|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Studies** | **D1** | **D2** | **D3** | **D4** | **D5** | **D6** | **D7** | **Overall** |
| **Wolfowitz BL, 1972**17 | x | - | xx | x | + | x | + | Critical Risk |
| **Wright JL, 1973**18 | x | - | xx | x | x | + | + | Critical Risk |
| **Lund WS, 1978**19 | xx | + | x | NI | xx | + | x | Critical Risk |
| **Bradley PJ, 1984**8 | x | - | + | + | x | x | + | Serious Risk |
| **Samuel J, 1986**20 | + | - | + | + | xx | + | + | Critical Risk |
| **Kulali A, 1990**21 | + | - | - | + | - | - | - | Moderate Risk |
| **Singh B, 1993**22 | x | - | + | x | + | + | + | Serious Risk |
| **Kurien M, 1998**23 | x | - | - | + | x | - | x | Serious Risk |
| **Djeric D, 2003**4 | x | - | + | + | x | + | + | Serious Risk |
| **Seven H, 2004**24 | x | - | + | x | - | - | + | Serious Risk |
| **Leskinen K, 2005**25 | x | - | x | x | - | - | + | Serious Risk |
| **Ozkaya S, 2005**5 | x | - | + | + | x | x | + | Serious Risk |
| **Penido Nde O, 2005**26 | x | - | xx | x | x | - | - | Critical Risk |
| **Bento R, 2006**27 | + | + | + | + | - | + | x | Moderate Risk |
| **Hafidh MA, 2006**11 | + | + | + | + | x | - | + | Moderate Risk |
| **Morwani KP, 2009**28 | + | - | - | NI | + | + | - | Moderate Risk |
| **Alaani A, 2010**29 | x | - | x | x | - | + | + | Serious Risk |
| **Dubey SP, 2010**30 | x | - | x | + | x | + | x | Serious Risk |
| **Wanna GB, 2010**31 | x | - | + | + | + | + | + | Serious Risk |
| **Nawaz G, 2013**32 | xx | - | NI | NI | xx | x | x | Critical Risk |
| **Borgohain R, 2015**9 | xx | - | xx | NI | x | + | + | Critical Risk |
| **Sharma N, 2015**10 | x | - | x | x | + | - | + | Serious Risk |
| **Mukherjee D, 2016**6 | x | - | x | + | x | - | - | Serious Risk |
| **Laulajainen Hongisto A, 2017**33 | + | - | - | NI | + | + | + | Moderate Risk |
| **Van der Poel NA, 2017**2 | x | - | xx | x | x | x | x | Critical Risk |
| **Burton BN, 2019**3 | + | - | + | + | + | - | + | Moderate Risk |
| **Yakobi A, 2019**34 | x | - | x | + | - | + | + | Serious Risk |
| **Song Y, 2020**7 | x | - | + | + | - | + | + | Serious Risk |

**Table S I:** Risk of Bias Assessment of Observational Included Studies

Footnote: D1; Domain 1: Bias due to confounding, D2; Domain 2: Bias due to selection of the participants, D3; Domain 3: Bias in classification of interventions, D4; Domain 4: Bias due to deviations from intended interventions, D5; Domain 5: Bias due to missing data, D6; Domain 6: Bias in measurement of outcomes, D7; Domain 7: Bias in selection of the reported result, Overall; Overall Risk of Bias, (-); Low Risk, (⁺) ; Moderate Risk, (×); Serious Risk, (××); Critical Risk

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| --- | --- | --- |
| **Studies** | **NIH Quality Assessment Tool for Case Series Studies Criteria Met** | **Quality (Total Quality Score)** |
| **Q1** | **Q2** | **Q3** | **Q4** | **Q5** | **Q6** | **Q7** | **Q8** | **Q9** |
| **Wolfowitz BL, 1972**17 | YES | YES | YES | YES | YES | YES | NO | NO | YES | Good (7) |
| **Wright JL, 1973**18 | YES | YES | YES | YES | YES | NO | NO | NO | YES | Fair (6) |
| **Lund WS, 1978**19 | YES | NO | YES | NA | YES | NO | NO | NO | NO | Poor (3) |
| **Bradley PJ, 1984**8 | YES | YES | YES | YES | YES | YES | NR | NO | YES | Good (7) |
| **Samuel J, 1986**20 | YES | YES | YES | YES | YES | YES | NR | NO | YES | Good (7) |
| **Kulali A, 1990**21 | YES | YES | YES | YES | YES | YES | YES | NO | YES | Good (8) |
| **Singh B, 1993**22 | YES | YES | YES | YES | YES | YES | YES | YES | YES | Good (9) |
| **Kurien M, 1998**23 | YES | YES | YES | YES | YES | YES | YES | NO | YES | Good (8) |
| **Djeric D, 2003**4 | YES | YES | NO | YES | YES | NO | NR | NO | YES | Fair (5) |
| **Seven H, 2004**24 | YES | YES | YES | YES | YES | YES | YES | YES | YES | Good (9) |
| **Leskinen K, 2005**25 | YES | YES | YES | YES | YES | YES | YES | YES | YES | Good (9) |
| **Ozkaya S, 2005**5 | YES | YES | YES | YES | YES | YES | NO | NO | YES | Good (7) |
| **Penido Nde O, 2005**26 | YES | YES | YES | YES | YES | NO | NR | NO | NO | Fair (5) |
| **Bento R, 2006**27 | YES | YES | NR | NΟ | YES | YES | NO | NO | YES | Fair (5) |
| **Hafidh MA, 2006**11 | YES | YES | YES | YES | YES | NO | NO | NO | YES | Fair (6) |
| **Morwani KP, 2009**28 | YES | YES | YES | YES | YES | YES | YES | NR | YES | Good (8) |
| **Alaani A, 2010**29 | YES | YES | YES | NA | YES | YES | NR | NO | YES | Fair (6) |
| **Dubey SP, 2010**30 | YES | YES | NR | NO | YES | YES | NR | NO | YES | Fair (5) |
| **Wanna GB, 2010**31 | YES | YES | YES | YES | YES | YES | NO | NO | YES | Good (7) |
| **Nawaz G, 2013**32 | YES | YES | YES | YES | NO | NO | NO | NO | YES | Fair (5) |
| **Borgohain R, 2015**9 | YES | YES | NR | YES | YES | YES | NR | NO | YES | Fair (6) |
| **Sharma N, 2015**10 | YES | YES | YES | YES | YES | YES | NO | NO | YES | Good (7) |
| **Mukherjee D, 2016**6 | YES | YES | YES | YES | YES | YES | YES | NO | YES | Good (8) |
| **Laulajainen Hongisto A, 2017**33 | YES | YES | YES | YES | YES | YES | NR | YES | YES | Good (8) |
| **Van der Poel NA, 2017**2 | YES | YES | YES | YES | YES | YES | NR | YES | YES | Good (8) |
| **Burton BN, 2019**3 | YES | YES | YES | YES | YES | YES | NR | YES | YES | Good (8) |
| **Yakobi A, 2019**34 | YES | YES | YES | YES | YES | YES | NO | YES | YES | Good (8) |
| **Song Y, 2020**7 | YES | YES | YES | YES | YES | YES | NR | YES | YES | Good (8) |

**Table S II:** NIH Quality Assessment of the included studies

Footnote: Q1: Was study question or objective clearly stated?, Q2: Was study population clearly and fully described, including case definition?, Q3: Were cases consecutive?, Q4: Were subjects comparable?, Q5: Was intervention clearly described?, Q6: Were outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?, Q7: Was length of follow-up adequate?, Q8: Were statistical methods well-described?, Q9: Were results well-described?, Good: Met 7–9 criteria, Fair: Met 4–6 criteria, Poor: Met 0–3 criteria. NA = not applicable, NIH = National Institutes of Health, NR = not reported

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| **Outcomes** | **Starting Grade** | **Risk of Bias** | **Imprecision** | **Indirectness** | **Inconsistency** | **Publication Bias** | **Large Effect** | **Dose Response** | **Confounding Factors** | **Final Grade** | **Quality of Evidence** |
| Males | 2 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Females | 2 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Right Ear | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Left Ear | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Bilateral | 2 | -2 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -2 | VERY LOW |
| Acute Otitis Media | 2 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Chronic Otitis Media | 2 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Cholesteatoma | 2 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Cholesteatoma + Granulomatous tissue | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Granulomatous tissue | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Previous Ear Surgery | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Diabetes | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Adrenogenital Syndrome | 2 | -2 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Intracranial Complications + Intratemporal Complications | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Multiple Intracranial Abscess | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Brain Abscess | 2 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Cerebral Abscess | 2 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Cerebellar Abscess | 2 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Epidural Abscess | 2 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Subdural Abscess | 2 | -1 | 0 | 0 | -1 | -1 | 0 | 0 | 0 | -1 | VERY LOW |
| Meningitis | 2 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Venous Sinus Thrombosis | 2 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Perisinus Abscess | 2 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Hydrocephalus | 2 | -2 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Hemiparesis | 2 | -2 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -2 | VERY LOW |
| Hemiplegia | 2 | -2 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -2 | VERY LOW |
| 6th Cranial Nerve Paralysis | 2 | -1 | -1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Intracranial Complications + Acute Otitis Media | 2 | -1 | -1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Brain Abscess + Acute Otitis Media | 2 | -1 | -1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Venous Sinus Thrombosis + Acute Otitis Media | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Brain Abscess + Cholesteatoma | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Extracranial Complications + Intracranial Complications | 2 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Acute Mastoiditis | 2 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Mastoid Abscess | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Postauricular Fistula | 2 | -2 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -2 | VERY LOW |
| Subperiosteal Abscess | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Labyrinthitis | 2 | -1 | -1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Facial Palsy | 2 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Bezold Palsy | 2 | -1 | -1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Fever | 2 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Otorrhea | 2 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Otalgia | 2 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Headache | 2 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Vomiting / Nausea | 2 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Balance Disturbances | 2 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Vertigo | 2 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Photophobia | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Neck Stiffness | 2 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Papilledema | 2 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Disturbances of Consciousness | 2 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Irritability | 2 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Drowsiness | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Nystagmus | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Aphasia | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Epilepsy | 2 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Diplopia | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Ataxia | 2 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Dysdiadochokinesia | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Mastoid Tenderness | 2 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Neurological signs / deficit | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Antibiotic Therapy Before Brain Complications | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| CT | 2 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| MRI | 2 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| No microbial growth | 2 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Klebsiella spp | 2 | -1 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | VERY LOW |
| Pseudomonas aeruginosa | 2 | -1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Escherichia coli | 2 | -1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Staphylococcus aureus | 2 | -1 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | VERY LOW |
| Proteus mirabilis | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Enterococcus spp | 2 | -1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Streptococcus Group A | 2 | -1 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | VERY LOW |
| Streptococcus pyogenes | 2 | -1 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | -1 | VERY LOW |
| Bacteroides | 2 | -1 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | VERY LOW |
| Fusobacterium | 2 | -1 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | VERY LOW |
| Haemophilus | 2 | -1 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | VERY LOW |
| Peptostreptococcus | 2 | -1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Single Organism growth | 2 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Multiple Organisms growth | 2 | -1 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Complications | 2 | -1 | 0 | 0 | -1 | -1 | 0 | 0 | 0 | -1 | VERY LOW |
| Mortality | 2 | 0 | 0 | 0 | -1 | -1 | 0 | 0 | 0 | 0 | VERY LOW |
| Mortality due to meningitis | 2 | -1 | -1 | 0 | -1 | -1 | 0 | 0 | 0 | -2 | VERY LOW |
| Mortality due to Venous Sinus Thrombosis | 2 | -1 | -1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Mortality due to subdural abscess | 2 | -1 | -1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Mortality due to extradural abscess | 2 | -1 | -1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Mortality due to brain abscess | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Mortality after mastoidectomy | 2 | -1 | -1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Mortality after neurosurgical procedure | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Mortality after mixed intervention | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Recurrence | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Recurrence after mixed intervention | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Revision Surgery | 2 | -1 | -1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Full Recovery | 2 | 0 | 0 | 0 | -1 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Hearing Loss | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Hydrocephalus | 2 | -1 | -1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | VERY LOW |
| Epilepsy | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Ataxia | 2 | -1 | -1 | 0 | -1 | 0 | 0 | 0 | 0 | -1 | VERY LOW |
| Hemiparesis | 2 | -1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | VERY LOW |
| Facial palsy | 2 | -1 | -1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | VERY LOW |

**Table S III:** Overall evidence Quality assessment according to the GRADE recommendations.
Footnote: Starting grade was 4 in outcomes where a RCT was included in the eligible studies. Starting grade was 2 for outcomes where only observational studies were included.