

Original Article

Predisposing factor, impactful adjunctive treatment or unfavorable prognostic marker: a meta-analysis on the elusive role of dexamethasone for *Listeria monocytogenes* meningitis

Alberto Enrico Maraolo¹, Maria Mazzitelli²

¹ First Division of Infectious Diseases, Cotugno Hospital, Naples, Italy

² Department of Molecular Medicine, Infectious and Tropical Diseases Unit, Padua University Hospital, Padua, Italy

Abstract

Introduction: There are no randomized controlled trials to inform the choice of using adjunctive dexamethasone (AD) against *Listeria monocytogenes* meningitis (LMM) and data from observational studies are pretty conflicting.

Methodology: We performed a rapid review of the literature with quantitative analysis. A pairwise random-effects meta-analysis was implemented, pooling unadjusted and adjusted data. The main outcome was mortality.

Results: Across all included studies (five) informing the main analysis on raw mortality data, 199 patients received AD, as opposed to 382 who did not receive AD. All-cause mortality was slightly lower in patients undergoing AD, but not in a statistically significant manner: odds ratio 0.96, 95% confidence interval 0.42-2.19. The prediction interval was very wide (0.06-15.99), suggesting that in future studies the effect of AD might be either beneficial or harmful.

Conclusions: The role of AD for LMM still needs to be established being the current evidence inconclusive and heterogeneous.

Key words: dexamethasone; meta-analysis; neurolisteriosis; therapy; steroid; systematic review.

J Infect Dev Ctries 2023; 17(12):1748-1752. doi:10.3855/jidc.18804

(Received 25 June 2023 – Accepted 17 October 2023)

Copyright © 2023 Maraolo *et al.* This is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

Recently an important article by Brower *et al.* on the role of adjunctive dexamethasone (AD) for *Listeria monocytogenes* meningitis (LMM), assessed in a prospective cohort, was published [1]. The ensuing findings completely overturned the message provided by the MONALISA French study, which had found reduced survival in patients with LMM treated with AD [2]. The same Dutch authors in an outstanding review published in 2021 had advised against the use of AD for patients with neurolisteriosis based on available evidence at that time [3].

Beyond antibiotics, steroids are the only drugs impacting the prognosis of acute bacterial meningitis (ABM). However, what kind of steroid is best to use and for which pathogen remains debated, as well as the outcome influenced the most [3]. According to a seminal Cochrane review, the highest benefit from AD is obtained in *Streptococcus pneumoniae* (for mortality) and *Haemophilus influenzae* (for neurological sequelae) meningitis [4]. Compared with encapsulated bacteria, *L. monocytogenes* is a less frequent cause of ABM for which immunosuppression, including the one steroid-related, is a strong risk factor [5]. Hence, the controversy over the benefits of AD ensued.

In light of the recent Dutch study [1], to compare AD with no AD use in adults with LMM, we performed a rapid review of the literature with quantitative analysis.

Methodology

A rapid review of the literature was conducted. Two databases were screened up to March 31st, 2023: PubMed/MEDLINE and EMBASE, without language restriction, according to the recommendations ("at least two bibliographic databases should be searched") provided by the updated version of AMSTAR (A MeaSurement Tool to Assess systematic Reviews), namely AMSTAR 2 [6]. Studies were included per the following criteria: availability of information regarding mortality stratified by treatment group (AD versus no AD); alternatively, the inclusion criterion was the availability of adjusted effect sizes regarding the clinical impact of AD were available. Articles devoid of this information were discarded.

The primary outcome of this meta-analysis was mortality. If available, data on other clinically relevant endpoints (for instance, coma) were extracted.

Unadjusted and adjusted effect sizes were pooled in the framework of a pairwise random-effects meta-

analysis, anticipating high heterogeneity due to the lack of known randomized clinical trials (RCTs) addressing the topic. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated for dichotomous data.

Moreover, prediction intervals were computed to provide information about statistical heterogeneity, by quantifying the extent of the dispersion in effects as described in other meta-analyses [7]. The I^2 statistics were calculated to measure the proportion of total variability in effects due to between-study heterogeneity.

Eventually, the leave-one-out method was employed for sensitivity analysis to show how the overall effect estimate changed when different studies were removed, describing also how I^2 modified when each study was omitted.

All statistical analyses were performed using R Statistical Software (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria), and by resorting to the following packages: *meta*, *metafor*, *ggplot2*, *gridExtra*, *dmatar*.

Results

After the de-duplication of records retrieved through the two aforementioned databases, 115 articles were screened, and six were included in the quantitative analysis. Further details on the inclusion process of the included studies are provided in Supplementary Tables 1-2.

As expected, no RCT was retrieved and only observational studies were included, being their features thoroughly illustrated in detail in Table 1 [1,2,8-11].

Table 1. Main characteristic of the included studies.

Study	Design	Time Span	Country	AD Protocol	Sample size (patients with LMM)	General features	Patients undergoing AD versus patients not undergoing AD	Follow-up
Amaya-Villar 2010	Prospective cohort, multicenter	39-month period (not further specified)	Spain	Not specified; in 14/21 patients, the first AD dose was given previously or concomitantly to the first antibiotic dose	43	Community-acquired LMM; median age 69 years; median time to admission 48.5 hours; median GCS at admission 13; positive CSF cultures in 93% (40/43) of patients; serotype 4b in 23 (82%) of 28 tested cases; appropriate empirical therapy in 93% (40/43) of patients	21 versus 22	Until death or discharge from hospital
Koopmans 2013	Prospective cohort, multicenter	Two periods: from 1998 to 2002 and from 2006 to 2012	The Netherlands	4 days 10 mg QID (started with or before first dose of antibiotics in 41/49 patients)	30 (first cohort) plus 62 (second cohort)	Community-acquired LMM; women 41% (38/92); immunodepression in 70% (64/92) of patients; coma at admission in 12% (11/92) of subjects; positive CSF cultures in all cases; sequence type 6 (ST6) genotype in 18/85 strains (21%)	49 (AD according to protocol in 30 patients) versus 43	Until death or discharge from hospital (mortality not stratified according to AD use; available only results from multivariable analysis)
Pelegrin 2014	Retrospective cohort, multicenter	From 1977 to 2009	Spain	4 mg QID for 48 h, eight doses in total, beginning 10–15 min before antibiotic therapy with a doubled first dose	59	Community-acquired LMM; median age 69 years; women 30% (18/59); any underlying condition of immunodepression in 39% (23/59) of patients; median time to presentation 3 days; positive CSF cultures in 64% (34/53) of subjects; appropriate empirical therapy in 75% (50/59) of patients	30 versus 29	Until death or discharge from hospital
Glimåker 2016	Retrospective evaluation of a national registry	From January 1995 to December 2014	Sweden	2-4 days 10 mg QID, initiated within 1 hour from the start of antibiotics; a fraction of patients was treated alternatively with betamethasone 8 mg QID	77 (but in 7 cases missing data on steroid use)	No demographic data for LMM cases, in the framework of a larger study involving 32 Swedish centers generating a registry on acute bacterial meningitis. The final analysis included 1746 patients	33 versus 37	In-hospital mortality
Charlier 2017	Prospective cohort, multicenter	From November 3rd 2009 to July 31st 2013	France	Not specified, but given within 24 hours of management in all cases	252	Median age 67 years; women 40% (100/252); at least one immunosuppressive comorbidity in 86% (216/252) of patients; median time interval from first symptoms to diagnosis 2 days; mean GCS at admission 12; positive CSF cultures in 39% (93/235) of patients; hypervirulent clones (clonal complex 1, 2, 4, 6) in 56% (142/252) of subjects	32 versus 216	3-month
Brouwer 2023	Prospective cohort, multicenter	From January 1st 2006 to July 1st 2022	The Netherlands	4 days 10 mg QID with or < 4 h of first dose of antibiotics	162	Community-acquired LMM; median age 70 years; women 35% (56/162); immunosuppressive medication in 74/161 subjects (46%); median GCS at admission 13; positive CSF cultures in 96% (156/162) of patients; appropriate empirical therapy in 80% (128/161) of patients	83 (AD according to the protocol; 4 days or less in case of death) versus 78 (including 10 subjects in which AD was stopped before the end of the 4 days because of LMM diagnosis; 11 patients receiving AD in a different dose, timing or duration)	Until death or discharge from hospital

AD: adjunctive dexamethasone; CSF: cerebrospinal fluid; GCS: Glasgow Coma Scale; LMM: *Listeria monocytogenes* meningitis; QID: quarter in die.

Five studies informed the main analysis, based on the pooling of crude, unadjusted data [1,2,8,10,11]: AD exerted a slight protective effect on mortality: OR 0.96, 95% CI, 0.42-2.19, but with no statistical significance, and a wide prediction interval was generated (Figure 1).

When considering only adjusted effect sizes, evidence from three cohorts [1,2,9] highlighted on the contrary a worse prognosis associated with AD (OR 1.32, 95% CI, 0.33-5.26), also in this case without reaching statistical significance, and with an even wider prediction interval crossing the no-effect threshold (Figure 2). That suggests that in future studies some patient populations might experience null effects or effects in the opposite direction. The covariates entered in the multivariable models that informed the pooling of adjusted effect sizes are described in Supplementary Table 3.

About the sensitivity analysis (upon the pooling of unadjusted data), the leave-one-out method demonstrated the influence of the Brower’s cohort [1] as an important source of between-study heterogeneity (I^2 from 75% to 41% when it was removed), but statistical significance was reached neither in one direction nor in the other when omitting any other study (Supplementary Figure 1).

Discussion

Neurolisteriosis accounts for about one-third of human listeriosis cases, among the most important

foodborne illnesses worldwide [12]. *Listeria monocytogenes* is responsible for approximately 1% of bacterial meningitis in neonates and approximately 5% of bacterial meningitis in subjects older than 16 years, most cases occurring in elderly or in those with cellular immunodeficiency [13]. Despite an overall decline in reported incidence, *L. monocytogenes* remains one of the top five most common causative pathogens of infections of the central nervous system, notably without chance of protection through active immunization as it happens for encapsulated bacteria [13].

Steroid usage, especially in chronic form, is a well-established clinical predisposing factor of listeriosis, but a clear association with mortality has not been highlighted [14].

Case-fatality rate of LMM in developed countries is still relevant and can be as high as 35% [15]. There are many possible explanations: the marked proclivity for the brain itself, differently from other common pathogens bringing about bacterial meningitis [11]; the tendency to generate more commonly meningoencephalitis than isolated meningitis, being encephalitis an unfavorable prognostic marker [2]; the considerable proportion of people not receiving appropriate initial antibiotic treatment (up to 20% in the Brower’s study [1]), when rapid administration of adequate antimicrobial treatment is crucial to prevent complications, death, and long-lasting sequelae in

Figure 1. The impact of adjunctive dexamethasone on mortality is described after pooling crude, unadjusted data.

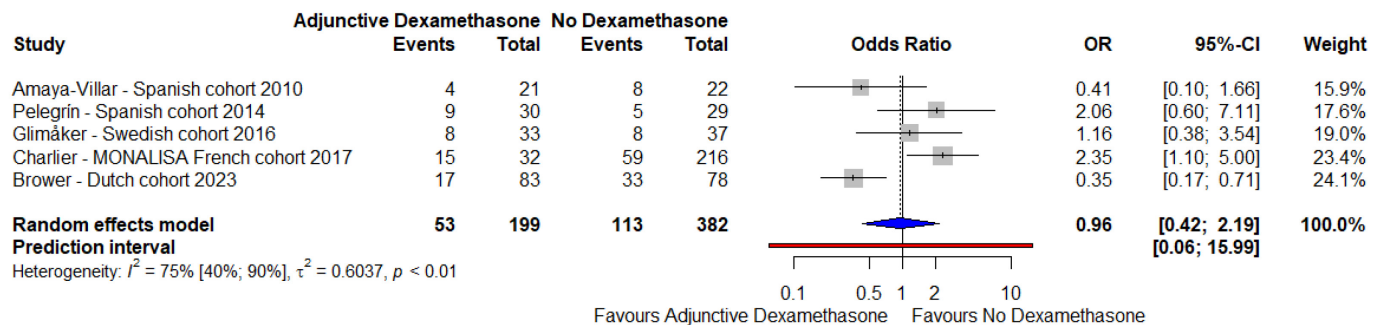
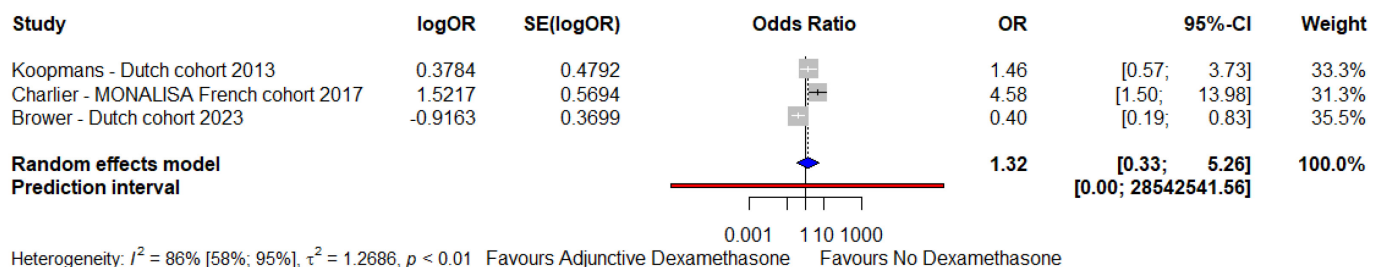


Figure 2. The pooling of adjusted odds ratio, describing the association of adjunctive dexamethasone with clinically relevant endpoints.



human listeriosis [11]. Unfortunately, no RCTs have been conducted so far to define a drug of choice or optimal duration of therapy; the first-line treatment is usually represented by aminopenicillins such as ampicillin or amoxicillin, but many questions remain about, for instance, the potential benefit of combination therapy or the best alternative in case of resistance or allergy to beta-lactams [11].

The further question, pertaining to the present work, is the role of steroids from a therapeutic perspective. The premise is well known: the subarachnoid space inflammatory response is a key factor contributing to morbidity and mortality in ABM, being the action of bacteriolytic antibiotics is a strong propellant in this respect [13]. Dexamethasone, interfering with the cyclooxygenase pathway of arachidonic acid metabolism, has been the agent most extensively studied in experimental animal models and patients, to assess whether the attenuation of this inflammatory response would ameliorate outcome in bacterial meningitis [13].

Conflicting results have emerged over the years upon the impact of AD, being quite apparent in its benefit in cases associated with *S. pneumoniae*, curtailing the strong inflammatory response induced by either live pneumococci themselves or pneumococcal cell wall components after bacteriolysis [3]. Nevertheless, the advantageous effect of AD on relevant outcomes is not so manifest in studies conducted in developing countries or other etiological subgroups, including cases of *L. monocytogenes* [3]. Many hypotheses have been generated to explain these findings: for instance, likely, steroids did not reduce mortality for bacterial meningitis in low-income countries since patients are sicker on presentation [13]. Timing of administration is indeed a crucial point: a delayed diagnosis of LMM for atypical presentation or other reasons may drive the use of AD outside the window of opportunity [1].

The results of the MONALISA study raised a red flag for the use of AD in LMM in the light of apparently deleterious effects [2], to the extent that reviews by renowned researchers posited the necessity to stop immediately steroids for ABM when the involvement of *L. monocytogenes* was ascertained [3,13]. Results from the recent Dutch cohort completely overturned the scenario [1], prompting the present meta-analysis to collate data from each available study on the topic.

What stands out is the relevant heterogeneity in AD protocols and their administration, as described in Table 1. The study conducted by Brower *et al.* is probably the soundest one from a methodological perspective [1]:

AD was administered according to the standard schedule for ABM according to authoritative guidelines [16] and its impact was assessed as if it were a trial using a per-protocol analysis. The MONALISA cohort on the other hand provided much fewer details regarding AD protocol and its implementation [2]. Furthermore, in the French study, there may have been confounding by indication, meaning that only the most severely ill patients were administered AD, since only a minority of the cohort received dexamethasone [2].

Nevertheless, in light of the available evidence, and the conflicting data from adjusted analyses, it is prudent to say that the jury is still out to settle the dispute about the effectiveness of AD in this setting.

Our brief research note has some limitations. It did not rely on a pre-registered protocol. Neither a formal evaluation of the risk of bias nor a systematic approach to rating the certainty of evidence was performed considering the observational nature of the included studies, which are *per se* prone to many biases, thus automatically implying a low or very low quality of the ensuing evidence. Clinical, methodological, and statistical heterogeneity was huge as showed by large prediction intervals, containing opposite effects.

At once, it represents the first evidence synthesis on the specific topic of the use of AD for neurolisteriosis, presenting a pooling of raw and adjusted data, as recommended when meta-analyzing observational studies [17].

Conclusions

In conclusion, indisputably chronic steroid usage is a risk factor for listeriosis. On the contrary, from the standpoint of therapy, the benefit or the harmfulness of AD in LMM remains a “known unknown”, requiring RCTs to settle the question, although it is difficult to run this kind of study for such a disease.

Acknowledgements

AEM conceptualized and conceived the work, contributed substantially to the acquisition of the data, carried out the analyses, interpreted the findings, and wrote the first draft. MM contributed substantially to the interpretation of the findings and revised the work critically for important intellectual content. Both authors had full access to all the data in the study, approved the final version of the work, and agreed to be accountable for all aspects of the work.

References

1. Brouwer MC, van de Beek D (2023) Adjunctive dexamethasone treatment in adults with listeria monocytogenes meningitis: a prospective nationwide cohort study. *eClinicalMedicine* 58: 101922. doi: 10.1016/j.eclinm.2023.101922

2. Charlier C, Perrodeau É, Leclercq A, Cazenave B, Pilmis B, Henry B, Lopes A, Maury MM, Moura A, Goffinet F, Dieye HB, Thouvenot P, Ungeheuer MN, Tourdjman M, Goulet V, de Valk H, Lortholary O, Ravaut P, Lecuit M, MONALISA study group (2017) Clinical features and prognostic factors of listeriosis: the MONALISA national prospective cohort study. *Lancet Infect Dis* 17: 510–519. doi; 10.1016/S1473-3099(16)30521-7
3. van de Beek D, Brouwer MC, Koedel U, Wall EC (2021) Community-acquired bacterial meningitis. *Lancet* 398: 1171–1183. doi: 10.1016/S0140-6736(21)00883-7
4. Brouwer MC, McIntyre P, Prasad K, van de Beek D (2015) Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev* 9: CD004405. doi: 10.1002/14651858.CD004405.pub5
5. Huang YT, Kuo YW, Lee MR, Tsai YH, Teng LJ, Tsai MS, Liao CH, Hsueh PR (2021) Clinical and molecular epidemiology of human listeriosis in Taiwan. *Int J Infect Dis* 104: 718–724. doi: 10.1016/j.ijid.2021.01.056
6. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA (2017) AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 358: j4008. doi: 10.1136/bmj.j4008
7. Maraolo AE, Mazzitelli M, Zappulo E, Scotto R, Granata G, Andini R, Durante-Mangoni E, Petrosillo N, Gentile I (2022) Oral vancomycin prophylaxis for primary and secondary prevention of clostridioides difficile infection in patients treated with systemic antibiotic therapy: a systematic review, meta-analysis and trial sequential analysis. *Antibiotics* 11: 183. doi: 10.3390/antibiotics11020183
8. Amaya-Villar R, García-Cabrera E, Sulleiro-Igual E, Fernández-Viladrich P, Fontanals-Aymerich D, Catalán-Alonso P, Rodrigo-Gonzalo de Liria C, Coloma-Conde A, Grill-Díaz F, Guerrero-Espejo A, Pachón J, Prats-Pastor G (2010) Three-year multicenter surveillance of community-acquired *Listeria monocytogenes* meningitis in adults. *BMC Infect Dis* 10: 324. doi: 10.1186/1471-2334-10-324
9. Koopmans MM, Brouwer MC, Bijlsma MW, Bovenkerk S, Keijzers W, van der Ende A, van de Beek D (2013) *Listeria monocytogenes* sequence type 6 and increased rate of unfavorable outcome in meningitis: epidemiologic cohort study. *Clin Infect Dis* 57: 247–253. doi: 10.1093/cid/cit250
10. Pelegrín I, Moragas M, Suárez C, Ribera A, Verdager R, Martínez-Yelamos S, Rubio-Borrego F, Ariza J, Viladrich PF, Cabellos C (2014) *Listeria monocytogenes* meningoenzephalitis in adults: analysis of factors related to unfavourable outcome. *Infection* 42: 817–827. doi: 10.1007/s15010-014-0636-y
11. Glimåker M, Brink M, Naucler P, Sjölin J (2016) Betamethasone and dexamethasone in adult community-acquired bacterial meningitis: a quality registry study from 1995 to 2014. *Clin Microbiol Infect* 22: 814.e1–814.e7. doi: 10.1016/j.cmi.2016.06.019
12. Koopmans MM, Brouwer MC, Vázquez-Boland JA, van de Beek D (2023) Human listeriosis. *Clin Microbiol Rev* 36: e0006019. doi: 10.1128/cmr.00060-19
13. Hasbun R (2022) Progress and challenges in bacterial meningitis: a review. *JAMA* 328: 2147–2154. doi: 10.1001/jama.2022.20521
14. Huang C, Lu TL, Yang Y (2023) Mortality risk factors related to listeriosis – a meta-analysis. *J Infect Public Health* 16: 771–783. doi: 10.1016/j.jiph.2023.03.013
15. Bijlsma MW, Brouwer MC, Kasanmoentalib ES, Kloek AT, Lucas MJ, Tanck MW, van der Ende A, van de Beek D (2016) Community-acquired bacterial meningitis in adults in the Netherlands, 2006–14: a prospective cohort study. *Lancet Infect Dis* 16: 339–347. doi: 10.1016/S1473-3099(15)00430-2
16. van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, Leib SL, Mourvillier B, Ostergaard C, Pagliano P, Pfister HW, Read RC, Sipahi OR, Brouwer MC, ESCMID Study Group for Infections of the Brain (ESGIB) (2016) ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. *Clin Microbiol Infect* 22 Suppl 3: S37–62. doi: 10.1016/j.cmi.2016.01.007
17. Paul M, Leeftang MM (2021) Reporting of systematic reviews and meta-analysis of observational studies. *Clin Microbiol Infect* 27: 311–314. doi: 10.1016/j.cmi.2020.11.006

Corresponding author

Dr. Alberto Enrico Maraolo, MD, MSc
 Antibiotic Stewardship, Advanced Biostatistics, FESCMID.
 Infectious Diseases Specialist.
 First Division of Infectious Diseases, Cotugno Hospital, Naples,
 Italy.
 Tel: +39-081-7067383
 Email: albertomaraolo@mail.com

Conflict of interests: No conflict of interests is declared.

Annex – Supplementary Items

Supplementary Table 1. Literature search strategy.

PICO framework	<ul style="list-style-type: none"> • adult subjects with <i>Listeria monocytogenes meningitis</i> (P—participants); • adjunctive dexamethasone (I—intervention); • no adjunctive dexamethasone (C—comparison); • mortality or neurological sequelae (O—outcome).
Further details	No language restriction. Search from inception to 31 March 2023. Exclusion of cohorts with less than 10 subject per arm.
MEDLINE/PubMed	((((steroid*[Text Word] OR dexamethasone[Text Word]))) AND ((neurolisteriosis[Text Word] OR meningitis[Text Word] OR meningoenzephalitis[Text Word]))) AND ((listeria[Text Word]))
EMBASE	((((steroid*:ti,ab,kw OR dexamethasone:ti,ab,kw))) AND ((neurolisteriosis:ti,ab,kw OR meningitis:ti,ab,kw OR meningoenzephalitis:ti,ab,kw))) AND ((listeria:ti,ab,kw))

Supplementary Table 2. Phases of the literature screening process.

Step 1	Step 2	Step 3	Step 4
From Medline/PubMed retrieved 73 records; From EMBASE retrieved 125 records	After deduplication, 114 records remained	After screening, 5 records were assessed for full-text review	Overall, 5 articles were included in the quantitative analysis

Supplementary Table 3. Variables adjusted for in the multivariable analyses assessing the impact of adjunctive dexamethasone on clinically relevant endpoints.

Study	Variables	Endpoint
Koopmans 2013	Advanced age, immunocompromised state, infection by <i>L. monocytogenes</i> genotype sequence type 6	Unfavourable outcome (Glasgow Coma Scale 1-4)
Charlier 2017	Age, gender, ongoing organ neoplasia, recent major weight loss, multi-organ failure, aggravation of any pre-existing organ dysfunction, influenza-like symptoms, mechanical ventilation, monocytopenia, positive blood cultures, protein concentration in the cerebral spinal fluid	3-month mortality
Brouwer 2023	Age, Glasgow Coma Scale, adequate initial antibiotic regimen	Mortality

Glasgow Coma Scale 1: death, 2: vegetative state; 3: severe disability; 4: moderate disability.

Supplementary Figure 1. Results of influential diagnostics related to the main analysis.

