**Supplemental files**

**Supplemental 1: PRISMA checklist**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic** | **#** | **PRISMA Checklist item** | **Reported on page #** |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | |  |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 1 |
| **INTRODUCTION** | | |  |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 2 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 2 |
| **METHODS** | | |  |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 3 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 3-4 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | Supplement 2,4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Supplement 2 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 4 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 4 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | N/A |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 4,5 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | N/A |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis. | N/A |
| **RESULTS** | | |  |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Figure 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 4 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Supplement 3 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Table 1-5 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | N/A |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | N/A |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | N/A |
| **DISCUSSION** | | |  |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 9-12 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 13 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 13 |
| **FUNDING** | | |  |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 13 |

**Supplemental 2**

Search Strategy Report

PubMed

PubMed (684 Documents)

"CNS"[All Fields] OR intracranial[All Fields] OR ("brain abscess"[MeSH Terms] OR ("brain"[All Fields] AND "abscess"[All Fields]) OR "brain abscess"[All Fields]) OR ("meningitis"[MeSH Terms] OR "meningitis"[All Fields]) OR spinal[All Fields] AND ("actinomycosis"[MeSH Terms] OR "actinomycosis"[All Fields]) AND ("1988/01/01"[PubDate] : "2022/12/31"[PubDate])

Google Scholar (262 documents)

“CNS" or “intracranial" or "brain abscess" or “meningitis" OR “spinal” OR “epidural abscess” and “actinomycosis”

Scopus (345 documents)

(TITLE-ABS-KEY ( CNS AND infection ) OR TITLE-ABS-KEY ( intracranial AND infection ) OR TITLE-ABS-KEY ( brain AND abscess ) OR TITLE-ABS-KEY ( meningitis ) OR TITLE-ABS-KEY ( spinal ) OR TITLE-ABS-KEY ( epidural AND abscess ) AND TITLE-ABS-KEY ( actinomycosis ) )

**Supplemental 3: Quality assessment**

Table1: JBI Critical Appraisal Checklist for Case Reports

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study reference | Were patient’s demographic characteristics clearly described? | Was the patient’s history clearly described and presented as a timeline?? | Was the current clinical condition of the patient on presentation clearly described? | Were diagnostic tests or methods and the results clearly described? | Was the intervention(s) or treatment procedure(s) clearly described? | Was the post-intervention clinical condition clearly described? | Were adverse events (harms) or unanticipated events identified and described?? | Does the case report provide takeaway lessons? | Risk of biasa |
| Smego et al., 1987 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Hotte et al., 2019 | yes | yes | no | no | yes | yes | no | yes | moderate |
| Hwang et al., 2018 | yes | yes | no | yes | yes | yes | no | yes | moderate |
| Wang et al.,2020 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Ham et al., 2011 | yes | yes | yes | yes | yes | yes | no | yes | low |
| Chicoine et al., 2021 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Rahiminejad et al.,2016 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Bonnefond et al., 2016 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Sah et al., 2020 | yes | yes | no | yes | yes | yes | no | yes | low |
| Narayan et al., 2009 | yes | yes | yes | no | yes | yes | no | yes | low |
| Hotte et al., 2019 | yes | yes | yes | yes | yes | yes | no | yes | low |
| Hwang et al., 2018 | yes | yes | no | yes | yes | yes | yes | yes | low |
| Wang et al., 2020 | yes | yes | no | yes | yes | yes | yes | yes | low |
| Ham et al., 2011 | yes | yes | no | yes | yes | yes | yes | yes | low |
| Ismail et al., 2015 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Kocsis et al., 2018 | yes | yes | yes | yes | yes | no | yes | yes | low |
| Mohamad et al., 2021 | yes | yes | yes | yes | no | yes | yes | yes | low |
| Abo-zed et al., 2021 | yes | yes | no | no | yes | yes | no | yes | moderate |
| Deora et al., 2018 | yes | yes | no | no | yes | yes | no | yes | moderate |
| Verma et al., 2008 | yes | yes | no | no | yes | yes | no | yes | moderate |
| Guillamet et al., 2017 | yes | yes | no | no | yes | yes | no | yes | moderate |
| Pareira et al., 2022 | yes | yes | no | no | yes | yes | no | yes | moderate |
| Funakoshi et al., 2020 | yes | yes | no | no | no | yes | no | yes | high |
| Narayanan et al., 2012 | yes | yes | no | no | yes | yes | no | yes | moderate |
| Chen et al., 2013 | yes | yes | no | yes | yes | no | yes | yes | moderate |
| Jain et al., 2021 | yes | yes | no | no | yes | yes | yes | yes | moderate |
| Miller et al., 2014 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Hadgaonkar et al., 2021 | yes | yes | no | yes | yes | yes | no | yes | low |
| stimac et al., 2020 | yes | yes | no | no | yes | yes | no | yes | moderate |
| Yang et al., 2019 | yes | yes | no | yes | yes | yes | yes | yes | low |
| Clancy et al., 2015 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Anderson et al., 2014 | yes | yes | no | yes | yes | yes | no | yes | moderate |
| Simpson et al., 1996 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Kumar et al., 2014 | yes | yes | no | yes | no | yes | no | yes | moderate |
| Perez et al., 2021 | yes | yes | yes | yes | yes | yes | no | yes | low |
| Vargas et al., 2020 | yes | yes | yes | yes | yes | no | yes | yes | low |
| Kapmaz et al., 2014 | yes | yes | no | yes | yes | yes | no | yes | low |
| Cano et al., 2020 | yes | yes | no | yes | yes | yes | no | yes | low |
| Park et al., 2011 | yes | yes | no | yes | yes | yes | no | yes | low |
| Bellingan et al., 1990 | yes | yes | yes | yes | yes | yes | no | yes | low |
| Yong na et al., 2013 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Park et al., 2014 | yes | yes | no | no | no | yes | yes | yes | moderate |
| Funaki et al., 1998 | yes | yes | yes | yes | yes | yes | no | yes | low |
| Honda et al., 2008 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Kim et al., 2017 | yes | yes | no | no | yes | yes | no | yes | moderate |
| Fadda et al., 2014 | yes | yes | no | yes | no | yes | no | yes | moderate |
| Hagiya et al., 2014 | yes | yes | no | no | no | yes | no | yes | high |
| Patil et al., 2014 | yes | yes | yes | yes | yes | no | yes | yes | low |
| Watkins et al., 2008 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Holland et al., 1998 | yes | yes | yes | yes | yes | yes | no | yes | low |
| Shen et al., 2018 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Kobayashi et al., 2020 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Habib et al., 2018 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Grach et al., 2020 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Hagiya et al., 2014 | yes | yes | yes | yes | yes | no | yes | yes | low |
| Patil et al., 2014 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Watkins et al., 2008 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Holland et al., 1998 | yes | yes | yes | yes | no | yes | yes | yes | low |
| Shen et al., 2018 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Kobayashi et al., 2020 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Habib et al., 2018 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Vikas et al., 2014 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Puzzulli et al., 1998 | yes | yes | no | yes | yes | yes | no | yes | moderate |
| King et al., 1998 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Ryu et al., 2020 | yes | yes | yes | yes | yes | no | no | yes | moderate |
| Gaini et al., 2006 | yes | yes | yes | yes | yes | no | yes | yes | low |
| Olah et al., 2004 | yes | yes | yes | yes | no | yes | yes | yes | low |
| sharma et al., 1990 | yes | yes | yes | yes | no | yes | no | yes | moderate |
| Ravindra et al., 2018 | yes | no | yes | yes | no | yes | no | no | high |
| Ravindra et al., 2018 | yes | yes | yes | yes | no | yes | no | yes | moderate |
| Ravindra et al., 2018 | yes | yes | yes | yes | no | yes | yes | yes | low |
| Ravindra et al., 2018 | yes | yes | yes | no | yes | yes | yes | yes | low |
| Ravindra et al., 2018 | yes | yes | yes | yes | yes | yes | no | yes | low |
| Ravindra et al., 2018 | yes | yes | yes | yes | yes | yes | no | yes | low |
| Ravindra et al., 2018 | yes | yes | yes | yes | yes | no | no | yes | low |
| Akhaddar et al., 2010 | yes | yes | no | no | yes | no | no | yes | high |
| Akhaddar et al., 2010 | yes | yes | yes | yes | yes | yes | no | yes | low |
| Akhaddar et al., 2010 | yes | yes | yes | yes | yes | yes | no | yes | low |
| Akhaddar et al., 2010 | yes | yes | no | yes | yes | yes | no | yes | low |
| Akhaddar et al., 2010 | yes | yes | yes | yes | yes | yes | no | yes | low |
| Jamjoom et al 1994 | yes | yes | yes | yes | yes | yes | no | yes | low |
| Jamjoom et al., 1994 | yes | yes | no | yes | no | yes | no | no | high |
| Jamjoom et al., 1994 | yes | yes | yes | yes | yes | yes | no | yes | low |
| Fabbrii et al., 2014 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Budenz et al., 2010 | yes | yes | no | yes | yes | no | yes | yes | low |
| Tsai et al., 2001 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Lad et al., 1991 | yes | yes | yes | yes | yes | yes | no | yes | low |
| Lad et al., 1991 | yes | yes | yes | yes | yes | yes | no | no | moderate |
| Lad et al., 1991 | yes | no | yes | yes | yes | yes | no | yes | low |
| Navas et al., 1994 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Lagunes et al., 2017 | yes | yes | yes | yes | no | yes | yes | yes | low |
| Nugent et al., 2010 | yes | yes | yes | yes | no | yes | yes | yes | low |
| Mohindra et al., 2012 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Mohindra et al., 2012 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Mishra et al., 2019 | yes | yes | no | yes | no | no | no | yes | high |
| Ghobrial et al., 2016 | yes | yes | no | yes | no | yes | no | yes | moderate |
| Opsomer et al., 2019 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Hernandez et al., 1999 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Haggerty et al., 2012 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Koda et al., 2003 | yes | yes | no | no | no | yes | no | yes | high |
| Rahiminejad et al., 2016 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Imamura et al., 2011 | yes | yes | yes | yes | no | yes | yes | yes | low |
| Chotmongkol et al., 2002 | yes | yes | yes | yes | no | yes | yes | yes | low |
| Adeyemi et al., 2008 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Saleem et al., 2017 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Ohta et al., 2002 | yes | yes | yes | yes | yes | no | yes | yes | low |
| Limaye et al., 2021 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Ushikoshi et al., 1998 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Ipek et al., 2017 | yes | yes | yes | yes | yes | yes | no | yes | low |
| Khare et al., 2019 | yes | yes | no | yes | yes | yes | no | yes | moderate |
| Trisha et al., 2010 | yes | yes | no | yes | no | yes | no | no | high |
| Takahashi et al., 2020 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Lubomski et al., 2018 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Dua et al., 2010 | yes | yes | yes | no | no | yes | yes | yes | moderate |
| Dua et al., 2010 | yes | yes | yes | yes | no | yes | yes | yes | low |
| Bouziri et al., 2011 | yes | yes | no | yes | yes | yes | yes | yes | low |
| Kumar et al., 2019 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Douleh et al., 2016 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Hall et al., 1994 | yes | yes | no | no | yes | no | no | yes | high |
| Adler et al., 1992 | yes | no | yes | yes | yes | no | no | yes | moderate |
| Wang et al., 2017 | yes | yes | yes | yes | yes | yes | yes | yes | low |
| Harshith et al., 2019 | yes | yes | yes | yes | yes | yes | yes | yes | low |

a Risk based on eight questions (Low risk = ≥ 7 yes; Moderate risk = 5-6 yes; High risk = ≤ 4 yes).

**Supplemental-4 (All references included in this review)**

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**Supplemental-5**

**Table 1: Other Microorganisms isolated in CNS Actinomycosis**

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| **Microorganisms Number of Cases** |
| *Fusobacterium* species 14  *Streptococcus intermedius* 6  *Streptococcus mitis* 4  *viridans group streptococci* (VGS) 4  *Staphylococcus epidermidis* 3  *Propionibacterium* 3  *Peptostreptococcus* 2  *S*t*aphylococcus haemolyticus*  2  *Coagulase-negative staphylococci (CoNS)*  2  *Escherichia coli* 2  *Aggregatibacter actinomycetemcomitans* 1  *Bacteroides species* 1  *Pseudomonas species* 1  *Proteus* 1 |

**Supplemental-6**

**Table 2:**

**The impact of polymicrobial infections on clinical outcome in CNS actinomycosis**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Polymicrobial infection** | **Monomicrobial infection** | **p-value** |
| Mortality | 3/35 (8.6%) | 10/83 (12%) | 0.42 |
| Neurological sequelae | 6/24 (25%) | 12/55 (21.8%) | 0.48 |
| Relapse | 1/25 (4%) | 2/46 (4.3%) | 0.71 |
| Mean duration of treatment (days) | 202±34 | 136±49 | 0.02 |
| Combination antibiotic use | 10/34 (29.4) | 16/70 (22.8%) | 0.51 |