British Journal of Neurosurgery

The rational use of antibiotics in the treatment of brain abscess

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To link to this article: DOI: 10.1080/02688690020005527
URL: http://dx.doi.org/10.1080/02688690020005527

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The rational use of antibiotics in the treatment of brain abscess

REPORT BY THE 'INFECTION IN NEUROSURGERY' WORKING PARTY OF THE BRITISH SOCIETY FOR ANTIMICROBIAL CHEMOTHERAPY*

Abstract
The Working Party was instituted to investigate the rationale of therapeutic antibiotic usage in patients with brain abscess and to make recommendations for current practice. A systematic review of English language publications on brain abscess over the last 25 years was carried out using electronic databases and secondary sources, and data were evaluated. Few publications were identified where the microbiological procedures were adequately described and many authors continue to report sterile pus in a proportion of cases. The vast majority of reports were retrospective neurosurgical assessments in which details of laboratory procedures and antibiotic regimens were missing. There are no published reports of controlled clinical trials or comparative therapeutic studies. The recommendations made by the Working Party are based on relevant published information and the expertise of Working Party members. Recommendations vary according to the location of the abscess which reflects the likely source of the infection and therefore the bacterial types most likely to be present in aspirated pus. Bacteria with multiple resistance to antimicrobial agents do not feature significantly in cases of brain abscess.

Keywords: Antibiotics, brain abscess, infection, intracranial sepsis, neurosurgery.

Introduction
In a climate of evidence-based medicine, medical audit and other procedures are being used increasingly to evaluate clinical experience, and as a basis for guidelines and recommendations on best clinical practice. In some areas of surgery and medicine a structured approach is not possible. For various reasons, the data on which the assessments depend are either not sufficiently robust or are non-existent. In a number of areas, including the management of brain abscess, it is unlikely that structured prospective studies on the use of antibiotics in the treatment of infection will ever be carried out. In such circumstances any attempt to provide guidance on the rational use of antibiotics has to be based on a critical review of the relevant literature, experience in the management of neurological infections and a thorough knowledge of the antimicrobials currently available.

Many regimens in current use date from the early antibiotic era, since when the available antibiotics and the risks of infection, and the antibiotic susceptibilities of the causative organisms have changed. Until relatively recently antibiotic regimens for the treatment of patients with brain abscess were based on chloramphenicol. The advent of alternative less toxic agents has led to a decline in the use of chloramphenicol and its routine use can no longer be recommended.

The relative infrequency of intracranial abscesses and the varying efficiency in the microbiological procedures used to examine aspirated pus mitigate against the possibility of any comparative studies to determine appropriate therapy. As a result, current practice is based largely on previous experience and, when available, the antibiotic susceptibility results on bacteria isolated from aspirated pus.

In order to address the problems associated with the management of complex infections of the central nervous system, the British Society for Antimicrobial Chemotherapy (BSAC) set up a Working Party with a remit to investigate, deliberate upon and produce recommendations for the appropriate use of antimicrobial drugs in areas of neurosurgical practice, where there was currently no recognized 'best practice'.

The objective of this study was to review the literature on the antimicrobial treatment of brain abscess in order to determine whether there have been any significant changes in the causative organisms and to make recommendations on the therapeutic regimens most likely to be useful. The
principles of surgical management are stated, but details of neurosurgical procedure, except where they impinge on the effectiveness of antimicrobial treatment, are outside the scope of this report.

**Procedure and methods**

The BSAC Council appointed to the Working Party microbiologists and neurosurgeons, who had extensive and acknowledged expertise in the management and treatment of intracranial sepsis.

**Survey procedures**

The Working Party reviewed all the major English language publications relating to the bacteriology of brain abscess and the use of antibiotics in its treatment for the period 1975–1999. The review was based on the results of a primary electronic search (Medline and Promed) and a secondary search for publications not included in Medline. The search terms used were brain abscess, bacteria, antibiotics, intracranial sepsis, infection and neurosurgery. Extensive use was made of the ‘related publications’ facility provided by Promed. All the relevant original papers identified by the search were examined.

Initial review established that almost all the published studies were retrospective, and that no controlled or comparative trials had been completed. In addition, most of the reports were predominantly neurosurgical in nature and, as a result, did not contain comprehensive information on microbiological procedures, and results or details of the antimicrobial regimens employed.

These factors therefore precluded a conventional metaanalytical approach, let alone a formal review process such as that used by Cochrane Collaborative Groups. Relevant information from the review process was used, together with the experience and knowledge of the Working Party members to formulate recommendations on the appropriate prophylactic and therapeutic use of antibiotics in this field. The consensus process consisted of two members of the Working Party drafting a report from the assembled data. This was debated and amended by the full Working Party during a series of meetings during which the database was further examined as necessary. The formalized consensus report was then submitted to the Council of the BSAC for endorsement before being submitted for publication.

**Morbid anatomy and pathogenesis**

The pathogenesis of brain abscess is complex, but has important implications for therapy as the original focus of infection influences both the location of the abscess and the actiological agents.

The lesions may arise as the result of either direct spread from contiguous anatomical structures, or following injury or local infection, or metastasis from a distant focus. Historically, 40% of all brain abscesses were secondary to the direct spread of infection from the middle ear or mastoid cavity. Such abscesses usually occurred in the temporal lobe of the brain, although they could be found in the cerebellum or frontal pole. Aggressive antibiotic treatment of patients with otitis media has led to a reduction in the number of abscesses from this source. Abscesses also develop as a result of direct spread of infection from the paranasal, frontal, ethmoidal or sphenoidal sinuses, or are odontogenic in origin. Abscesses arising from these foci usually localize in the frontal lobes. Less commonly, abscesses present following penetrating injury of the cranium, compound fracture of the skull or neurosurgery. Brain abscesses are also recognized to complicate congenital cyanotic heart disease in patients with right-to-left shunts, cavernous sinus thrombosis arising from septic thrombophlebitis of the anterior facial vein or malignant tumours involving the cranial bones. In these instances, the location of the abscess is less predictable.

Metastatic abscesses, which are almost always monomicrobial, occur widely throughout the brain parenchyma, although they tend to develop in areas supplied by the middle cerebral artery. They are most commonly sequela of suppurative infections in the lungs, particularly bronchiectasis, or of acute or chronic pelvic infection. They may also arise as complications of bacterial endocarditis, dental abscess, bacteraemia or suppuration elsewhere in the body.

Metastatic abscesses are more likely to be multiple or multiloculated, and are fatal more often than solitary abscesses. They are characteristically less well encapsulated, thereby leading to a tendency to spread. This, and their multiplicity, may make a surgical approach difficult or impossible. The septic process may also give rise to septic infarcts. Regardless of the pathogenesis, once the bacteria have lodged in the brain, the capillaries dilate and neutrophils and monocytes enter the tissues. The adventitial cells of the blood vessels separate off as fibroblasts, and begin to lay down granulation tissue and collagen fibres, thus beginning the process of limiting the potential abscess.

The development of abscesses near the corticomedullary junction results in the capsule being thinner on the medial side due to the relative hypovascularity of the white matter. This may account for the tendency of these abscesses to rupture into ventricles, rather than into the subarachnoid space. The failure of an infective focus to lay down granulation tissue, and ultimately a capsule, results in a spreading encephalitis, which is more often a feature of metastatic abscesses than of those which are otogenic. Unless drained or excised, the abscess will rupture, either into a ventricle or onto the surface of the brain, causing a terminal leptomeningitis. Whatever the origin of the infection, a brain abscess is thought to develop only in an area of pre-existing necrosis and this is a prime requirement for its initiation. The area
of oedema surrounding an abscess is often greater in volume than the abscess itself and controlling raised intracranial pressure is an important part of management.

**Bacteriology of brain abscess**

There are few published works devoted solely to the bacteriology of intracranial sepsis. While many reports have provided details of the bacteriological findings, few have specified the laboratory procedures used. ‘Sterile pus’ has been a finding common to almost all studies of the bacteriology of intracranial pus from unselected patients. The numerous reports of bacteria seen in a Gram-stained film of intracranial pus, but not grown, are in many cases the result of culture techniques being inadequate to support the growth of fastidious microorganisms, or of normally non-fastidious organisms adopting a fastidious nutritional mode in response to host factors in a chronic infection. In some cases, failure to isolate the infecting organism(s) may be due to previous treatment with antibacterial agents.

Studies undertaken in the pre-antibiotic era showed that brain abscesses were caused predominantly by *Staphylococcus aureus*, and aerobic and microaerophilic streptococci. Coincident with the decline in the incidence of serious staphylococcal infection, this pattern has changed. Reported isolation rates of Enterobacteriaceae from intracranial abscesses have also declined since the pre-antibiotic era. The availability of broad-spectrum antimicrobial agents, improved microbiological techniques for the isolation of fastidious anaerobic and aerobic bacteria, as well as changes in the overall pattern of disease, have led to significant changes in the bacteriology of intracranial sepsis. The association between sinusitis or a ‘flu-like’ illness, *Streptococcus milleri* and subsequent frontal lobe abscesses, strongly suggests that the source of infection of many brain abscesses is the upper respiratory tract, organisms reaching the brain substance from the paranasal sinuses.²

Although much is known of the pathogenesis of brain abscess in man, no attempt was made to correlate the clinical, morbid anatomical and microbiological findings until de Louvois and colleagues² demonstrated the associations between the site of the abscess, the predisposing factors and the bacteria that caused it. Abscesses of the frontal lobe and intracranial subdural abscesses are usually preceded by episodes of sinusitis or influenza; the predominant cause is *S. milleri*, which is often isolated in pure culture, and other constituents of the nasopharyngeal flora. Otogenic abscesses usually develop in the temporal lobe, but sometimes in the parietal or frontal lobe or the cerebellum, and almost invariably yield a mixed flora, including anaerobes, various *Streptococcus* spp., and Enterobacteriaceae and/or *Pseudomonas aeruginosa*. Abscesses which are secondary to trauma, whether surgical or accidental, are usually caused by *S. aureus*, although, if the trauma involves the paranasal air sinuses, *S. milleri* may also be isolated. The organisms predominantly associated with metastatic and cryptogenic abscesses are *Streptococcus* spp., isolated either in pure culture or with other pathogens, depending on the site of the primary focus. Such abscesses may complicate episodes of septicaemia, in which case the aetiological agent can be isolated from blood culture. While anaerobes are frequently recovered from otogenic abscesses, and may also be implicated in sinugenic, odontogenic and metastatic abscesses, they are rarely associated with traumatic or cryptogenic brain abscesses. If a predisposing infection and the site of the abscess are known, the probable pathogen(s) can be anticipated and appropriate therapy initiated before the results of bacteriological investigations are available. The results of a Gram-stained film of a sample of pus, reported as soon as possible after aspiration, and the presence of a foul smelling odour, indicative of the presence of anaerobic bacteria, also facilitate the choice of empirical therapy. Gas liquid chromatography can be of value for rapidly demonstrating the presence of anaerobic bacteria and may yield useful information when cultures are negative.

**Management of brain abscess**

Drainage or, less commonly, excision remains the treatment of choice for almost all brain abscesses. The guiding principles for surgical management are:

1. to urgently reduce raised intracranial pressure by aspiration of the cavity using image guidance (ultrasound or frame-less stereotaxy) as necessary. Multiple abscesses are best treated by aspiration of the largest one for diagnosis and of others if they are causing a mass effect. Where a peripherally placed abscess fails to respond to aspiration consideration should be given to craniotomy and excision;
2. to confirm the diagnosis;
3. to obtain pus for microbiological diagnosis;
4. to enhance the efficacy of antibiotic therapy;
5. to avoid iatrogenic spread of infection into the ventricles.

Implicit in the effective management of patients with brain abscess is resolution of the original focus of infection.

**Non-operative treatment of intracranial infection**

There are relatively few indications for the non-surgical management of intracranial infections. In general, these are restricted to neurologically intact patients who, for various reasons, are unable to undergo the necessary surgical procedure and in whom the pathogen(s) can be identified from specimens other than intracranial pus. Some lesions
are sufficiently small that even stereotactic surgery may not permit a reliable biopsy, but small brain abscesses can be treated successfully with antibiotics alone. The introduction of newer techniques, especially stereotactic techniques and intraoperative ultrasound guidance, which allow aspiration to be performed accurately and with a low morbidity, justify surgical intervention in patients who might previously have been treated conservatively. Similarly, multiple abscesses, and those which are located deeply or in eloquent parts of the brain should no longer be contraindications to surgical aspiration.

Penetration of antibiotics into the brain

The penetration of antimicrobial drugs from the systemic circulation into brain tissue is complex, and various studies have demonstrated that the physiological properties of the blood–brain barrier and the blood–cerebrospinal fluid barrier are distinct. As a consequence, the penetration of drugs into CSF differs from that into brain tissue or intracranial pus. Equally, the concentrations of antibiotics in plasma cannot be used to predict the concentrations of these agents in brain tissue or intracranial pus.

The extent to which an antibiotic passes from plasma into the central nervous system depends on both the physical properties of the drug, including its ability to cross the blood–brain barrier, and on host factors. Once the abscess has been drained, appropriate systemic therapy should control the residual local infection.

Many antibiotics have been detected in intracranial pus after their systemic injection and have been shown clinically to be effective as treatment for intracranial abscesses. However, the infrequency of intracranial infection has precluded comparative clinical trials. In recent studies, penicillin, ampicillin, cefuroxime, chloramphenicol, co-trimoxazole, ceftazidime and metronidazole have been shown to achieve therapeutic concentrations in intracranial pus, and have been administered successfully as treatment in various combinations. Experimental and clinical studies have demonstrated that even when antibiotics penetrate into the abscess, they may be inactivated by tissue β-lactamases in pus by mechanisms which do not include β-lactamase-producing bacteria.

Antimicrobial treatment of patients with brain abscess

The complexity of the physiological, surgical, pharmacological and bacteriological factors, which affect the successful treatment of patients with brain abscesses, together with the lack of data from prospective clinical trials, have confounded efforts to make recommendations for optimal empirical therapy. For many years the most widely used regimen consisted of high-dosage benzylpenicillin (20 mega units/day), together with chloramphenicol (3–4 g/day) and, indeed, many patients were treated successfully with this combination. The use of probenicid as a means of increasing the plasma and tissue concentrations of penicillins and cephalosporins (except cephaloridine) has not been evaluated in patients with intracranial infections, but may be of benefit. It has been widely held that chloramphenicol given in high dosage is the most appropriate agent before bacteriological results are available. Metronidazole, which is active only against anaerobic organisms, can be given with any other common therapeutic agent. However, since neurological sequelae have been reported after the use of this drug, it should be administered with caution to patients with active disease of the central nervous system.

As well as penetrating into the abscess cavity, therapeutic agents must be shown to be active there; for β-lactam antibiotics, this means being resistant to inactivation by microbial and tissue β-lactamases.

There have been few published studies of the use of third-generation cephalosporins, such as cefotaxime, ceftriaxone and ceftazidime, in the treatment of patients with intracranial infections. Sjölin et al. successfully treated 15 patients with a combination of cefotaxime (3 g tds) and metronidazole (500 mg tds) for a minimum of 3 weeks. This followed an earlier report by the same group describing the penetration of cefotaxime and desacetylcefotaxime into brain abscesses in humans. There are also a number of other reports of the successful use of cefotaxime to treat patients with brain abscess. Both ceftriaxone and ceftazidime achieve therapeutic concentrations in intracranial pus. However, to date, the numbers of patients treated with third-generation cephalosporins are small.

A review of the literature on CNS infections caused by Salmonella spp. identified 36 patients who had been treated with cefotaxime, ceftriaxone, cefuroxime, ceftazidime or moxalactam. Of the 29 evaluable patients, 23 were cured, both clinically and microbiologically, four relapsed and two (7%) failed to respond. It is of note that three of the four patients who relapsed received only 10–14 days of antibiotic therapy. The low mortality rate [one of 29 (3%) patients] compares favourably with those (approximately 20%) from other studies in which ampicillin and chloramphenicol were used.

Cerebral abscesses in neonates caused by Proteus mirabilis, Escherichia coli or Serratia marcescens have been successfully treated with combinations of cefotaxime and gentamicin or, with an even higher success rate, ceftriaxone and amikacin. There is very little information on the efficacy of more recently introduced antibiotics, such as the carbapenems, in the treatment of brain abscess.

Empirical therapy of brain abscess

The initial choice of empirical therapy can be facilitated by a number of considerations, including
the location of the abscess, the precipitating source of infection (e.g. middle ear infection, a history of sinusitis or trauma, etc.), the odour of the pus (which may suggest the presence of anaerobes) and a Gram’s stain of the pus. Initial therapy should be based on these factors and the likely pathogens associated with them. It can be modified, if necessary, once culture results on aspirated pus are known. It is established practice that patients with intracranial abscesses should commence empirical treatment with antibiotics as soon as the diagnosis is confirmed. Empirical therapy tailored to cover the most likely pathogens in individual cases has been used successfully.

**Instillation of antibiotics into the abscess cavity**

The efficacy of instilling antibiotics into the abscess cavity is unknown. Antibiotics administered by this route may diffuse rapidly into the surrounding tissue and cause seizures. On the evidence available, the Working Party concludes that there is no justification for the routine instillation of antimicrobial agents into an intracranial abscess cavity.

**Duration of antibiotic therapy**

Recommendations based on past clinical practice favour a minimum of 4–6 weeks of therapy if the abscess has been excised or aspirated or 6–8 weeks, and possibly longer, if the patient has been treated conservatively. More recently, it has been proposed that, based on a correlation between follow-up CT findings and clinical observations, 3–4 weeks of parenteral therapy are adequate for patients whose abscesses have been excised and 4–6 weeks for those treated by aspiration, with a minimum of 4 weeks for those given antibiotics alone, assuming the absence of ring enhancing lesions on CT performed at the time of discharge. The Working Party considers CT to be an unreliable means of monitoring the response to treatment since radiological appearances lag behind both the reduction in the size of the cavity and the clinical response.

In patients whose abscesses have been aspirated or excised, there is preliminary evidence to suggest that antibiotics can be discontinued once the serum C-reactive protein (CRP) concentration returns to normal. In most cases, this will be after 2 weeks. If the CRP was within the normal range and the patient exhibited no signs of infection at the time of presentation, treatment need not exceed 2 weeks on the basis that the absence of inflammation (cerebritis) is compatible with the abscess being completely walled off and, therefore, the site of infection being contained. There is also evidence to support a switch from parenteral to oral therapy once the CRP has begun to fall, there is an absence of systemic signs of infection (i.e. fever), the patient is able to tolerate antibiotics by mouth and there are appropriate agents available. If the patient is showing clinical response to treatment further aspirations of the abscess cavity are unnecessary.

**Recommended antibiotic regimens**

On the basis of the limited published information and the experience of Working Party members it is recommended that the following be used as first-line empirical therapy: a combination of either cefuroxime, cefotaxime or ceftriaxone, and metronidazole for patients with sinogenic or odontogenic brain abscesses; a combination of ampicillin, metronidazole, and either cefazidime or gentamicin for those with otogenic abscesses; fluclaxacinil or cefuroxime/cefotaxime/ceftriaxone for abscesses secondary to trauma; and, depending on the presumptive source, benzylpenicillin or cefuroxime/cefotaxime/ceftriaxone (±metronida- zole) for patients with metastatic abscesses.

The antibiotics comprising these regimens are not associated with the side-effects attributed to chloramphenicol; their antibacterial activities against enteric bacilli are greater than that of chloramphenicol and they provide cover against a wider range of bacteria. These therapeutic regimens are summarized in Table I. If the chloramphenicol/penicillin combination is

### Table I. Initial empirical antibiotic therapy for patients with brain abscess

<table>
<thead>
<tr>
<th>Infective source</th>
<th>Intracerebral location</th>
<th>Antimicrobial regimen*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paranasal sinuses</td>
<td>Fronto temporal lobe</td>
<td>Cefuroxime 1.5 g tds or cefotaxime 2 g qds or ceftriaxone 3–4 g od and metronidazole 500 mg tds</td>
</tr>
<tr>
<td>Teeth</td>
<td>Fronto temporal lobe</td>
<td>Cefuroxime 1.5 g tds and metronidazole 500 mg tds</td>
</tr>
<tr>
<td>Middle ear (less often, sphenoidal sinuses)</td>
<td>Temporal lobe</td>
<td>Ampicillin 2–3 g tds and metronidazole 500 mg tds together with cefazidime 2 g tds or gentamicin 5 mg/kg od**</td>
</tr>
<tr>
<td>Middle ear (less often, sphenoidal sinuses)</td>
<td>Cerebellum</td>
<td>Ampicillin 2–3 g tds and metronidazole 500 mg tds together with cefazidime 2 g tds or gentamicin 5 mg/kg od**</td>
</tr>
<tr>
<td>Penetrating trauma</td>
<td>Depends on site of wound</td>
<td>Fluclaxacinil 2–3 g qds or cefuroxime 1.5 g tds/cefotaxime 2 g qds/cetrixone 3–4 g od</td>
</tr>
<tr>
<td>Metastatic and cryptogenic</td>
<td>Multiple lesions (usually in area supplied by middle cerebral artery)</td>
<td>Depends on source: benzylpenicillin 1.8–2.4 g 6-hourly if endocarditis or cyanotic congenital heart disease; alternatively cefuroxime 1.5 g tds or cefotaxime 2 g qds or ceftriaxone 3–4 g od with or without metronidazole 500 mg tds</td>
</tr>
</tbody>
</table>

* Adult dosages.
** Gentamicin serum concentrations must be monitored.
used the dosages should be chloramphenicol 0.5 g every 6 h plus penicillin 2.4 g every 4 h. Once the results of culture of pus and of susceptibility testing of isolates are available, antibiotic therapy can be adjusted, if necessary, to address more appropriately the bacteria present. It is probable that the agents listed in the table will cover the vast majority of potential pathogens. Initially, all antibiotics should be administered by the intravenous route. After 1–2 weeks, depending on clinical response, an appropriate oral regimen can be considered.

Intraventricular rupture is a particularly serious complication of intracranial abscess and is associated with a mortality rate exceeding 80%. As well as the administration of appropriate antibiotics systematically, management should include open craniotomy with aggressive debridement of the abscess cavity and lavage of the ventricular system with normal saline containing one or more appropriate antibiotics suitable for intraventricular instillation, i.e. vancomycin and gentamicin each in a concentration of 10 mg/l. CSF examination of patients with brain abscess is not a useful investigation. Cultures are rarely positive, unless the abscess has ruptured, and cell and protein levels may be normal. There is also the increased risk of brain stem herniation. For these reasons lumbar puncture is not advised.

Acknowledgements

We are grateful to Mrs Rosamund Lewis for the administrative support she has given the Working Party and for her patient preparation of this manuscript.

References