000 of 5,894 [34%, 95% CI 33%–35%]). Streptococci most frequently isolated belonged to the viridans group (*S mitis*, *S mutans*, *S salivarius*, *S sanguinis*, and *S constellatus*). *S pneumoniae* was found in only 2.4% of patients (95% CI 2.0%–2.8%). Throughout the past 6 decades, streptococci were reported to cause approximately one-third of cases, without fluctuations in relative frequency (figure 1). The second most common group of bacteria identified was *Staphylococcus* spp reported in 1,076 cases (18%, 95% CI 17%–19%). Of 930 cases in which the staphylococcal cluster was determined, 782 (84%, 95% CI 82%–86%) were found to be *S aureus* while 148 (16%, 95% CI 14%–18%) belonged to the *S epidermidis* cluster. No reliable estimate of infection caused by methicillin-resistant *S aureus* (MRSA) could be distilled. A total of 861 (15%, 95% CI 14%–16%) of the identified bacteria were gram-negative

Figure 1 **Distribution of causative microorganisms through time and per continent**



(A) Relative incidence over time of the 6 most frequent pathogens reported in cohort studies including >10 patients reported for the middle year of the study period. (B) Studies describing causative pathogens performed in the following continents: Africa, 1 (651 cultured bacteria; time span 1952–2003); America, 16 (778 cultured bacteria; 1945–2010); Asia, 44 (2,005 cultured bacteria; 1940–2009); Australia, 3 (83 cultured bacteria; 1961–1986); and Europe, 41 (2,377 cultured bacteria; 1935–2011). All percentages have been rounded off without decimals to increase the clarity of the figure.

enteric bacteria (*Proteus* spp, *Klebsiella* spp, *Escherichia coli*, and *Enterobacteriae*), which were frequently identified in polymicrobial brain abscesses.

A difference in relative occurrence of gram-negative enteric bacteria was observed among continents (figure 1). In Europe, Asia, and Africa, 7% to 10% of brain abscess cases were caused by *Proteus* species compared with 1.7% in North America. *Klebsiella* spp were identified frequently in Asia. In Taiwan, 10% of cases were caused by *Klebsiella pneumoniae*.[23,e38,e39,e44,e59] Despite these distinct differences among continents, the majority of microorganisms causing brain abscesses were similar. Identified bacteria in adults and children were similar (children: *Streptococcus* spp 35%, *Staphylococcus* spp 18%, gram-negative enteric 15%; table 1). One study of brain abscesses in a neonatal cohort reported that 27 of 30 cases (90%) were caused by *Proteus mirabilis*.[e51]

Clinical characteristics. The average age of patients was 33.6 years and 70% were male (95% CI 69%–71%; table 2). Predisposing conditions for brain abscesses were identified in the 8,134 of 9,484 patients (86%, 95% CI 85%–87%). The most common predisposing conditions were contiguous foci of infection: otitis or mastoiditis (33%, 95% CI 31%–33%), sinusitis (10%, 95% CI 9%–11%), meningitis (6%, 95% CI 5%–6%), and odontogenic foci (5%, 95% CI 4%–6%).

Table 2 Clinical characteristics and laboratory and CSF examinations in patients with brain abscess

Characteristic	n/N (%)[a]
Age, y, mean[b]	33.6
Sex, male	5,333/7,585 (70)
Predisposing conditions[c]	
Otitis/mastoiditis	2,754/8,727 (32)
Sinusitis	660/6,499 (10)
Heart disease[d]	911/6,841 (13)
Posttraumatic	950/6,858 (14)
Hematogenous[e]	384/3,025 (13)
Pulmonary disease	403/4,909 (8)
Postoperative	469/5,421 (9)
Odontogenic	178/3,721 (5)
Immunocompromise	172/1,957 (9)
Meningitis	216/3,883 (6)
Unknown	1,350/7,198 (19)
Other	230/4,361 (5)
Symptoms and signs	
Headache	4,526/6,575 (69)
Nausea/vomiting	1,993/4,286 (47)
Fever	3,718/6,970 (53)
Altered consciousness	3,207/7,479 (43)
Neurologic deficits	2,996/6,241 (48)
Seizures	1,647/6,581 (25)
Nuchal rigidity	1,465/4,629 (32)
Papilloedema	845/2,428 (35)
Mean duration of symptoms[f]	8.3 d
Triad of fever, headache, focal neurologic deficits	131/668 (20)
Blood investigation	
Leukocytosis	1,366/2,273 (60)
Elevated CRP	196/316 (60)
Elevated ESR	311/434 (72)
Positive blood culture	135/484 (28)
CSF investigation	1,392/3,955 (35)
LP	1,286/1,298 (99)
Normal CSF	96/588 (16)
Pleocytosis	758/1,063 (71)
Elevated CSF protein	222/381 (58)
Culture positive	263/1,108 (24)
Clinical deterioration attributed to LP	76/1,030 (7)

Abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; LP = lumbar puncture.
[a] All data are presented with the total number of patients included in studies that presented the specific patient characteristic.
[b] The mean age was recalculated from averages presented in 85 studies including 5,391 patients.
[c] Numbers do not add up to 100% because multiple predisposing conditions could be present in 1 patient.
[d] Heart disease includes congenital heart defects and endocarditis.
[e] Source not specified.
[f] Recalculated from averages presented in 15 studies including 989 patients.

Metastatic infection from a pulmonary focus, heart disease, or other source of hematogenous spread was identified in 33% (95% CI 32%–34%) of patients. Neurosurgical operation preceded brain abscess in 9% (95% CI 8%–9%) of patients and head trauma in 14% (95% CI 13%–15%).

The mean duration of symptoms in patients with brain abscesses recalculated from 15 studies including 989 patients was 8.3 days. The classic symptoms and signs of brain abscesses were present in many patients: headache was reported in 69% (95% CI 68%–70%) of cases, fever in 53% (95% CI 52%–55%), and focal neurologic deficits in 48% (95% CI 47%–50%). However, the classic triad consisting of fever, headache, and focal neurologic deficits in brain abscesses was present in only 20% of patients (95% CI 17%–23%).

Ancillary investigations. CSF examination was described in 43 studies including 3,955 patients and was performed in 1,392 patients (35%, 95% CI 33%–37%). CSF examination was completely normal in 96 of 588 patients (16%, 95% CI 14%–20%). Data on CSF cultures were reported for 1,108 patients of whom 263 (24%, 95% CI 21%–26%) had a positive culture. Clinical deterioration attributed to the lumbar puncture was reported to occur in 76 of 1,030 patients (7%, 95% CI 6%–9%) included in 19 studies.

Cranial imaging was reported in 65 studies and modality of imaging was specified in 56 (86%). Cranial CT was used in 37 studies (2,668 patients) and cranial MRI and CT results were reported in 18 studies (1,121 patients). Confirmation of the diagnosis of brain abscess on cranial imaging was an inclusion criterion for the majority of studies. Cranial CT was false-negative for brain abscesses in 44 of 728 patients (6%, 95% CI 5%–8%). In these patients, the diagnosis was made perioperatively (n = 13) or with cranial MRI (n = 31). In 6,019 of 7,336 patients (81%, 95% CI 81%–83%), the brain abscess was found to be a single lesion (perioperatively, by cranial imaging, or during autopsy; table 3). The preferential localizations were the frontal and temporal lobe, accounting for 31% and 27% of all brain abscesses. Serum inflammatory markers were reported in 30 studies and were frequently within normal range (table 3). Data on blood cultures were available for 779 patients: blood cultures were positive in 135 of 484 patients (28%, 95% CI 24%–32%) in whom culture was performed.

Treatment. Treatment modality was reported for 7,697 patients, and a total of 6,728 patients (87%) underwent at least one neurosurgical procedure (table 3). The rate of neurosurgical procedure was 4,588 of 5,461 (84%, 95% CI 83%–85%), when excluding studies including only operated patients. Abscess aspiration was performed in 3,902 of 5,894 patients (66%) and primary abscess excision was performed in 1,343 of 5,167 patients (26%). Stereotactic aspiration was

Table 3 Brain abscess location, treatment characteristics, and outcome	
Characteristic	n/N (%)[a]
Abscess location	6,171
Frontal	1,917 (31)
Temporal	1,652 (27)
Parietal	1,240 (20)
Occipital	387 (6)
Basal ganglia	164 (3)
Cerebellum and brainstem	812 (13)
Extra-axial	326/4,712 (7)
Single abscess	6,019/7,336 (82)
Multiple abscesses	1,317/7,336 (18)
Treatment	
Operation	6,728/7,697 (87)
Aspiration[a]	3,902/5,894 (66)
Excision[a]	1,343/5,167 (26)
Aspiration and excision[a]	342/2,497 (14)
Stereotactic operation	390/1,809 (22)
Reoperation	882/2,830 (31)
Medical treatment	637/5,471 (12)
Steroids	892/1,611 (55)
Outcome	
Mortality	1,823/9,011 (20)
Mortality studies using only stereotactic aspiration	5/147 (3)
Good outcome	2,716/4,752 (57)

[a] Numbers do not add up to 100% because of differences in reporting among studies.

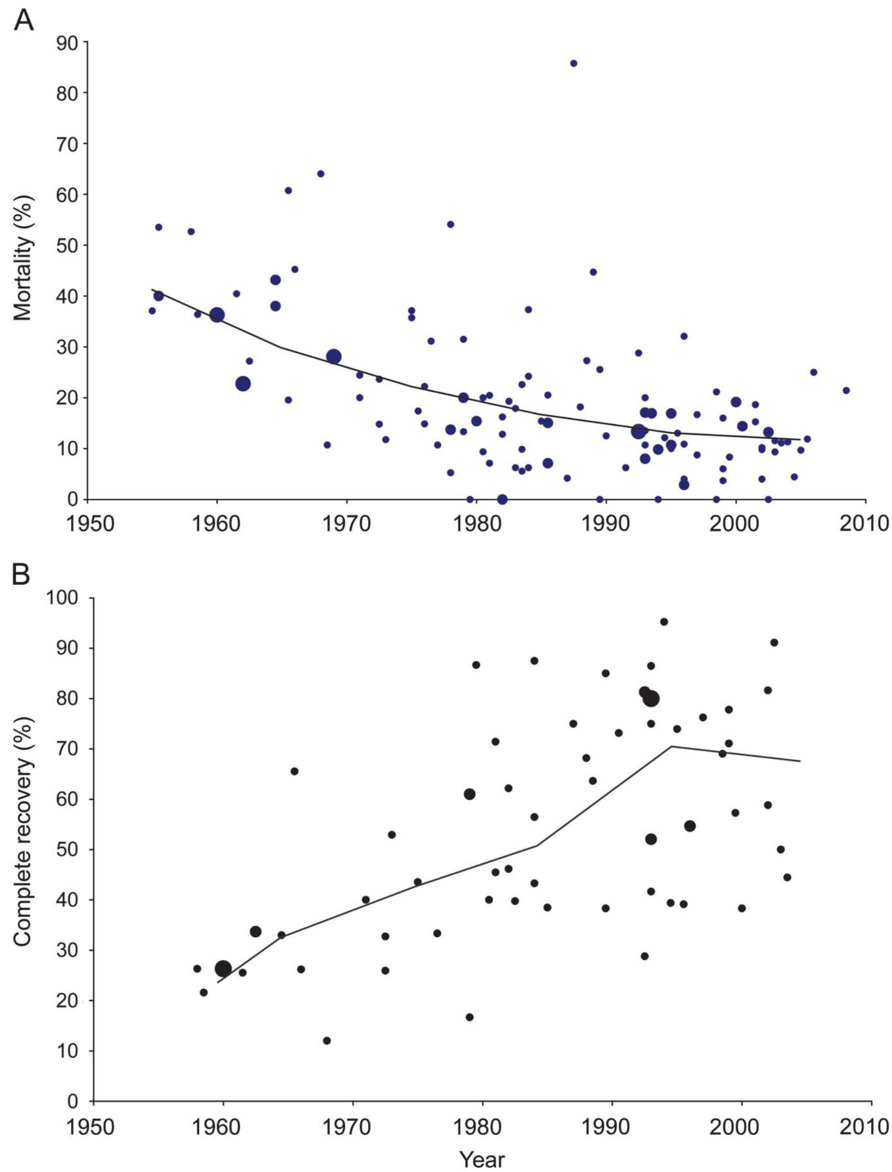
performed in 390 of 1,809 patients (22%) reported in 19 studies. Reoperation of the abscess was performed in 882 of 2,830 cases (31%), but only 38 of 91 studies (42%) describing operation characteristics reported reoperation rates. Initial antibiotic treatment strategies were reported for 44 studies, but only 17 studies described how many patients received which regimen. The most common empiric treatment consisted of a third-generation cephalosporin combined with metronidazole, which was given in 490 of 928 patients (53%, 95% CI 50%–56%). A third-generation cephalosporin in combination with metronidazole and vancomycin was given to 138 patients (15%, 95% CI 13%–17%). Other regimens consisted of combinations of chloramphenicol, metronidazole, and penicillin (9%), ampicillin, gentamicin, and metronidazole (9%), and imipenem monotherapy (4%). Corticosteroids were administered to 892 of 1,611 patients (55%).

Outcome. A total of 1,823 of 9,011 patients (20%, 95% CI 19%–21%) with brain abscesses died. The mortality rate declined substantially in the past 60 years (figure 2) and was approximately 10% in studies since 2000. Studies reporting on stereotactic operations showed a mortality rate of only 3% (5 of 147 patients). Other outcome parameters than survival were available for 4,752 patients: 2,716 (57%, 95% CI 56%–59%) of the patients had a good outcome, while the remainder died or had neurologic sequelae. Mortality was 22% for studies performed in Europe, 31% for studies in the Americas, 25% for studies in Australia, 19% for studies in Africa, and 15% for studies performed in Asia. The average starting year of inclusion for studies in Europe, Australia, and Africa was mid-1970s (1974–1976), for the Americas 1968, and for studies performed in Asia 1985.

DISCUSSION In the systematic review and meta-analysis, we found that the prognosis of patients with brain abscesses has gradually improved. The case fatality rate decreased from 40% to 10% over the past 6 decades, and the rate of patients with full recovery increased from 33% to 70%. This finding is in line with reports from single-center studies.[15,16,38,e1,e2,e8] Important changes over time are improvements in cranial imaging, neurosurgical techniques, and antimicrobial regimens. A retrospective cohort study comparing 100 cases of brain abscesses diagnosed between 1962 and 1967, before the introduction of CT, with 100 historical controls diagnosed between 1974 and 1984, after the introduction of CT, showed a decrease in mortality from 40% to 20% ($p < 0.001$).[e46] The improvements in cranial imaging have facilitated less invasive and more precise neurosurgical procedures such as stereotactic aspiration of abscesses.[e12,e26,e27,e31] Before 1980, anaerobes were often not covered by the empiric antibiotic regimens, whereas afterward, metronidazole was frequently included in the standard regimen.[e52,e86]

Many patients with brain abscess presented with headache, nausea, fever, and altered consciousness. However, the classic triad of fever, headache, and focal neurologic deficits is unreliable in identifying brain abscesses because only 20% of patients present with all 3 symptoms. Ancillary investigations such as laboratory examination of blood may show increased parameters of inflammation that indicate bacterial infection, but normal results of C-reactive protein, erythrocyte sedimentation rate, or white blood cell count are not uncommon in patients with brain abscess. In our meta-analysis, we found that the 5% of cases that were initially missed on CT were all identified on MRI. Diffusion-weighted imaging (DWI) has shown to be superior to CT or conventional MRI in differentiating brain abscesses from other cystic lesions, mostly primary brain tumors.[e87] Typical DWI of brain abscesses show a hyperintense signal on

Figure 2 Mortality (A) and complete recovery rate (B) in cohort studies of patients with brain abscess in the past 60 years reported for the middle year of the study period



Small dots indicate studies including fewer than 100 patients, middle-sized dots studies of 100 to 300 patients, and large dots studies including more than 300 patients. Lines indicate weighted means per decade.

DWI and hypointense signal on apparent diffusion coefficient images. Sensitivity and specificity of DWI for differentiating brain abscess from other intracranial cystic masses were both 96% in a case series of 147 patients.[e87]

Predisposing conditions were present in the majority of patients (86%). Identification and treatment of primary foci of infection should be a priority in patients with brain abscess because removal of the primary infection focus is essential to avoid further spread of bacteria. Therefore, consultation of an otorhinolaryngologist, cardiologist, and dentist is indicated to detect and treat ear, sinus, heart, or odontogenic infections.

The most common causative bacteria were *Streptococcus* and *Staphylococcus* species. Fungi, parasites, and mycobacteria were found in less than 2% of cases. Because the primary focus of infection does not accurately predict the causative microorganism, initial antimicrobial therapy should cover all common causes of brain abscesses until culture results are known.[26,e1,e16,e88] Frequently advised empiric antimicrobial therapy consists of a third-generation cephalosporin combined with metronidazole to cover anaerobes.[1,3] This regimen was most frequently used in studies included in our meta-analysis (53% of cases). Addition of vancomycin to this regimen to cover for MRSA was described in 15% of cases and can be considered based on local MRSA rates.

The yield of lumbar puncture in patients with a cerebral abscess is limited, because CSF pleocytosis or elevated CSF protein levels do not contribute to the diagnosis, and the causative microorganism is identified in only 24% of CSF cultures. Brain abscesses often cause brain shift that potentially may increase after CSF withdrawal at the lumbar level. Increased brain shift may cause compression of vital structures of the brain. A study in a large South African cohort focusing on clinical deterioration after lumbar puncture included 1,411 patients with brain abscesses or subdural empyema and showed that 272 of 422 (65%) receiving a lumbar puncture clinically deteriorated, and this was directly attributed to the lumbar puncture in 81 patients (19%), of whom 20 died (5%).[e89] Lumbar puncture should only be performed in patients with suspected cerebral abscesses if brain shift is ruled out by cranial imaging. Blood cultures showed the causative microorganism in 28% of cases and should always be performed on admission, preferably before antibiotics are initiated.

Limitations. Our meta-analysis has several limitations, as most included studies have methodologic flaws. First, most included studies do not represent the complete population of patients with brain abscess because of a selection bias inherent to the retrospective design. Many studies only included patients with bacterial brain abscesses, and therefore the rate of abscesses due to parasites and fungi may be underestimated. Second, the single-center design of most studies limits the external validity. Such centers will most likely have more experience in treating (and operating on) brain abscesses, which may result in a higher level of care, distorting the outcome data in a positive way.[e90] However, specialized centers may be reference centers and have to deal with the most complex cases, resulting in higher mortality. Finally, reporting of clinical characteristics, causative microorganisms, ancillary investigations, and outcome was highly diverse among studies. Therefore, we have consequently presented the total number of patients in whom the specific characteristic was reported. The lack of differences in case fatality among continents is somewhat surprising considering differences in diagnostic and treatment tools between high- and low-income countries. This lack of difference can be explained by the paucity of African studies. Two of the 3 Africans studies were from South Africa, which has a relatively high standard of care compared with other African countries.[6,e2,e17] Despite the lack of reports in the literature, it is to be expected that for patients in Sub-Saharan Africa—where the rate of HIV infection is high, access to health care facilities is limited, and over-the-counter antibiotics are often freely available, leading to inadequate coverage, dose, and duration of antibiotic treatment—prognosis of brain abscesses is substantially worse.[e91]

To gain more insight into the epidemiology of brain abscess and patient characteristics, future research should be performed prospectively in a multicenter design. National or international collaborations of neurosurgical and/or neurologic departments using standardized clinical scoring systems would provide opportunities to better understand this condition and simultaneously build a platform for clinical trials. Currently, treatment for cerebral abscesses is highly diverse, depending on local experience and resources. Randomized controlled trials evaluating antibiotic regimens or neurosurgical interventions, such as prolonged drainage of brain abscesses by means of leaving a drainage catheter or an Ommaya reservoir for direct antibiotic delivery into the abscess, are needed to rationalize treatment.[30,e92]

AUTHOR CONTRIBUTIONS

Matthijs Brouwer, Jonathan Coutinho, and Diederik van de Beek performed the data analyses and wrote the manuscript.

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DISCLOSURE

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