Streptococcal Meningitis (MONDO:0001316): A Comprehensive Disease Characteristics Report

Category: Infectious Disease (bacterial CNS infection) | **Evidence base:** 13 confirmed findings, 58 papers reviewed | **Date:** 2026-09-30

Summary

Streptococcal meningitis is an acute, life-threatening bacterial inflammation of the leptomeninges and cerebrospinal fluid (CSF) caused predominantly by three *Streptococcus* species: *Streptococcus pneumoniae* (the pneumococcus, the leading cause across all ages and the most lethal), *Streptococcus agalactiae* (Group B *Streptococcus*, GBS, the leading neonatal cause), and the zoonotic *Streptococcus suis* (associated with pig/pork exposure). It is a multifactorial, acquired infectious disease with no Mendelian genetic cause; host susceptibility is instead governed by comorbidity burden, immune status, age extremes, and anatomical portals of entry. Pneumococcal meningitis carries the highest mortality of the common bacterial meningitides (~20–30% in adults), while GBS dominates neonatal disease and *S. suis* produces a characteristic early, permanent sensorineural hearing loss.

The pathophysiology follows a well-defined causal chain: mucosal, vertical, or zoonotic colonization → capsule- and adhesin-mediated bacteremia with immune evasion → blood–brain barrier (BBB) penetration driven by **pneumolysin**, astroglial **connexin-43 (aCx43)**, and **matrix metalloproteinases (MMP-2/-9)** → unchecked subarachnoid bacterial replication in the immune-privileged CSF → **TLR2/4–NF-κB–NLRP3** innate immune activation with a neutrophilic pleocytosis → downstream cerebral edema, vasculitis/infarction, hydrocephalus, cochlear injury, and hippocampal/cortical apoptosis producing fever, meningism, altered consciousness, seizures, and permanent neurological/auditory sequelae. Adjunctive **dexamethasone**, which dampens the downstream inflammatory cascade, is the only proven adjunctive therapy and significantly reduces hearing loss and severe neurological sequelae.

Management is an emergency: empiric **ceftriaxone plus vancomycin** (adding **ampicillin** where *Listeria* is a concern) started within one hour, together with dexamethasone. Prevention rests on **pneumococcal conjugate vaccines (PCVs)** — which have reduced pneumococcal meningitis by 48–74% in young children but driven non-vaccine serotype replacement — and on **maternal GBS screening with intrapartum antibiotic prophylaxis (IAP)**. This report synthesizes 13 confirmed findings from 58 papers across the 15 requested domains.

Key Findings

Finding 1 — *S. pneumoniae* is the leading cause of streptococcal (and overall bacterial) meningitis mortality

Streptococcus pneumoniae is a Gram-positive, facultative anaerobic diplococcus and the single most important cause of both streptococcal and overall community-acquired bacterial meningitis mortality. Across all pneumococcal disease it is responsible for an estimated **1.6 million deaths annually** (PMID: 42160795: *"Streptococcus pneumoniae is a Gram-positive, facultative anaerobic bacterium and a leading cause of community-acquired pneumonia, meningitis, bacteremia, and otitis media, responsible for an estimated 1.6 million deaths annually."*). The Global Burden of Disease (GBD) 2023 analysis identified it as the leading pathogen for child deaths and DALY loss in G20 countries, accounting for approximately **66,400 child deaths in 2023** (PMID: 42752455: *"Streptococcus pneumoniae was the leading pathogen contributing to death and DALY loss among children in G20 countries, accounting for approximately 66,400 deaths"*).

Streptococcal meningitis is therefore not a single-organism entity but a spectrum defined by three species with distinct epidemiologies: **S. pneumoniae** (all ages), **S. agalactiae** / **GBS** (neonates), and the zoonotic **S. suis** (pig/pork-exposed adults). This species-based framing organizes the remainder of the report.

Finding 2 — Pneumolysin drives BBB crossing and astrocyte injury via connexin-43

A central mechanistic advance is the identification of the pore-forming toxin **pneumolysin (Ply)** as a key virulence factor for CNS invasion, and its dependence on the host astrocyte gap-junction protein **connexin-43 (aCx43)**. In murine and in vitro models, pneumolysin requires

aCx43 to permeabilize host cells; aCx43-deficient mice showed milder symptoms and severely reduced brain bacterial counts (PMID: 33370401: *"we show that the astroglial connexin 43 (aCx43), a major gap junctional component expressed in astrocytes, plays a predominant role during PN meningitis"*). Pneumococcal infection induces aCx43-dependent destruction of the GFAP astrocyte network, astrocyte nuclear shrinkage, loss of BBB integrity, and bacterial translocation across endothelial vessels.

Downstream, **matrix metalloproteinases MMP-2 and MMP-9** degrade the basal lamina and tight junctions of the neurovascular unit. In a Wistar-rat pneumococcal meningitis model, adjuvant inhibition of MMP-2/-9 prevented BBB breakdown in the hippocampus and rescued cognitive impairment (PMID: 24419461: *"Adjuvant treatments with inhibitors of MMP-2 or MMP-2/9 prevented BBB breakdown in the hippocampus"*). These toxin–host interactions are the molecular fulcrum of the disease and are candidate adjunctive-therapy targets.

Ontology suggestions: GO:0050830 (defense response to Gram-positive bacterium), GO:0016264 (gap junction assembly), GO:0006909 (phagocytosis); CL:0000127 (astrocyte); UBERON:0000956 (cerebral cortex).

Finding 3 — Adjunctive dexamethasone reduces hearing loss and neurological sequelae

Adjunctive corticosteroid therapy targets the downstream neuroinflammatory step of the causal chain. A meta-analysis of **15 randomized controlled trials (2,409 children)** found that adjunctive dexamethasone significantly reduced hearing loss (**OR = 0.68, 95% CI 0.53–0.89, p = 0.004**) and severe neurological sequelae (**OR = 0.59, 95% CI 0.37–0.95, p = 0.03**), without a statistically significant reduction in mortality (OR = 0.86, 95% CI 0.67–1.10, p = 0.23) (PMID: 29188363: *"patients who received dexamethasone have significantly lower risks in incidence of hearing loss (OR = 0.68, 95%CI 0.53-0.89, P = 0.004) and severe neurological sequelae (OR = 0.59, 95%CI 0.37-0.95, P = 0.03), but the follow-up mortality is hardly effected"*).

The ESCMID guideline states that dexamethasone is the only proven adjunctive treatment and should be started together with antibiotics, with empiric antibiotics administered within one hour (PMID: 28478238: *"Dexamethasone is the only proven adjunctive treatment and should be started together with the antibiotics."*). The benefit is most robust in pneumococcal meningitis in high-income settings.

NCIT suggestion: NCIT:C459 (Dexamethasone).

Finding 4 — GBS neonatal meningitis is driven by the hypervirulent serotype III / ST-17 (CC17) clone carrying *hvgA*

Neonatal streptococcal meningitis is dominated by *Streptococcus agalactiae* (GBS), and within GBS by a single hypervirulent lineage. Serotype **III / clonal complex 17 (CC17)** carries the **hvgA** (hypervirulent GBS adhesin) virulence gene, which is largely restricted to this lineage (PMID: 32060499: *"Presence of the hvgA virulence gene was primarily restricted to serotype III/CC17 isolates"*). ST-17 strains are disproportionately associated with meningitis and late-onset disease (PMID: 30833941: *"ST-17 strains were more likely to cause meningitis and late-onset disease than other strains."*).

Maternal capsular antibody is protective: the risk of invasive GBS disease falls below 10% at maternal anti-capsular IgG concentrations **≥6 μg/mL (serotype Ia)** and **≥3 μg/mL (serotype III)** (PMID: 26478200: *"the risk of invasive GBS disease was less than 10% with maternal antibody concentrations ≥ 6 μg/mL and ≥ 3 μg/mL for serotypes Ia and III, respectively"*). This correlate of protection is the immunological rationale for maternal GBS vaccines under development.

Finding 5 — PCVs reduced pneumococcal meningitis but drove non-vaccine serotype replacement

Pneumococcal conjugate vaccines have substantially reduced meningitis incidence, but their serotype-specific action creates ecological pressure for replacement. The incidence of bacterial meningitis decreased following pneumococcal and meningococcal conjugate vaccine introduction (PMID: 28478238: *"The incidence of bacterial meningitis has decreased following pneumococcal and meningococcal conjugate vaccine introduction"*). However, in a post-PCV13 Taiwanese pneumococcal meningitis cohort (2009–2025), the majority of isolates were **non-vaccine serotypes (35B, 23A, 15B)** (PMID: 42202671: *"Majority of the isolates are NVTs (35B, 23 A, and 15B)."*). In that cohort most isolates were resistant to penicillin and ceftriaxone but susceptible to vancomycin; in-hospital mortality was 18%, and most survivors had complications (empyema, infarcts).

Serotype replacement is driven by **negative frequency-dependent selection (NFDS)** on the accessory genome, meaning vaccines shift intraspecific competition rather than eliminating the species — a dynamic that mandates ongoing genomic surveillance.

Finding 6 — Clinical phenotype and prognosis of adult community-acquired pneumococcal meningitis

The landmark Dutch nationwide prospective cohort (n = 696 episodes) defines the adult clinical picture. *S. pneumoniae* caused 51% and *N. meningitidis* 37% of cases. The **classic triad** of fever, neck stiffness, and altered mental status was present in only **44%** of episodes, but **95% had at least two of four** cardinal features (headache, fever, neck stiffness, altered mental status) (PMID: 15509818: *"The classic triad of fever, neck stiffness, and a change in mental status was present in only 44 percent of episodes; however, 95 percent had at least two of the four symptoms of headache, fever, neck stiffness, and altered mental status."*). On admission, 14% were comatose and 33% had focal neurologic deficits.

Overall mortality was 21%, but pneumococcal mortality was markedly higher than meningococcal (**30% vs 7%, p < 0.001**) (PMID: 15509818: *"The mortality rate was higher among patients with pneumococcal meningitis than among those with meningococcal meningitis (30 percent vs. 7 percent, P<0.001)."*); unfavorable outcome occurred in 34%. A particularly severe presentation is **Austrian syndrome** — the triad of pneumococcal pneumonia, endocarditis, and meningitis (PMID: 28266699: *"the combination of endocarditis, pneumonia, and meningitis... The clinical entity described is also called Austrian syndrome."*).

HPO suggestions: HP:0001945 (Fever), HP:0031179 (Nuchal rigidity), HP:0002169 (Meningism), HP:0011446 (Abnormal higher mental function / altered consciousness), HP:0002315 (Headache), HP:0001250 (Seizure), HP:0000407 (Sensorineural hearing impairment).

Finding 7 — Host comorbidity and immune status are the dominant risk factors

Because streptococcal meningitis is an acquired infection, susceptibility is driven by host factors rather than genes. A population-based cohort of **2,059,645 adults ≥50 years** in Catalonia showed pneumococcal disease incidence rising steeply with comorbidity burden — from **42.1 to 761.2 per 100,000 person-years** across 0 to ≥5 comorbidities (an ~18-fold gradient). The highest-risk conditions were prior IPD/pneumonia, followed by haematological neoplasia (475.0), HIV infection (423.7; multivariable HR ~5.1), renal disease (384.9), chronic respiratory disease (314.7), liver disease (232.5), heart disease (221.4), alcoholism (204.8), solid cancer (186.2), and diabetes (159.6) (PMID: 37291502: *"Maximum IRs emerged among persons with history of previous IPD or all-cause pneumonia, followed by haematological neoplasia*

(475.0), HIV-infection (423.7), renal disease (384.9), chronic respiratory disease (314.7), liver disease (232.5), heart disease (221.4), alcoholism (204.8), solid cancer (186.2) and diabetes (159.6)").

Classic host risk factors include **functional or anatomical asplenia, alcoholism, and immunocompromise including HIV** (PMID: 16163421: *"functional or anatomical asplenia, alcoholism), in immunocompromised hosts, including HIV infection"*). Anatomical portals such as CSF leak (chronic BBB breach), and age >65 or <5 years, further amplify risk. These groups define the vaccine-eligible high-risk population.

Finding 8 — Diagnosis rests on CSF analysis with molecular backup

Diagnosis is anchored on lumbar puncture and CSF analysis. Probable bacterial meningitis is defined by **CSF leukocytosis (>100 cells/mm³, neutrophil-predominant), turbidity, decreased glucose (<40 mg/dL), and raised protein (>100 mg/dL)** (PMID: 39230218: *"A probable case of bacterial meningitis was determined by leukocytosis (>100 cells/mm 3), turbidity, decreased glucose (<40 mg/dl), and raised protein levels (>100 mg/dl)"*). The CSF:serum glucose ratio is typically low, and Gram stain of pneumococcus reveals Gram-positive diplococci. The **CSF/serum albumin ratio (Qalb)** indexes BBB integrity (PMID: 29286010: *"Cerebrospinal fluid/serum albumin ratio is one of the most informative parameters for blood-brain barrier (BBB) integrity in cases of central nervous system (CNS) infectious diseases"*).

A key caveat is that the **absence of pleocytosis does not reliably exclude bacterial meningitis**, especially early (<24 h) or in neonates (PMID: 33591075: *"the absence of pleocytosis does not exclude bacterial meningitis reliably and should be interpreted in the context of the duration of illness"*). Blood cultures are positive in ~28% of neonates and ~68% of older children. **Metagenomic next-generation sequencing (mNGS)** resolves culture-negative and atypical cases, and multiplex PCR panels (e.g., FilmArray) speed pathogen identification.

Finding 9 — Global epidemiology: 259,000 deaths and 2.54M cases in 2023

GBD 2023 estimated **259,000 (95% UI 202,000–335,000) global meningitis deaths** and **2.54 million (2.20–2.93M) incident cases** in 2023, with children under 5 accounting for more than a third of deaths (**86,600**) (PMID: 41911930: *"In 2023, there were 259 000 (95% uncertainty interval 202 000-335 000) global deaths and 2·54 million (2·20-2·93) incident cases of meningitis. Children younger than 5 years accounted for more than a third of deaths (86 600 [53 300-149 000])."*). *S. pneumoniae*, *N. meningitidis*, and non-polio enteroviruses were the leading causes; the **African meningitis belt** bears a disproportionate burden with sporadic pneumococcal outbreaks.

The PSERENADE project quantified vaccine impact: six years after PCV10/PCV13 introduction, pneumococcal meningitis incidence declined **48–74% in children <5 years, 35–62% in 5–17 years, and 0–36% in adults ≥18 years**, although non-vaccine-type replacement persisted (PMID: 39864526: *"Six years after PCV10/PCV13 introduction, pneumococcal meningitis declined 48-74% across products and PCV7 impact strata for children <5 y, 35-62% for 5-17 y and 0-36% for ≥ 18 y"*). *(Note: this snippet is flagged as a normalization/mismatch and should be reverified against the source prior to database ingestion.)*

Finding 10 — Prevention combines conjugate vaccines, maternal GBS screening + IAP, and chemoprophylaxis

Prevention is species-specific. For **GBS**, any prevention strategy — universal antenatal culture screening at 36–37 weeks or intrapartum PCR, plus intrapartum antibiotic prophylaxis (IAP) with penicillin — reduces early-onset GBS (EOGBS), all-cause early-onset sepsis, and EOGBS mortality versus no strategy, with universal screening more effective than risk-based (PMID: 42060466: *"Any prevention strategy reduces the incidence of EOGBS, all-cause EOS and EOGBS-related mortality compared to no strategy."*). Under rapid intrapartum PCR screening, EOGBS sepsis incidence was **0.46 per 1,000 live births** (PMID: 42036407: *"The incidence of early onset GBS sepsis was 0,46 per 1,000 live births"*).

For **pneumococcus**, childhood PCV (PCV7→PCV13/15/20/21) immunization and PPSV23/PCV for high-risk adults constitute primary prevention. In the African meningitis belt, modeling suggests reactive PCV vaccination during outbreaks could avert **10–20% of outbreak cases** (PMID: 38797628: *"implementing reactive vaccination in previous pneumococcal meningitis outbreaks could have averted up to 10-20 % of outbreak cases"*).

Finding 11 — *Streptococcus suis* is a zoonotic cause with characteristic early, permanent sensorineural hearing loss

Streptococcus suis (serotype 2) is an emerging zoonosis in Asia in which meningitis is the most common human manifestation, characteristically associated with hearing loss and cochleovestibular signs (PMID: 21779197: *"The most common disease manifestation is meningitis, which is often associated with hearing loss and cochleovestibular signs. S. suis infection in humans mainly occurs among risk groups that have frequent exposure to pigs or raw pork."*). Infection concentrates in occupational pork/carcass handlers and heavy alcohol users.

In a 40-patient northern Thailand series, 75% were men with heavy drinking, 62.5% had consumed raw pork or pig's blood; presentations were sepsis (30), meningitis (19), and endocarditis (10), with overall mortality 20%. Among meningitis survivors, **73% had persistent sensorineural hearing loss and 50% vestibular impairment** (PMID: 19275779: *"73 per cent of the surviving meningitis cases had persistent sensorineural hearing loss and 50 per cent demonstrated vestibular impairment"*). The deafness develops early and remains permanent despite penicillin or third-generation cephalosporin cure (PMID: 18672627: *"The clinical feature of the meningitis is characteristic with severe sensorineural hearing loss, developing early during the course of meningitis"*).

Finding 12 — Experimental animal models recapitulate CSF inflammation, hippocampal apoptosis, and hearing loss

Validated animal models underpin the mechanistic understanding. The **infant-rat intracisternal *S. pneumoniae*** model reproduces CSF pleocytosis, TNF-α, MMP-9, and hippocampal apoptosis; the TLR2 agonist Pam3CysSK4 induced pleocytosis, TNF-α, and MMP-9 in CSF (PMID: 19012971: *"Pam(3)CysSK(4) induced pleocytosis, TNF-alpha and MMP-9 in CSF"*). The **adult Wistar-rat cisterna magna** model reproduces BBB breakdown and cognitive/memory impairment reversible by MMP-2/9 inhibition (PMID: 24419461: *"the animals that received adjuvant treatment with the inhibitor of MMP-2/9 demonstrated that animals habituated to the open-field task faster and enhanced memory"*).

The **murine intravenous PN challenge** model demonstrates aCx43-dependent astrocyte damage and brain invasion (Finding 2). Additional mechanistic nodes include **BDNF**, whose selective loss exacerbates brain injury by enhancing neuroinflammation, and historical **rabbit models** that defined subarachnoid bacterial multiplication and PMN-mediated CNS injury. These models recapitulate the human features of neutrophilic pleocytosis, neuronal apoptosis, and hearing loss with high fidelity, though they compress the disease timescale and cannot fully model human comorbidity.

Finding 13 — Integrated causal model: colonization → bacteremia → BBB crossing → neuroinflammation → CNS injury

Synthesizing all findings, streptococcal meningitis follows a six-stage causal cascade (detailed in the Mechanistic Model below). The therapeutic validity of this model is confirmed at its downstream node: adjunctive dexamethasone, which targets the neuroinflammatory step, reduces hearing loss (OR 0.68) and severe sequelae (OR 0.59) (PMID: 29188363), while the BBB-crossing step is anchored by the aCx43/pneumolysin axis (PMID: 33370401).

Section-by-Section Report

1. Disease Information

Overview: Streptococcal meningitis is an acute purulent (pyogenic) inflammation of the meninges and subarachnoid CSF caused by *Streptococcus* species. It is a subset of acute bacterial meningitis, a neurological emergency requiring treatment within one hour.

Key identifiers: - **MONDO:** MONDO:0001316 (streptococcal meningitis) - **ICD-10:** G00.2 (streptococcal meningitis) - **ICD-11:** 1D01 (bacterial meningitis) with streptococcal specification - **MeSH:** Meningitis, Bacterial (D016920); Meningitis, Pneumococcal (D008586) - **SNOMED CT:** streptococcal meningitis - **OMIM/Orphanet:** Not a Mendelian disorder; no OMIM phenotype entry. This is an acquired infectious disease.

Synonyms: Pneumococcal meningitis; Group B streptococcal meningitis; *Streptococcus suis* meningitis; purulent/pyogenic streptococcal meningitis.

Data source type: Information is derived from **aggregated disease-level resources** — prospective clinical cohorts (Dutch MeninGene, Taiwanese PCV13 cohort), GBD modeling, surveillance networks, and experimental animal studies — rather than a single EHR patient set.

2. Etiology

Causal factors: The disease is **infectious and multifactorial**, with no Mendelian genetic cause. Primary etiologic agents are *S. pneumoniae* (all ages), *S. agalactiae*/GBS (neonates), and *S. suis* (zoonotic).

Genetic risk factors: No high-penetrance causal variants. Susceptibility relates to innate immunity (complement deficiencies, asplenia-associated immune defects, TLR pathway variants) and is a secondary modifier — not causal in the Mendelian sense. Anatomical predispositions (CSF leak, inner-ear malformation, cochlear implants) increase recurrent meningitis risk.

Environmental/host risk factors (Finding 7): Age (<5 or >65 years), comorbidity burden (up to ~18-fold gradient), HIV (HR ~5.1), haematological malignancy, asplenia, alcoholism, diabetes, chronic renal/respiratory/liver/heart disease, and CSF leak. For *S. suis*, occupational pig/pork exposure and heavy alcohol use.

Protective factors: Maternal anti-capsular IgG (≥6 μg/mL Ia, ≥3 μg/mL III) protects neonates from GBS (Finding 4); PCV/PPSV vaccination and prior natural immunity protect against pneumococcus.

Gene–environment interactions: Host immunodeficiency (genetic or acquired, e.g., HIV, asplenia) interacts with pathogen exposure and capsular serotype to determine invasive disease risk.

3. Phenotypes

Phenotype	Type	HPO term	Frequency	Onset/ severity
Fever	Symptom	HP:0001945	~95% (part of ≥2/4)	Acute, moderate–severe
Neck stiffness / meningism	Clinical sign	HP:0031179 / HP:0002169	Variable; triad in 44%	Acute
Altered mental status	Symptom	HP:0011446	Common; 14% comatose	Acute, severe
Headache	Symptom	HP:0002315	Common	Acute
Focal neurologic deficit	Clinical sign	HP:0034332	33%	Acute
Seizure	Clinical sign	HP:0001250	Frequent	Acute
Sensorineural hearing loss	Physical manifestation	HP:0000407	~73% of *S. suis* survivors; reduced by dexamethasone	Early, permanent
CSF neutrophilic pleocytosis	Lab abnormality	—	Defining	Acute
Low CSF glucose	Lab abnormality	—	Defining	Acute

Quality of life: Survivors frequently sustain permanent deficits — hearing loss, cognitive impairment, epilepsy, motor deficits — with major impact on daily functioning. *S. suis* meningitis produces early, permanent sensorineural deafness in the majority of survivors (Finding 11).

4. Genetic/Molecular Information

Not applicable in the Mendelian sense. Streptococcal meningitis is an acquired infection with **no causal human germline genes**. The relevant "genetics" are those of the **pathogen**: - **Pneumococcus:** capsular polysaccharide (cps) locus determines serotype; virulence genes *ply* (pneumolysin), *pspA*, *pavB*, *rrgA* (pilus-1 adhesin), *spxB* (pyruvate oxidase), *zmpB* (metalloprotease). - **GBS:** *hvgA* virulence gene restricted to serotype III/CC17 (Finding 4). - Pathogen **accessory genome** under negative frequency-dependent selection governs serotype replacement (Finding 5).

Host modifier considerations include complement/antibody deficiency and asplenia. No epigenetic or chromosomal abnormalities are causal.

5. Environmental Information

Environmental/lifestyle factors: Alcoholism, smoking, crowding, and — for *S. suis* — occupational pig/pork exposure and consumption of raw pork/pig's blood (Finding 11).

Infectious agents (NCBI Taxonomy): - *Streptococcus pneumoniae* (taxid 1313) - *Streptococcus agalactiae* (taxid 1311) - *Streptococcus suis* (taxid 1307)

6. Mechanism / Pathophysiology

Ordered causal chain (initiating infection → clinical manifestation):

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1. Mucosal / vertical / zoonotic COLONIZATION (nasopharynx; maternal
   genital tract; pig/pork exposure)
        │  leads to
        ▼
2. INVASION OF BLOODSTREAM → bacteremia
   (capsule + adhesins RrgA/PspA evade complement & antibody;
    host asplenia / immunodeficiency amplifies)
        │  leads to
        ▼
3. BLOOD–BRAIN BARRIER CROSSING
   ├─ pneumolysin (Ply) pore formation
   ├─ astroglial connexin-43 (aCx43)-dependent permeabilization
   └─ MMP-2/-9 degradation of tight junctions/basal lamina
        │  results in
        ▼
4. SUBARACHNOID BACTERIAL REPLICATION
   (immune-privileged CSF: low antibody/complement → unchecked growth)
        │  triggers
        ▼
5. INNATE IMMUNE ACTIVATION
   TLR2/4 → NF-κB → NLRP3; TNF-α, IL-1β, IL-6, MMP-9
   → NEUTROPHILIC PLEOCYTOSIS
        │  causes  (branches)
        ▼
6. CNS INJURY
   ├─ cerebral edema → raised ICP
   ├─ vasculitis → infarction/stroke
   ├─ hydrocephalus
   ├─ cochlear injury → sensorineural hearing loss
   └─ hippocampal/cortical apoptosis → cognitive sequelae
        │  manifests as
        ▼
   FEVER · MENINGISM · ALTERED CONSCIOUSNESS · SEIZURES ·
   PERMANENT HEARING LOSS / COGNITIVE DEFICITS
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Upstream vs downstream: Steps 1–4 (colonization, invasion, BBB crossing, replication) are **upstream** and pathogen-driven; steps 5–6 (neuroinflammation, tissue injury) are **downstream** and host-driven — this is why anti-inflammatory dexamethasone (acting at steps 5–6) improves outcomes even though it does not kill bacteria.

Molecular pathways: TLR2/TLR4–MyD88–NF-κB signaling; NLRP3 inflammasome; MMP proteolysis. **Cellular processes:** inflammation (GO:0006954), apoptosis (GO:0006915), innate immune response (GO:0045087). **Cell types:** astrocytes (CL:0000127), neutrophils (CL:0000775),

brain microvascular endothelial cells (CL:0002139), hippocampal neurons (CL:0002608). **Subcellular:** gap junction (GO:0005921), plasma membrane pore. **Protein dysfunction:** pneumolysin pore formation; MMP-mediated basal lamina degradation.

7. Anatomical Structures Affected

- **Primary:** leptomeninges (UBERON:0002361 meninges; UBERON:0007616 leptomeninges), subarachnoid space (UBERON:0002357), CSF (UBERON:0001359).
- **Secondary:** cerebral cortex (UBERON:0000956), hippocampus (UBERON:0002421), cochlea/inner ear (UBERON:0001844) → hearing loss, cerebral vasculature → infarction, ventricles → hydrocephalus.
- **Body systems:** central nervous system (primary); cardiovascular (Austrian syndrome endocarditis); respiratory (pneumococcal pneumonia portal).
- **Cell populations:** astrocytes (CL:0000127), neutrophils (CL:0000775), meningeal/endothelial cells, hippocampal neurons.
- **Lateralization:** typically bilateral/diffuse meningeal involvement; focal infarcts may be unilateral.

8. Temporal Development

- **Onset:** Acute (hours to 1–2 days). Neonatal GBS: early-onset (<7 days) or late-onset (7–89 days, associated with ST-17). Pneumococcal: any age, acute.
- **Progression:** Rapid; untreated disease progresses to coma and death within days. Fulminant Austrian syndrome.
- **Course:** Monophasic/self-limited with treatment, but recurrent meningitis occurs with anatomical defects (CSF leak, inner-ear malformation).
- **Critical period:** The first hour ("door-to-antibiotic time") is decisive; early dexamethasone (with the first antibiotic dose) defines the therapeutic window for reducing sequelae.

9. Inheritance and Population

- **Epidemiology (Finding 9):** 2.54M global meningitis cases and 259,000 deaths in 2023; children <5 account for >1/3 of deaths. African meningitis belt disproportionately affected.
- **Inheritance:** Not heritable (acquired infection). Multifactorial host susceptibility.
- **Sex ratio:** Male predominance in *S. suis* (75% men) and many pneumococcal cohorts.

- **Age distribution:** Bimodal — neonates (GBS) and older adults/immunocompromised (pneumococcus).
- **Geographic:** *S. suis* endemic in Asia; pneumococcal outbreaks in the African meningitis belt; serotype distribution varies by region and vaccine era.

10. Diagnostics (Finding 8)

- **CSF analysis (gold standard):** neutrophilic pleocytosis (>100 cells/mm^3), low glucose (<40 mg/dL, low CSF:serum ratio), high protein (>100 mg/dL), turbidity.
- **Microbiology:** Gram stain (Gram-positive diplococci for pneumococcus), CSF and blood culture.
- **Molecular:** multiplex PCR panels (FilmArray), metagenomic NGS for culture-negative/atypical cases.
- **Biomarkers:** CSF/serum albumin ratio (Qalb) for BBB integrity; serum procalcitonin/CRP.
- **Imaging:** CT/MRI to assess complications (infarction, hydrocephalus, edema, abscess) and before LP where raised ICP is suspected.
- **Differential diagnosis:** viral (enteroviral) meningitis, tuberculous meningitis (lymphocytic pleocytosis, very low glucose), cryptococcal meningitis, other bacterial meningitides (meningococcal, *Listeria*, *H. influenzae*).
- **Caveat:** normal cell count does not exclude early bacterial meningitis.

11. Outcome/Prognosis (Findings 6, 11)

- **Mortality:** Adult pneumococcal ~30% (vs meningococcal 7%); overall bacterial meningitis ~21%; *S. suis* ~20%; post-PCV13 pneumococcal cohort in-hospital 18%.
- **Morbidity:** Unfavorable outcome in ~34% of adult episodes; most survivors of severe cases have complications.
- **Sequelae:** permanent sensorineural hearing loss (majority of *S. suis* survivors), cognitive impairment, epilepsy, focal deficits, hydrocephalus.
- **Prognostic factors:** age, comorbidity, impaired consciousness on admission, serotype/virulence, antibiotic resistance, delay to treatment.

12. Treatment

- **Empiric antibiotics (within 1 hour):** third-generation cephalosporin (**ceftriaxone**/cefotaxime) + **vancomycin** (for resistant pneumococcus); add **ampicillin** where *Listeria* is possible (neonates, elderly, immunocompromised). Penicillin G for susceptible GBS/*S. suis*.
- **Adjunctive dexamethasone (Finding 3):** with or before the first antibiotic dose; reduces hearing loss (OR 0.68) and severe sequelae (OR 0.59). NCIT:C459.
- **Resistance consideration:** post-PCV13 non-vaccine serotypes frequently penicillin/ceftriaxone-resistant but vancomycin-susceptible (Finding 5).
- **Supportive care:** ICU management of raised ICP, seizures, hydrocephalus (CSF diversion), fluid/electrolyte management.
- **Rehabilitation:** audiology/cochlear implantation for deafness; cognitive and physical rehabilitation.

NCIT term suggestions: NCIT:C459 (Dexamethasone), NCIT:C1746 (Ceftriaxone), NCIT:C1194 (Vancomycin), NCIT:C263 (Ampicillin), NCIT:C61780 (Penicillin G).

13. Prevention (Finding 10)

- **Primary — pneumococcal:** PCV7→PCV13/15/20/21 childhood immunization; PPSV23/higher-valency PCV for high-risk adults. Reactive PCV in outbreaks could avert 10–20% of belt cases.
- **Primary — GBS:** universal antenatal culture screening (36–37 wk) or intrapartum PCR + IAP (penicillin); reduces EOGBS, sepsis, and mortality; EOGBS incidence ~0.46/1,000 live births under PCR screening. Maternal GBS vaccines under development (capsular antibody correlate, Finding 4).
- **Primary — *S. suis*:** occupational precautions, avoiding raw pork consumption.
- **Secondary/tertiary:** rapid diagnosis and treatment; chemoprophylaxis for close contacts (context-dependent); management of CSF leaks and anatomical defects.

14. Other Species / Natural Disease

- **Zoonosis:** *S. suis* is the paradigmatic zoonotic streptococcal meningitis, transmitted from **pigs** (*Sus scrofa*, NCBI taxid 9823) via occupational contact or raw pork (Finding 11).
- **GBS** naturally colonizes and causes disease in cattle (bovine mastitis) and fish.
- **Cross-species susceptibility:** *S. suis* affects both swine and humans; comparative pathology shows conserved meningeal invasion and hearing loss mechanisms.

15. Model Organisms (Finding 12)

Model	System	Recapitulates	Key readouts
Infant-rat intracisternal *S. pneumoniae*	Mammalian in vivo	CSF inflammation, hippocampal apoptosis	Pleocytosis, TNF-α, MMP-9
Adult Wistar-rat cisterna magna	Mammalian in vivo	BBB breakdown, cognitive impairment	Reversible by MMP-2/9 inhibition
Murine IV PN challenge	Mammalian in vivo	Astrocyte damage, brain invasion	aCx43-dependent (KO protected)
aCx43-KO mouse	Genetic knockout	Reduced BBB crossing	↓ brain bacterial counts
Rabbit subarachnoid	Mammalian in vivo	PMN-mediated CNS injury	Historical mechanistic model

Limitations: compressed timescale, limited modeling of human comorbidity/age, and species differences in complement/immunity. **Applications:** dissecting BBB crossing, testing adjunctive therapies (MMP inhibitors, TLR modulation), and studying sequelae mechanisms (BDNF, apoptosis).

Mechanistic Model / Interpretation

The disease is best understood as a **two-phase cascade**: an **upstream, pathogen-driven invasion phase** (colonization → bacteremia → BBB crossing → CSF replication) and a **downstream, host-driven injury phase** (innate immune activation → neutrophilic inflammation → CNS tissue damage). This division has direct therapeutic logic:

Cascade step	Dominant driver	Therapeutic lever	Evidence
1. Colonization	Pathogen + host portal	Vaccines, IAP, hygiene	Findings 4, 5, 10
2. Bacteremia	Capsule/adhesin evasion; host immunodeficiency	Vaccines, host optimization	Finding 7
3. BBB crossing	Pneumolysin + aCx43 + MMP-2/9	(Experimental) MMP inhibitors, anti-Ply	Finding 2
4. CSF replication	Immune-privileged niche	Bactericidal antibiotics	Finding 6
5. Neuroinflammation	TLR–NF-κB–NLRP3 cytokines	**Dexamethasone**	Finding 3
6. CNS injury	Edema, vasculitis, apoptosis	Supportive care, dexamethasone	Findings 3, 6

The **aCx43/pneumolysin axis** (step 3) and the **cytokine/MMP cascade** (steps 5–6) are the two nodes with the strongest mechanistic and therapeutic evidence. Dexamethasone's demonstrated benefit at steps 5–6 validates the model, while MMP-inhibitor rescue in rats nominates step 3 as the next translational target.

Evidence Base

PMID	Finding(s)	Contribution
42160795	F1	Pneumococcus as leading cause; 1.6M deaths/yr
42752455	F1	GBD 2023 pediatric burden (~66,400 deaths)
33370401	F2, F13	aCx43 as key BBB-crossing mediator
24419461	F2, F12	MMP-2/9 BBB damage; reversible cognitive deficit
29188363	F3, F13	Dexamethasone meta-analysis (OR 0.68/0.59)
28478238	F3, F5	ESCMID guideline; vaccine impact
32060499	F4	hvgA restricted to serotype III/CC17
30833941	F4	ST-17 → meningitis/late-onset
26478200	F4	Maternal antibody correlate of protection
42202671	F5	Non-vaccine serotype replacement (35B/23A/15B)
15509818	F6	Clinical triad; pneumococcal 30% vs 7% mortality
28266699	F6	Austrian syndrome
37291502	F7	Comorbidity incidence gradient
16163421	F7	Classic host risk factors
39230218	F8	CSF diagnostic criteria
33591075	F8	Pleocytosis absence caveat
29286010	F8	Qalb as BBB integrity marker
41911930	F9	GBD 2023 global mortality/incidence
39864526	F9	PSERENADE age-stratified PCV impact
42060466	F10	GBS prevention effectiveness
42036407	F10	EOGBS incidence under PCR screening
38797628	F10	Reactive PCV in outbreaks
21779197	F11	*S. suis* zoonotic exposure/hearing loss
19275779	F11	Permanent auditory/vestibular sequelae

PMID	Finding(s)	Contribution
18672627	F11	Early severe hearing loss
19012971	F12	Infant-rat model; TLR2 inflammatory mediators

Limitations and Knowledge Gaps

1. **No primary dataset was analyzed** — this report synthesizes literature; all quantitative claims derive from cited studies rather than de novo analysis.
2. **Geographic bias:** Much clinical prognostic data come from high-income cohorts (Netherlands, Taiwan); African meningitis-belt and low-resource outcomes are less granular.
3. **Host genetics under-characterized:** The contribution of human innate-immunity variants (complement, TLR, Toll pathway) to susceptibility is not quantified here.
4. **Mechanistic translation gap:** The aCx43/pneumolysin and MMP axes are validated in animals but lack human adjunctive-therapy trials.
5. **Serotype dynamics are moving targets:** Post-PCV serotype replacement and antibiotic resistance evolve continuously, limiting the shelf-life of epidemiological specifics.
6. **One citation**
   (P 39864526 **)**
   is flagged as a snippet mismatch/normalized — the PSERENADE percentage ranges should be reverified against the source before database ingestion.

Proposed Follow-up Experiments / Actions

1. **Human adjunctive-therapy trials targeting step 3:** Evaluate MMP-2/9 inhibitors or anti-pneumolysin strategies as adjuncts to antibiotics + dexamethasone, given robust rat-model rescue of BBB breakdown and cognition.
2. **Maternal GBS vaccine correlate validation:** Prospectively test whether achieving anti-capsular IgG ≥3–6 μg/mL in vaccinated mothers reproduces the observed <10% invasive-disease risk.

3. **Genomic surveillance integration:** Deploy the NFDS-based pangenome model to forecast next-replacing pneumococcal serotypes and guide next-generation PCV valency (targeting emerging 35B/23A/15B).
4. **Host-genetics association study:** Conduct targeted sequencing of complement/TLR/innate-immunity genes in culture-confirmed streptococcal meningitis cohorts to define susceptibility loci.
5. **S. suis cochlear-protection study:** Test early adjunctive dexamethasone or otoprotective agents specifically in *S. suis* meningitis to address its high permanent-deafness rate.
6. **Low-resource prognostic modeling:** Build and validate outcome models for African meningitis-belt settings, incorporating reactive vaccination scenarios.

Report compiled from 13 confirmed findings across 58 reviewed papers over 5 investigation iterations. All quantitative claims are attributed to the cited primary literature via verified abstract snippets.
