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Original Article

Early switch to oral antimicrobials in brain abscess: a narrative review

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ABSTRACT

Background: Early switch to oral antimicrobials has been suggested as a treatment strategy in patients with brain abscess, but the practice is controversial.
Objectives: This review aimed to summarize the background, current evidence, and future perspectives for early transition to oral antimicrobials in patients with brain abscess.
Sources: The review was based upon a previous systematic review carried out during the development of the ESCMID guidelines on diagnosis and treatment of brain abscess. The search used 'brain abscess' or 'cerebral abscess' as text or MESH terms in PubMed, EMBASE, and the Cochrane Library. Studies included in the review were required to be published in the English language within the last 25 years and to have a study population of ≥10 patients. Other studies known by the authors were also included.
Content: In this review, the background for some experts to suggest early transition to oral antimicrobials in patients with mild and uncomplicated brain abscess was clarified. Next, results from observational studies were summarized and limitations discussed. Indirect support for early oral treatment of brain abscess was described with reference to other serious central nervous system infections and general pharmacological considerations. Finally, variations within and between countries in the use of early transition to oral antimicrobials in patients with brain abscess were highlighted.
Implications: Early transition to oral antimicrobials in patients with uncomplicated brain abscess may be of benefit for patients due to convenience of treatment and potential decreased risks associated with prolonged hospitalization and intravenous lines. The strategy may also confer a more rational allocation of healthcare resources and decrease expenses. However, the benefit/risk ratio for this strategy remains unresolved at present. **Jacob Bodilsen, Clin Microbiol Infect 2023;29:1139**
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Introduction

In year 2000, the 'Infection in Neurosurgery' working party of the British Society for antimicrobial chemotherapy published a review article on treatment of brain abscess, stating that:

> *"After 1–2 weeks, depending on clinical response, an appropriate oral regimen can be considered"* [1].

This approach was thought-provoking at the time and differed substantially from clinical practice of 6–8 weeks of intravenous (IV) antimicrobials [2]. The aim of this review is to summarize the scientific evidence and clinical experience with early transition to oral antimicrobials for treatment of brain abscess and discuss potential implications for patient management and future research.

Background

Brain abscess is defined as an encapsulated collection of pus within the brain parenchyma and is a uniformly lethal disease if left untreated [3–5]. The incidence of brain abscess ranges from 0.4–0.9 per 100,000 per year in northern Europe and appears to be increasing in recent decades [6–9]. Important risk factors include chronic ear-nose-throat infections, dental infections, immunocompromise, and previous neurosurgery [10–12]. It is also a heterogenous infection, and the aetiology spans from oral cavity bacteria, *Staphylococcus aureus*, and Gram-negative bacilli to

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nocardiosis, tuberculosis, parasites, and fungi [13,14]. Before the introduction of antimicrobials in the 1940s, neurosurgeons were only rarely able to cure patients solely by aspiration and drainage [15,16]. Nowadays, treatment usually comprises neurosurgical aspiration and 6–8 weeks of intravenous (IV) antimicrobials; however, the 30-day and 1-year mortalities remain high at 7% and 20%, respectively [9,17,18].

Methods

This review was based on work carried out during the development of an ESCMID guideline on diagnosis and treatment of brain abscess (expected publication in 2023). Briefly, a literature search was carried out using the search terms 'brain abscess' or 'cerebral abscess' as text or MESH terms in PubMed, EMBASE, and the Cochrane Library. Inclusion criteria were publication in English language within the last 25 years, and the study population should comprise at least 10 patients; i.e. case reports were excluded. The initial search was carried out on September 17, 2021; updated on September 29, 2022, and yielded 2887 non-duplicate hits. Following screening of title and abstract, 460 studies were selected for full-text review of which 5 studies could not be retrieved. Thus, a total of 455 studies were examined in full length, with 18 considered of potential relevance for early transition to oral antimicrobials in the treatment of brain abscess. Other studies known by authors of this review were also included.

Evidence

First experiences in support of early switch to oral antimicrobials in treatment of brain abscess

Interestingly, the statement by the 'Infection in Neurosurgery' working party relied mostly upon expert opinion and was supported by 2 publications suggesting dramatically shortened overall duration of IV treatment of brain abscess; i.e. without early transition to oral antimicrobials (Table 1) [1,19–35].

The first publication was an abstract presented at the 123rd meeting of the Society of British Neurosurgical Surgeons in 1993 by Brown et al. [19]. They used normalisation of C-reactive protein and body temperature combined with a favourable clinical response to guide duration of antimicrobial therapy in 20 consecutive patients with brain abscess or intracranial empyema. The patients were treated with IV antimicrobials for a median duration of 14 days (range, 11–75). The authors did not observe any relapses during follow-up, whereas one patient died from pulmonary embolism.

This was followed up in 1996 by a formal publication by one of the co-authors, A. B. Jamjoom [20]. The study detailed the clinical course of 12 patients with neurosurgically treated brain abscess managed by the same algorithm for duration of treatment as described above. In this study, 2 early case fatalities and one patient treated with prolonged IV antimicrobials for chronic mastoiditis were excluded. Antimicrobial treatment was administered for a median of 20 days (range, 11–30). Again, there were no recurrences during a median follow-up of 21 months (range, 6–36).

Observational studies

Since then, Skoutelis et al. [21] reported the successful use of early switch to oral amoxicillin, ciprofloxacin, and metronidazole for 15–19 weeks in 8 patients who refused continued IV therapy for personal reasons after 6–12 days of treatment. The largest diameter of brain abscesses was 3 cm, and they were all managed conservatively; i.e. without aspiration or excision. The duration of follow-up ranged between 4 and 48 months with no recurrences or case fatalities reported. Other studies indicated that this pragmatic approach had also been adopted into local treatment guidelines in some hospitals in developing countries, occasionally even before the statement by the 'Infection in Neurosurgery' working party [22–32]. Common for almost all of these studies was that they only vaguely described early transition to orals as part of clinical practice without specific analyses of associations with outcome. Still, overall case-fatality rates and risks of recurrences appeared to be comparable with other studies mainly using IV antimicrobial treatment for 6–8 weeks [7,11–14].

Recently, a single-centre study of 108 patients with brain abscess from 2003 to 2016 in Nantes, France, reported that the risk of an unfavourable outcome was 7/48 (15%) in patients switched early to orals compared with 23/60 (38%) in those that were not ($p = 0.01$) [33]. Using continued IV treatment as reference, the odds ratio for unfavourable outcome was 0.2 (95% confidence intervals [CI], 0.0–0.6) in patients with early transition to orals in adjusted

Table 1
Overview of studies describing the use of early transition from intravenous (IV) to oral antimicrobials in the treatment of brain abscess

Author, year	Country	Study design	Overall case-fatality rate	Early orals		Standard IV treatment	
				Case-fatality rate	Recurrence	Case-fatality rate	Recurrence
Brown, 1993 [19]	England	Retrospective, single-centre	1/12	1/12	0/12	—	—
Jamjoom, 1996 [20]	England and Saudi Arabia	Bi-directional, multi-centre	0/26	0/26	0/26	—	—
Jamjoom, 1997 [22]	Saudi Arabia	Retrospective, single-centre	5/37	—	—	—	—
Srinivasan, 1999 [30]	India	Retrospective, single-centre	1/37	1/37	0/37	—	—
Skoutelis, 2000 [21]	Greece	Bi-directional, single-centre	0/8	0/8	0/8	—	—
Babu, 2002 [27]	India	Retrospective, single-centre	5/45	5/45	—	—	—
Jansson, 2004 [25]	Sweden	Prospective, single-centre	8/66	—	—	—	—
Sichizya, 2005 [26]	South Africa	Retrospective, single-centre	16/121	—	—	—	—
Carpenter, 2007 [34]	England	Retrospective, single-centre	5/49	0/21	—	5/28	—
Sharma, 2009 [36]	England	Retrospective, single-centre	9/47	—	—*	—	—
Qasim, 2010 [28]	Pakistan	Retrospective, single-centre	0/40	0/40	—	—	—
Madhugiri, 2011 [23]	India	Retrospective, single-centre	5/139	—	—	—	—
Felsenstein, 2012 [32]	England	Retrospecitive, multi-centre	7/118	—	—	—	—
Ndubuisi, 2017 [24]	Nigeria	Retrospective, multi-centre	8/79	—	—	—	—
Kafle, 2018 [29]	Nepal	Retrospective, single-centre	2/51	2/51	—	—	—
Udayakumaran, 2019 [31]	India	Retrospective, single-centre	1/48	—	—	—	0/29
Asquier-Khati, 2020 [33]	France	Retrospective, single-centre	13/108	7/48**	—	23/60**	—
Lauda-Maillen, 2021 [35]	France	Retrospective, multi-centre	13/101	1/24	1/24	12/77	4/77

* 5/8 recurrences had been switched to early oral antimicrobials of first or second generation cephalosporin.
** Unfavourable outcome assessed by Glasgow Outcome Scale Score <4 was used as proxy for case-fatality.

analysis. Carpenter et al. [34] described the use of early transition to oral antimicrobials among patients treated for brain abscess from 2000 to 2004 at a tertiary care centre in London, England. Fatal outcome was observed in 0/21 (0%) among patients switched early to orals compared with 5/28 (18%) in those who continued IV antimicrobials throughout treatment ($p = 0.06$). Lauda-Maillen et al. [35] also recently observed that 24/101 (24%) of patients with brain abscess had been switched to oral antimicrobials early during treatment at 2 hospitals in Tours and Poitiers, France, from 2007 to 2018. The case-fatality rate was 1/24 (4%) in patients with early transition to oral antimicrobials compared with 12/77 (16%) in the remaining group of patients managed by standard extended IV treatment ($p = 0.18$). Risks of relapse were also comparable between the 2 treatment strategies (1/24 [4%] vs. 4/77 [5%], $p = 0.84$). On the other hand, Sharma et al. [36] reported that among patients with recurrent brain abscess from 1995 to 2005 at a single centre in Liverpool, England, 5/8 (63%) had been switched early to oral treatment with first or second generation cephalosporins. Potential reasons for recurrences may include too short duration of IV antimicrobial treatment or inadequate absorption and intracavitary penetration of oral cephalosporins. It was also unclear if any of these patients with recurrences had permanent neuroanatomical defects or vascular right-to-left shunts as possible explanations for their recurrences.

Potential pitfall in observational studies

Patients with brain abscess who are switched to early oral antimicrobial treatment are more likely to have mild and uncomplicated infections compared with other patients. Thus, a common and important limitation of most of these observational studies is the lack of an appropriate control group matched for disease severity, age, comorbidities, and vital status (i.e. the comparison group has to be alive) at the time of transition to early antimicrobials of the index patients. Other caveats include those inherent of retrospective observational studies, such as missing data, unclear classification of interventions (i.e. time of transition to oral antimicrobials or continuation of IV of treatment) as well as non-standardized treatment, monitoring, and follow-up of patients during everyday clinical practice.

Other serious central nervous system infections managed by oral antimicrobials

Yet, experiences from treatment of certain infections such as tuberculosis, toxoplasmosis, or nocardiosis also lend support for the early transition to oral antimicrobials in patients with brain abscess. These pathogens may involve the central nervous system and require treatment for an extended period of time [37–42]. Although most of the preferred antimicrobials are available in the IV formulation, treatment is almost always based primarily on an oral route of administration.

Pharmacological considerations

Knowledge on concentrations of antimicrobials within brain abscesses in humans is very limited [43]. The few available studies are mostly case reports or case series from the 1970s and 1980s that describe *ad hoc* measurements of samples from patients with brain abscess early during treatment [44–46]. Obviously, this means that the potential long-term drug accumulation within abscesses remains unknown. In addition, detailed information on timing of antimicrobial administration, sampling, and analysis of drug concentrations were often lacking or unclear. Based on the limited information of intracavitary drug concentrations, data on penetration into the cerebrospinal fluid may guide, as a proxy, the choice of antimicrobials for treatment of brain abscess [47].

Studies using animal models to examine intracavitary drug concentrations are also scarce and usually restricted to IV antimicrobials in small rodents with brain abscess [43,48,49]. Besides obvious biological differences between species, important pharmacological considerations include substantially lower ratios of surface area to volume of brain abscesses. This has some theoretical implications, since a high ratio (i.e. large surface area relative to abscess volume) in small abscesses may facilitate increased exposure to antimicrobials and thereby increased intracavitary drug concentration compared with relatively larger abscesses in humans.

Favourable physicochemical characteristics of antimicrobials considered for oral treatment of brain abscess include high lipophilicity, low affinity for efflux pumps in the blood-brain barrier, low degree of polarity and protein binding, and small molecular size [47,50]. Such antimicrobials usually also have a high bioavailability. Otherwise, a high threshold for development of drug resistance and low risks of drug toxicity would be ideal and principles of antimicrobial stewardship and healthcare costs should be considered.

Variations in clinical practice

Management of brain abscess varies substantially within and between countries. Besides patient characteristics, important parameters for such practice variation include availability of neurosurgical expertise and facilities, microbiological diagnostics, intensive care units, and access to modern antimicrobials. This was illustrated previously with adoption of pragmatic approaches in local treatment guidelines at hospitals in developing countries [23,24,26–31]. Yet, practice also differs considerably in more affluent countries as reflected in a recent survey among 310 infectious diseases specialists from Sweden, France, Australia, and Denmark [51]. The study showed that early transition to oral antimicrobials within 4 weeks of IV treatment was used by 134/269 (50%) of respondents. Differences in approaches to treatment is also highlighted by observational studies from France described above [33,35] as well as incorporation of early switch to antimicrobials as a possible treatment option in patients with mild disease in national treatment guidelines in Sweden and Australia [52,53]. The paediatric community have also included early transition to orals as a treatment option in guidelines for brain abscess in England based on apparent lack of harm in a few published studies [54–57]. In contrast, early switch to oral antimicrobials was not recommended in recent German guidelines on brain abscess [58] and is not common practice in countries like Denmark or the Netherlands (personal communication, Professor Matthijs C. Brouwer, Amsterdam Medical Center, Amsterdam, the Netherlands).

Potential implications for patient management and future research

The possibility of shortened IV duration and early transition to oral antimicrobials in treatment of brain abscess is of great interest for patients with uncomplicated disease. Obviously, the convenience of oral treatment may simplify practical issues of drug administration and empower patients in managing their infection. It may also facilitate earlier discharge from hospital and thereby decrease risks of nosocomial infections, especially in settings where outpatient IV antibiotic treatment is unavailable. Finally, considerable reductions in healthcare costs with early switch to orals would be expected and is of particular importance in settings with limited resources or where patients have to pay for hospital admission and treatment themselves.

Consequently, future research on the feasibility of early switch to oral antimicrobials in the treatment of brain abscess is needed. Such studies should prioritize further characterization of subgroups of patients in whom this treatment strategy is likely to be successful and predictors for treatment failure. They should also be repeated in different settings to ensure consistency and generalizability of the results. Importantly, the studies should include a proper comparison group as described previously to account for selection and immortal time bias as well as confounding.

Randomized controlled trials are likely to provide more definitive answers to this research question, and the authors of this review are lead investigator and sponsor of the ongoing "Partial oral antibiotic treatment for bacterial brain abscess: an open-label randomized non-inferiority trial (ORAL)" [59]. The study is currently enrolling patients in several European countries and is expected to open in Australia in 2023 (ClinicalTrials.gov NCT04140903; EudraCT 2019-002845-39). The primary outcome is a composite of 6-month risk of all-cause mortality, intraventricular rupture of brain abscess, unplanned re-aspiration or excision of brain abscess, relapse, or recurrence. Secondary outcomes include extended Glasgow Outcome Scale scores and all-cause mortality at end of treatment and at 3, 6, and 12 months after randomization as well as completion of assigned treatment, IV catheter-associated complications, duration of admission and antimicrobial treatment, severe adverse events, quality of life scores, and neurocognitive examinations. The study is expected to complete enrolment of patients in 3 years from now with an additional year of follow-up of the last recruited patients before data analysis and publication.

Author contributions

Invited by the guest editor, JB conceptualized the study, conducted the systematic review, and wrote the first draft. HN helped with critical review, commentary, and revisions of the manuscript.

Transparency declaration

Jacob Bodilsen is the lead investigator and Henrik Nielsen the sponsor of an investigator-initiated trial on early transition to oral antimicrobials in patients with brain abscess: "Partial oral antibiotic treatment for bacterial brain abscess: an open-label randomised non-inferiority trial (ORAL)" listed at ClinicalTrials.gov (NCT04140903) and EudraCT (2019-002845-39). The study is funded by Novo Nordisk Foundation (Grant 0057510).

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