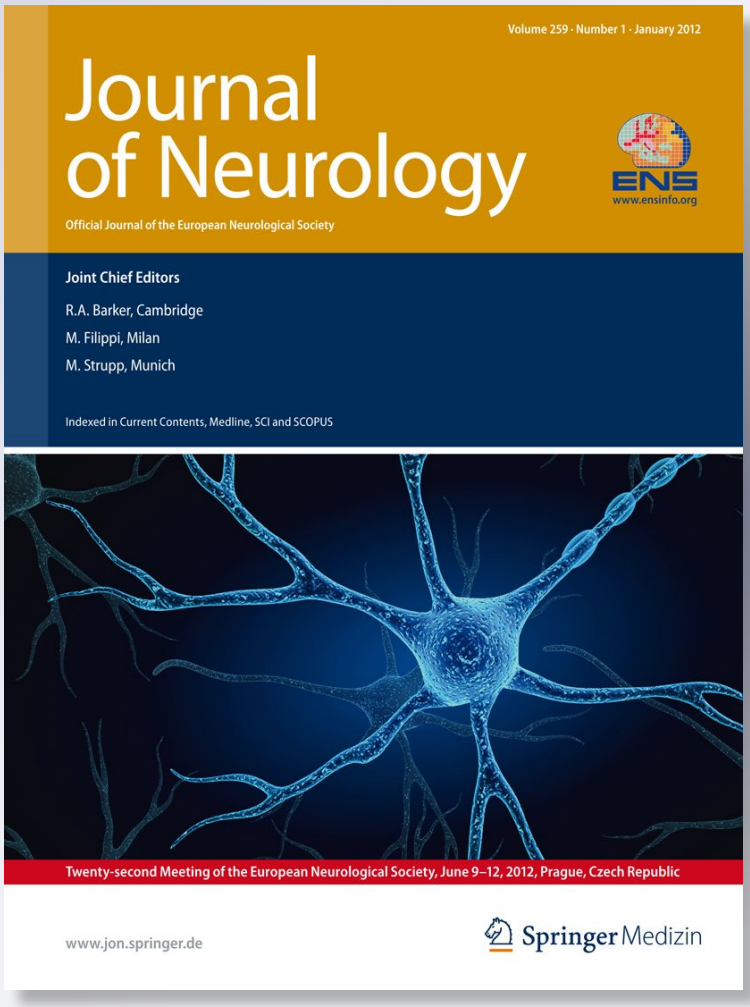
Dexamethasone for adult community-acquired bacterial meningitis: 20 years of experience in daily practice

Vjerislav Peterković, Vladimir Trkulja, Marko Kutleša, Vladimir Krajinović & Dragan Lepur

Journal of Neurology
Official Journal of the European Neurological Society

ISSN 0340-5354
Volume 259
Number 2

J Neurol (2012) 259:225-236
DOI 10.1007/s00415-011-6150-6



Springer

J Neurol (2012) 259:225–236
DOI 10.1007/s00415-011-6150-6

ORIGINAL COMMUNICATION

Dexamethasone for adult community-acquired bacterial meningitis: 20 years of experience in daily practice

Vjerislav Peterković · Vladimir Trkulja · Marko Kutleša · Vladimir Krajinović · Dragan Lepur

Received: 31 January 2011 / Accepted: 14 June 2011 / Published online: 25 June 2011

Abstract The aim of the study was to assess adjunctive intravenous dexamethasone in adult community-acquired bacterial meningitis (BM) in daily practice. Analysis of consecutive patients (1990–2009) with acute community-acquired bacterial meningitis in a single centre in Zagreb, Croatia, $N = 304$. Adjusted relative risks [RR, dexamethasone vs. no dexamethasone (control)] of Glasgow Outcome Scale (GOS) = 1 (death) and GOS = 5 (full recovery) at discharge/end of specific treatment were estimated considering demographics; co-morbidity; BM pathogenesis and on-admission characteristics, and cerebrospinal fluid (CSF) inflammation markers; causative agent and antibiotic use. Two hundred forty (79%) patients had proven BM (43.1% *Streptococcus pneumoniae*, any other agent ≤8.2%). No independent effects of dexamethasone on GOS = 1 or GOS = 5 were observed in the entire cohort (dexamethasone $n = 119$, control $n = 185$; RR = 1.06, 95% CI 0.77–1.45 and RR = 0.99, CI 0.83–1.20, respectively), microbiologically proven disease (dexamethasone $n = 104$, control $n = 136$; RR = 0.97, CI 0.69–1.38 and RR = 1.03, CI 0.82–1.28), pneumococcal disease (dexamethasone $n = 71$, control $n = 60$; RR = 0.95, CI 0.53–1.70 and RR = 0.82, CI 0.57–1.18), and also in other BM, subgroups based on consciousness disturbance, CSF markers, prior use of antibiotics and timing of appropriate antibiotic treatment. CSF markers did not predict the outcomes. Conclusions: Our experience does not substantiate the reported benefits of adjunctive dexamethasone in adult BM. Socio-economic and methodological factors do not seem to explain this discrepancy. Empirical use of dexamethasone in this setting appears controversial.

Keywords Adults · Community-acquired bacterial meningitis · *S. pneumoniae,* dexamethasone

V. Peterković
Department of Neurosurgery, University Hospital Center Zagreb, Kišpatićeva 12, Zagreb, Croatia
e-mail: vpeterkovic@gmail.com

V. Trkulja
Department of Pharmacology, Zagreb University School of Medicine, Šalata 11, 10000 Zagreb, Croatia
e-mail: vtrkulja@mef.hr

M. Kutleša · V. Krajinović · D. Lepur (✉)
Department of Intensive Care Medicine and Neuroinfectology, University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Mirogojska 8, 10000 Zagreb, Croatia
e-mail: lepurix@inet.hr

M. Kutleša
e-mail: marko.kutlescha@gmail.com

V. Krajinović
e-mail: vkrajinovic@bfm.hr

Background

Extensive experimental and animal data accumulated over the years strongly suggest that neuronal damage associated with poor outcomes in acute bacterial meningitis is largely mediated by a severe inflammatory host response triggered by bacterial invasion of the central nervous system. Bacterial toxins and cell lysis products, particularly in pneumococcal meningitis, augment the harmful effects on the brain through direct cytotoxicity and perpetuation of inflammation [1–4]. These observations fuelled a therapeutic concept advocating the use of non-bacteriolytic antibiotics and suppression of inflammation [3, 5]. In this context, corticosteroids seemed to be a natural choice as an adjunctive anti-inflammatory treatment. However, clinical usefulness of corticosteroids in adult bacterial meningitis

(BM) had long lacked sound empirical evidence [5]. In 2002, a multicenter, randomized, placebo-controlled trial demonstrated the potential of an adjunctive intravenous dexamethasone regimen (10 mg immediately before or with the first parenteral antibiotic dose and every 6 h thereafter, over 4 days) to reduce mortality and unfavourable outcomes in European adults with community-acquired BM, particularly those with pneumococcal disease (the most prevalent bacteriological form) [6]. This particular schedule was recently reported to apparently improve the outcomes of pneumococcal diseases in daily practice in a developed European country [7]. On the other hand, recent meta-analyses of placebo-controlled trails indicate that the effect of early dexamethasone in adults is seemingly less robust than theoretically expected, and might be affected by trial quality, socio-economic level of the country (reflecting on access to medical care, HIV infection prevalence and treatment possibilities, but probably also on other factors), causative agent and level of evidence of bacterial infection [5, 8–10]. Overall, the survival benefit is uncertain, although some benefit might be confined to the patients with pneumococcal meningitis in high-income countries [5, 8–10]. The most consistent benefit seems to be the reduced risk of hearing loss, but this again does not seem to hold in the low-income countries and a trend was only observed in high quality trials [8, 9]. Interestingly, as indicated by both a recent meta-analysis of individual patient data from five trials and a recent Cochrane group meta-analysis (by the same authors)—the (lack of) dexamethasone effect was not affected by its commencement prior to (or with) the first antibiotic dose (as advocated in agreement with the "anti-inflammation" concept) versus its commencement after antibiotic treatment had already begun [8, 9].

Hence, although some patients in some societies (parts of the world) could benefit from adjunctive dexamethasone, its routine use in adult community-acquired BM is controversial [5, 10].

Over the past 20 years we have been using adjunctive dexamethasone in treatment of adult community-acquired BM in line with the developments in the field. The primary objective of the present analysis of our patient database was to assess its effects on the disease outcome in daily practice. Secondary objective was to assess standard markers of subarachnoid inflammation determined on admission as outcome predictors.

Patients and methods

General design

This is a retrospective analysis of consecutive adult (≥18 years of age) patients treated for acute community-acquired BM between 1 January 1990 and 31 December 2009 at the Zagreb Hospital for Infectious Diseases, a tertiary care university-affiliated teaching hospital with 320 beds. During this period, all patients suspected of having acute BM underwent the same standardized in-house protocol with a detailed prospective data recording. All patients were managed at the department for neuroinfections and intensive care by adequately trained staff. For the purpose of the present analysis, the hospital electronic database and source data were searched independently by two investigators to identify qualifying patients and to double-check the extracted data. The analysis was approved by the institution's ethics committee.

Patients

Bacterial meningitis was diagnosed based on clinical presentation (fever, headache, neck stiffness and disturbed consciousness with or without seizures and/or neurological deficits); supportive cerebrospinal fluid (CSF) findings (pleocytosis, increased protein concentration and decreased CSF/blood glucose ratio); and microbiological evidence: positive CSF culture or a negative CSF culture with a positive CSF polymerase chain reaction assay, positive blood culture, or a positive Gram stain of a CSF sample. Microbiologically not proven (probable) BM was diagnosed based on a compatible clinical picture and neutrophilic pleocytosis (≥1,000 white cells/mL of CSF with >50% neutrophils) or CSF-blood glucose ratio <0.4 and CSF protein concentration >45 mg/dL [11].

The disease was considered community-acquired if a patient had not been previously hospitalized, or if it occurred more than 2 weeks after a previous hospital discharge, or more than 4 weeks after a previous surgical treatment [11].

Out of a total of 586 adults with BM treated during the observed period, the present analysis embraced 304 patients. Exclusions were due to: nosocomial or shunt meningitis ($n = 184$); missing or unclear data (based on agreement between the two investigators in charge of data extraction): on timing of antibiotic and/or dexamethasone commencement relative to disease occurrence, on relevant on-admission assessment (e.g., consciousness level, laboratory findings) or assessment of the disease outcome ($n = 72$); brain abscess or subdural empyema ($n = 18$); meningitis limited to the spinal cord ($n = 8$).

Antibiotic treatment and treatment with dexamethasone

Antibiotic treatment always followed the same scheme: initial empirical treatment recommended by the Hospital Drugs Committee was followed by, when applicable, a bacteriologically targeted treatment (adequate dose of a

parenteral antibiotic that penetrates the blood–brain barrier and to which one or more of the isolated pathogens were sensitive). During the observed period, the recommended empirical therapy consisted of ceftriaxone or cefotaxime for subjects 18–50 years of age, and of parenteral ampicillin plus ceftriaxone in patients >50 years of age or in immunocompromised subjects and alcohol abusers. The majority of patients (189/304, 62.1%) received the initial empirical treatment with ceftriaxone or cefotaxime.

The decision to introduce adjunctive dexamethasone in treatment of adult BM 20 years ago was based on the then existing reports of its favourable effects in pediatric *Haemophilus influenzae* type B meningitis [12, 13]. Dexamethasone was to be used in patients with clinical and CSF signs supporting the diagnosis of BM, except those with a recent history (within a month before admission for meningitis) of upper gastrointestinal bleeding or peptic ulcer. No other strict criteria were set, but the decision to use it in a particular patient was left at the attending physician's discretion and clinical judgement. The lowest dose of intravenous dexamethasone was 4 × 8 mg/24 h and the highest dose was 4 × 12 mg/24 h, and dexamethasone was delivered over 48 (minimum) to 96 h (maximum). The first dose was always delivered 15–20 min prior to or concomitantly with the first dose of parenteral antibiotic. The same routine was applied with other doses - whenever the antibiotic and dexamethasone delivery schedules overlapped.

Outcomes

We used the Glasgow Outcome Scale (GOS) score as a measure of disease outcome, as assessed at discharge/end of specific treatment for meningitis [7, 14]. GOS grades the outcomes as: death (GOS = 1); vigil coma (GOS = 2); conscious with severe neurological deficit (dependent) (GOS = 3); moderate disability (independent, professionally incapable) (GOS = 4) and independent, professionally capable, no or minor disability (GOS = 5). Two (co)primary outcomes were defined: (a) proportion of patients with GOS = 1 (i.e., mortality); (b) proportion of patients with GOS = 5 (i.e., full recovery, as opposed to unfavourable outcomes: GOS < 5). The interobserver agreement of GOS is high [7].

Data analysis

Data were summarized for the entire cohort and also separately for patients who received dexamethasone treatment and those who did not. Since the individual patient data were collected prospectively in a standardized manner and since the occurrence of both outcomes (GOS = 1 and GOS = 5) was relatively high (>10%), the analysis was based on determination of relative risks (RR) rather than odds ratios, using modified Poisson regression with robust error variance [15].

The *main analysis* intended to detect potential associations between dexamethasone treatment (primary objective) and CSF indicators of inflammation (secondary objective) and either of the two primary outcomes within the entire cohort. Univariate analysis was performed using regression models with only one independent: dexamethasone (yes/no) or each of the three standard CSF inflammation indicators (CSF pleocytosis, protein concentration and CSF/blood glucose ratio). Additionally, cluster analysis (using least *p*th powers clustering criterion [$p = 1$] to reduce the effect of outliers on cluster centres) demonstrated that the patients could be separated based on the three CSF parameters into two clusters: those with more and those with less pronounced "CSF inflammation". The contrast between the two clusters was also estimated as a measure of the effect of CSF inflammation on the outcomes. The following further independent variables were considered in multivariate analysis: age; sex; time (days) elapsed since first symptoms (any) to admission; use of antibiotics (any) before the diagnosis of meningitis; presence of serious comorbidity [includes malignancy, immunodeficiency (immunosuppressants, human immunodeficiency virus infection or splenectomy), diabetes mellitus (DM), other endocrinological diseases, alcohol abuse and liver cirrhosis, other chronic organ diseases (lungs, heart, kidney, liver)]; presence of focal neurological symptoms on admission (includes aphasia, cranial nerve palsy, monoparesis or hemiparesis); leukocyte count on admission; pathophysiological mechanism of the disease (e.g., meningitis following septicemia, or following middle ear infection or trauma; dichotomized as "following septicemia" and "other"); microbiologically verified BM (considered as yes/no, and also as pneumococcal/other bacterial/probable); worst Glasgow Coma Score (GCS) within 24 h since admission as a continuous variable and also categorized into levels of consciousness disturbance as: none (GCS ≥15), mild (GCS 13–14), moderate (GCS 10–12) or severe (GCS ≤9); and timing of the appropriate antibiotic treatment (empirical as per in-house guidelines, or bacteriologically targeted, see above) commencement specifically in relation to the onset of consciousness disturbance and/or overt meningitis symptoms (e.g., fever, headache, vomiting, malaise) [16]. Namely, although the "door-to-antibiotic" delay negatively affects the outcomes in community-acquired adult BM (particularly if >2 h), timing of the *appropriate* antibiotic treatment relative to the onset of consciousness disturbance and/or other specific meningitis symptoms appears to be a particularly relevant predictor of the disease outcome [17, 18]. Therefore, considering that the database included anamnestic/heteroanamnestic data on disease course before hospital

admission, appropriate antibiotic timing relative to the onset of meningitis symptoms was assessed as "within 24 h" or "later", based on agreement between two investigators unaware of the patients outcome and dexamethasone treatment. Regarding the primary objective, multivariate models were built by entering "dexamethasone treatment" (default) and all other independents showing at least a trend of univariate association with the outcome ($p < 0.1$), followed by consecutive removal of the independents with $p > 0.05$ in the order of the highest p value. If not already included, independents showing baseline imbalance between dexamethasone-treated and not treated patients were then forced into the model and were kept if model fit was significantly improved (based on the Chi-square test of the log-likelihood difference). The procedure was the same regarding the secondary objective, except that default variables were the three individual CSF markers of inflammation (individually and simultaneously) or alternatively, "more pronounced CSF inflammation" (vs. less) from the cluster analysis.

Exploratory analysis intended to evaluate the effects of dexamethasone on disease outcomes in subgroups of patients based on: causative agent (pneumococcal/other bacterial/probable); appropriate antibiotic timing relative to the onset of meningitis symptoms (within 24 h or not); antibiotic treatment prior to admission (i.e., prior to diagnosis and potential dexamethasone commencement); worst GCS score within the first 24 h since admission (GCS <12 or ≥12) and severity of on-admission CSF inflammation markers (the cluster with more pronounced vs. less pronounced inflammation). Considering the rather small subgroup sizes, multivariate models were built based on information obtained from the main analysis. We used SAS 9.1.3 software (SAS Inc., Cary, NC).

Results

Patient and disease characteristics

Of the 304 patients, 119 (39.1%) were treated with dexamethasone. There were certain baseline imbalances between the dexamethasone-treated and not treated patients: the former slightly more frequently suffered from immunodeficiency, DM or malignancy; more frequently had the worst GCS score within the first 24 h since admission at <13; had somewhat more pronounced CSF pleocytosis, higher CSF protein concentration and lower CSF/blood glucose ratio, and hence, were more frequently categorized as having "more pronounced CSF inflammation" by the cluster analysis (Table 1). Meningitis secondary to septicaemia was equally prevalent in the two subgroups, while minor imbalance existed regarding other pathophysiological mechanisms of the disease (Table 1). Also, dexamethasone-treated patients somewhat more frequently had a microbiologically verified disease and particularly pneumococcal disease (with minor imbalance regarding other etiological agents) (Table 2). Timing of the adequate antibiotic treatment relative to the onset of typical meningitis symptoms (which also indicates the timing of dexamethasone commencement, where applicable) appeared similar in the two groups; however, treatment commencement within 24 h was slightly less frequent in the dexamethasone group (Table 2). Slightly more dexamethasone-treated than not treated patients died (GOS = 1) and somewhat less fully recovered (GOS = 5) (Table 2).

Main analysis: effects of dexamethasone treatment and on-admission CSF inflammation markers on disease outcome

No univariate association was observed between dexamethasone and mortality (incidence of GOS = 1), whereas dexamethasone treatment appeared associated with a slightly reduced risk of full recovery (GOS = 5) (Table 3), likely reflecting the mentioned imbalances in disease characteristics. Weak (statistically significant or borderline significant) univariate associations were observed between worse on-admission values of CSF inflammation markers and higher incidence of GOS = 1 or lower incidence of GOS = 5 (Table 3). The unadjusted risk of GOS = 1 was clearly higher and the risk of GOS = 5 was clearly lower in patients ($n = 86$) categorized by the cluster analysis as having "more pronounced CSF inflammation" (based on the above three markers) versus those categorized as having "less pronounced CSF inflammation" ($n = 218$) (Table 3).

Multivariate models testing the effects of dexamethasone on mortality (GOS = 1) or full recovery (GOS = 5) included all adjustments relevant either because of their effect on the outcomes, or because of the imbalances between dexamethasone-treated and not treated patients (Table 4). No independent effect of dexamethasone on either outcome was observed (GOS = 1, RR = 1.06, 95% CI 0.77–1.45; GOS = 5, RR = 0.99, 95% CI 0.83–1.20) (Table 4).

Multivariate models testing the effects of CSF inflammation markers on mortality (GOS = 1) or full recovery (GOS = 5) also accounted for relevant adjustments and no independent effect on either outcome was observed (Table 5).

Exploratory analysis: effects of dexamethasone on disease outcome in patient subgroups

Mortality appeared comparable for dexamethasone-treated and not treated patients in the subgroups of subjects with

Table 1 Patient characteristics on admission and pathogenesis of meningitis, overall and for those treated (dexa) and not treated (no dexa) with dexamethasone

	All patients ($N = 304$)	Dexa ($n = 119$, 39.1%)	No dexa ($n = 185$, 60.9%)
Age (years)	50 (18–91)	49 (18–84)	50 (18–91)
Men	187 (61.5)	72 (60.5)	115 (62.2)
Immunodeficiency, DM or malignancy[a]	56 (18.4)	25 (21.0)	31 (16.8)
Other serious comorbidity[b]	86 (28.3)	33 (27.7)	53 (28.7)
Any antibiotic prior to diagnosis	102 (33.6)	40 (33.6)	62 (33.5)
Lag-time: any symptoms-admission (days)	2 (1–14)	2 (1–14)	3 (1–13)
GCS (worst in 24 h since admission)	10 ($Q_{1,3}$ 7.3–14)	9 ($Q_{1,3}$ 7–13)	12 ($Q_{1,3}$ 9–15)
Consciousness disturbance (GCS-based)			
None (GCS 15)	74 (24.3)	20 (16.8)	54 (29.2)
Mild (GCS 13–14)	75 (24.7)	22 (18.5)	53 (28.7)
Moderate (GCS 10–12)	123 (40.5)	61 (51.3)	62 (33.5)
Severe (GCS $\leq$9)	32 (10.5)	16 (13.5)	16 (8.7)
Focal neurological deficit[c]	32 (10.5%)	15 (12.6)	17 (9.2)
Leukocyte count ($\times 10^9$ per L)	15.7 (0.7–43.3)	17.6 (2.2–43.3)	15.1 (0.7–35.3)
CSF WBC ($\times 10^3$ cells/μL)	12.0 (0.05–300)	18.4 (0.1–206)	10.2 (0.05–300)
CSF proteins (mg/dL)	311 (24–3,400)	383 (24–2,826)	251 (36–3,400)
CSF/blood glucose ratio (%)	17.4 (0–97.8)	7.5 (0–79.2)	21.5 (0–97.8)
More pronounced CSF inflammation[d]	86 (28.3)	46 (38.7)	40 (21.6)
Pathogenesis of meningitis			
Following septicaemia	92 (30.3)	36 (30.3)	56 (30.3)
Following middle ear infection	78 (25.7)	37 (31.1)	41 (22.2)
Following trauma	55 (18.0)	19 (16.0)	36 (19.5)
Recurrent	3 (0.99)	1 (0.84)	2 (1.1)
Other mechanisms	76 (25.0)	26 (21.9)	50 (27.0)

If not otherwise specified, data are median (range) or count (percent)

DM diabetes mellitus, *GCS* Glasgow Coma Scale score, *CSF* cerebrospinal fluid, *WBC* white blood cells, $Q_{1,3}$ lower and upper quartile

[a] Includes: immunodeficiency due to immunosuppressants, HIV infection or splenectomy (three patients overall), diabetes mellitus [29 patients overall (dexa 13/119, no dexa 16/185)] and malignancy [25 patients overall (dexa 11/119, no dexa 14/185)]

[b] Includes: alcohol abuse or cirrhosis [48 patients overall (dexa 16/119, no dexa 32/185)], endocrinological disease except DM (6 patients overall) and chronic heart, lung, kidney or liver disease [37 patients overall (dexa 18/119, no dexa 19/185)]. Some patients suffered from more than one comorbidity (including malignancy, immunodeficiency and DM)

[c] Includes one or more of the following: aphasia, cranial nerve palsy, monoparesis or hemiparesis

[d] Cluster analysis classified patients into two subgroups (clusters), one with more pronounced indicators of CSF inflammation ($n = 86$; median values: CSF WBC 25.6, CSF proteins 786 and CSF/blood glucose ratio 2.1%), and the other with less pronounced indicators of CSF inflammation ($n = 218$; median values: CSF WBC 10.0; CSF proteins 221 and CSF/blood glucose ratio 26%)

bacteriologically proven disease, pneumococcal disease or disease caused by other agents (Table 6). The rate of full recovery was somewhat lower in treated than not treated patients with pneumococcal disease (Table 6). Both outcomes appeared much better in not treated patients in the small subgroup of subjects with probable BM (Table 6). However, no consistent, statistically significant independent effect of dexamethasone on either mortality or full recovery was observed in any of these subgroups, or other patient subgroups based on starting consciousness disturbance (GCS <12 or GCS ≥12), timing of the appropriate antibiotic treatment relative to the onset of overt meningitis symptoms (≤24 or >24 h), baseline level of CSF inflammation markers (more or less pronounced), or antibiotic use before admission/diagnosis verification (i.e., before, where applicable, dexamethasone commencement) (Table 7).

Discussion

The present analysis of our 20-year experience (1 January 1990 to 31 December 2009) indicates no benefit of adjunctive intravenous (iv) dexamethasone in reducing mortality or increasing the likelihood of full recovery (GOS = 5, in the literature commonly depicted as

Table 2 Bacteriological disease characteristics, timing of adequate antibiotic treatment and Glasgow Outcome Score at discharge/end of specific treatment of meningitis

	All patients ($N = 304$)	Dexa ($n = 119$)	No dexa ($n = 185$)
Microbiologically verified bacterial	240 (79.0)	104 (87.4)	136 (73.5)
CSF, culture (or PCR) positive	215 (70.7)	94 (79.0)	121 (65.4)
CSF, Gram stain positive	172 (56.6)	77 (64.7)	95 (51.4)
Blood culture positive	104 (34.2)	39 (32.8)	65 (35.1)
Common etiological agents			
Streptococcus pneumoniae	131 (43.1)	71 (59.7)	60 (32.4)
Listeria monocytogenes	25 (8.2)	6 (5.0)	19 (10.3)
Neisseria meningitidis	19 (6.3)	11 (9.2)	8 (4.3)
Other *Streptococcus* strains	11 (3.6)	1 (0.8)	10 (5.4)
Staphylococcus aureus strains	10 (3.3)	3 (2.5)	7 (3.9)
Other (mostly Gram-negative aerobes)	44 (14.5)	12 (10.1)	32 (17.3)
Meningitis symptoms, adequate antibiotic (days)	1 (0–10)	1 (0–10)	1 (1–8)
Treatment started within 24 h	203 (66.8)	74 (62.2)	129 (69.7)
Glasgow Outcome Score (GOS)			
GOS 1 (death)	73 (24.0)	32 (26.9)	41 (22.2)
GOS 2 (vigil comma)	4 (1.3)	3 (2.5)	1 (0.6)
GOS 3 (severe deficits, dependent)	23 (7.6)	12 (10.1)	11 (6.0)
GOS 4 (independent, professionally incapable)	41 (13.5)	17 (14.3)	24 (13.0)
GOS 5 (independent, no/minor disability)	163 (53.6)	55 (46.2)	108 (58.4)

Data are counts (percent) or median (range)

Timing of adequate antibiotic treatment relative to the onset of consciousness disturbance or other overt meningitis symptoms (e.g., fever, neck stiffness, headache, vomiting). Appropriate antibiotic: empirical as *per* in-house guidelines (see "Patients and methods") or bacteriologically targeted (appropriate dose of a parenteral antibiotic that passes the blood–brain barrier and to which one or more isolated pathogens was sensitive)

CSF cerebrospinal fluid, *PCR* polymerase chain reaction

Table 3 Unadjusted effects of treatment with dexamethasone and on-admission cerebrospinal fluid (CSF) inflammation indicators on mortality (Glasgow Outcome Score [GOS] = 1) and full recovery (GOS = 5) in adult community-acquired acute bacterial meningitis ($N = 304$)

	GOS = 1		GOS = 5	
	RR (95% CI)	*p*	RR (95% CI)	*p*
Dexamethasone treatment	1.21 (0.81–1.81)	0.344	0.79 (0.63–0.99)	0.046
CSF WBC (10^4 cells/μL increase)	1.05 (1.02–1.08)	<0.001	0.96 (0.92–1.00)	0.066
CSF proteins (100 mg/dL increase)	1.07 (1.05–1.08)	<0.001	0.90 (0.85–0.93)	<0.001
CSF/blood glucose (10% decrease)	1.12 (1.00–1.25)	0.043	0.89 (0.86–0.93)	<0.001
More pronounced CSF inflammation[a]	1.67 (1.12–2.48)	0.011	0.55 (0.40–0.75)	<0.001

Relative risks (RR) are given with 95% confidence interval (CI)

WBC white blood cells

[a] From cluster analysis, see "Patients and methods" and footnote to Table 1 for details

"favourable outcome", as opposed to GOS <5) in adult community-acquired BM, pneumococcal or caused by other common agents, in daily practice [6, 9]. It also indicates no predictive value of the standard on-admission CSF markers of subarachnoid inflammation for these two outcomes. Considering the theoretical background emphasizing the need to suppress the inflammatory host response in order to improve the disease outcome, these two observations might be perceived as closely related [1–5].

The presently observed lack of benefit of adjunctive iv dexamethasone is in contrast with the results of a double-blind placebo-controlled European trial (conducted between 1993 and 2001) that showed reduced mortality

Table 4 Adjusted effects of dexamethasone treatment on mortality [Glasgow Outcome Score (GOS) = 1] and full recovery (GOS = 5) in adult community-acquired acute bacterial meningitis ($N = 304$)

	GOS = 1[a]		GOS = 5[e]	
	RR (95% CI)	*p*	RR (95% CI)	*p*
Dexamethasone	1.06 (0.77–1.45)	0.724	0.99 (0.83–1.20)	0.999
Age (by 10 years)	1.20 (1.05–1.37)	0.008	0.93 (0.88–0.98)	0.019
GCS[b] (by 1 unit lower)	1.24 (1.18–1.31)	<0.001	0.90 (0.86–0.93)	<0.001
Meningitis following septicaemia	1.53 (1.07–2.18)	0.019	0.79 (0.63–0.98)	0.032
Pneumococcal meningitis	1.88 (1.37–2.59)	<0.001	–	–
Immunodeficiency[c], malignancy or DM	1.55 (1.10–2.20)	0.013	–	–
Meningitis symptoms, atb: ≤24 h[d]	0.48 (0.31–0.75)	0.001	2.63 (1.69–4.10)	<0.001
Proven bacterial (any agent)	–	–	1.30 (1.08–1.56)	0.005
Other serious comorbidity	–	–	0.74 (0.58–0.94)	0.014
More pronounced CSF inflammation	–	–	0.80 (0.63–1.02)	0.071

Relative risks (RR) are given with 95% confidence interval (CI)

GCS Glasgow Coma Score, *DM* diabetes mellitus, *Atb* antibiotic

[a] Initial model included "dexamethasone" by default and variables showing at least possible univariate association ($p < 0.1$) with the outcome. They were then removed consecutively if $p > 0.05$. Removed variables: cerebrospinal fluid (CSF)/blood glucose ratio, CSF white blood cells count, CSF protein concentration (and, alternatively, "more pronounced CSF inflammation" from the cluster analysis, see footnote to Table 1), other serious comorbidity (besides immunodeficiency, malignancy or DM), microbiologically proven bacterial disease (vs. probable). When forced into the model, "more pronounced CSF inflammation" did not improve the model fit ($p = 0.530$) and did not relevantly change the size or statistical significance of the dexamethasone effect

[b] Worst within the first 24 h since admission

[c] See footnote to Table 1

[d] Timing of adequate antibiotic treatment, see footnote to Table 2

[e] Model building followed the same procedure as for GOS = 1. Almost identical variables were consecutively removed, except that "pneumococcal meningitis" was replaced by "proven, any agent" (there was no difference between pneumococcal disease and other proven agents) and "immunodeficiency, malignancy or DM" was replaced by "other serious comorbidity". Also, when forced into the model, "more pronounced CSF inflammation" improved the model fit ($p = 0.040$) and was included, although its p value was >0.05

and increased full recovery (i.e., reduced "unfavourable outcome" defined as GOS <5) in adults with community-acquired BM (particularly pneumococcal) receiving a specific dexamethasone regimen: 10 mg iv 15–20 min before or with the first parenteral antibiotic dose, and every 6 h thereafter, over 96 h [6]. It is also in contrast with the recent observational report from the Netherlands indicating that this regimen, when transferred to daily practice, might reduce mortality and increase the likelihood of full recovery from pneumococcal disease [7]. Several points need to be considered in an attempt to identify the reasons for discrepancy between the present and reported results [6, 7].

Study design

It is not the purpose of observational "real-life" data to question the existence of a treatment effect observed in a well-designed trial, rather it is to assess the transferability of the observed benefit into daily practice. Doing so through a retrospective analysis could be potentially burdened by susceptibility to bias. However, the standards of good clinical practice and the reflection of the real situation contribute somewhat to the strength of this study.

Socio-economic level of the country, patient characteristics and causative agents

According to clinical trials, the benefits of adjunctive dexamethasone seen in high-income countries do not seem to hold in the low-income countries [5, 9, 10]. Potential reasons for this discrepancy include reduced/delayed access to medical care (to an extent at which benefits of any intervention are reduced), overall low socio-economic standard (that may affect various aspects of medical care) and high prevalence of HIV infection with reduced possibility of its treatment in the low-income countries [5, 10]. The present data refer to a cohort of patients from Croatia, a central-eastern European transitional country. According to the 2009 World Bank data, regarding the gross domestic product and purchasing power parity per capita, Croatia ranks 33rd out of 162 countries and the two indices are at

Table 5 Adjusted effects of on-admission cerebrospinal fluid (CSF) indicators of inflammation[a] on mortality [Glasgow Outcome Score (GOS) = 1] and full recovery (GOS = 5) in adult community-acquired acute bacterial meningitis ($N = 304$)

	GOS = 1[b]		GOS = 5[b]	
	RR (95% CI)	*p*	RR (95% CI)	*p*
More pronounced CSF inflammation	0.84 (0.60–1.19)	0.326	0.81 (0.63–1.02)	0.078
Age (by 10 years)	1.19 (1.04–1.37)	0.012	0.93 (0.88–0.98)	0.014
GCS[c] (by 1 unit lower)	1.26 (1.19–1.33)	<0.001	0.90 (0.86–0.94)	<0.001
Meningitis following septicaemia	1.49 (1.04–2.14)	0.028	0.78 (0.63–0.98)	0.030
Pneumococcal meningitis	1.88 (1.37–2.60)	<0.001	–	–
Immunodeficiency[d], malignancy or DM	1.52 (1.07–2.16)	0.019	–	
Meningitis symptoms, atb: ≤24 h[e]	0.47 (0.30–0.74)	0.001	2.55 (1.62–4.02)	<0.001
Proven bacterial (any agent)	–	–	1.27 (1.06–1.52)	0.011
Other serious comorbidity			0.74 (0.59–0.94)	0.014

Relative risks (RR) are given with 95% confidence interval (CI)

GCS Glasgow Coma Score, *DM* diabetes mellitus, *Atb* antibiotic

[a] No multivariate model indicated any adjusted effect of indicators of CSF inflammation (pleocytosis, protein concentration and CSF/blood glucose ratio, considered separately or simultaneously) on the outcomes. Presented models include "more pronounced CSF inflammation", a binary variable obtained by cluster analysis of the three individual CSF indicators (see footnote to Table 1), which showed the most pronounced unadjusted effect (see Table 3) on the outcomes

[b] Multivariate model-building followed the same methodology as depicted in footnote to Table 4, except that "CSF inflammation" variables were default variables instead of "dexamethasone treatment". As demonstrated, use of dexamethasone did not satisfy criteria to enter either model

[c] Worst within the first 24 h since admission

[d] See footnote to Table 1

[e] Timing of adequate antibiotic treatment, see footnote to Table 2

Table 6 Mortality [Glasgow Outcome Score (GOS) = 1] and full recovery (GOS = 5) in subgroups of adult patients with community-acquired bacterial meningitis in respect to causative agent

	All patients		Dexamethasone		No dexamethasone	
	n	Count (%)	*n*	Count (%)	*n*	Count (%)
Proven bacterial[a]	240		104		136	
GOS = 1		65 (27.1)		27 (26.0)		38 (27.9)
GOS = 5		119 (49.6)		48 (46.2)		71 (52.2)
S. pneumoniae	131		71		60	
GOS = 1		34 (26.0)		18 (25.4)		16 (26.7)
GOS = 5		61 (46.6)		30 (42.3)		31 (51.7)
Other agents[a,b]	109		33		76	
GOS = 1		31 (28.4)		9 (27.3)		22 (29.0)
GOS = 5		58 (53.2)		18 (54.6)		40 (52.6)
Probable bacterial[a]	64		15		49	
GOS = 1		8 (12.5)		5 (33.3)		3 (6.1)
GOS = 5		44 (68.8)		7 (46.7)		37 (75.5)

[a] See "Patients and methods" for microbiological diagnostic criteria

[b] See Table 2 for the list of other identified agents

the level of 40–80% of that in developed European Union member states [19]. Urban population by far predominates and practically 100% of the population is embraced by a health insurance system that guarantees completely free access to a wide network of primary, secondary and tertiary care institutions [20]. Prevalence of HIV infection in

Table 7 Effects of dexamethasone treatment on mortality [Glasgow Outcome Score (GOS) = 1] and full recovery (GOS = 5) in subgroups of adult patients with community-acquired acute bacterial meningitis

Subgroup	GOS = 1		GOS = 5	
	RR (95% CI)	*p*	RR (95% CI)	*p*
Proven bacterial ($n = 240$)				
Dexamethasone, unadjusted effect	0.93 (0.61–1.42)	0.733	0.88 (0.68–1.15)	0.358
Dexamethasone, adjusted effect[a]	0.97 (0.69–1.38)	0.877	1.03 (0.82–1.28)	0.827
Pneumococcal meningitis ($n = 131$)				
Dexamethasone, unadjusted effect	0.95 (0.53–1.70)	0.864	0.82 (0.57–1.18)	0.281
Dexamethasone, adjusted effect[a]	0.80 (0.52–1.23)	0.303	1.12 (0.83–1.50)	0.456
Other causative agents ($n = 109$)				
Dexamethasone, unadjusted effect	0.94 (0.49–1.82)	0.860	1.04 (0.71–1.51)	0.853
Dexamethasone, adjusted effect[a]	1.36 (0.81–2.26)	0.240	0.94 (0.70–1.26)	0.664
Probable bacterial ($n = 64$)				
Dexamethasone, unadjusted effect	5.44 (1.47–20.2)	0.011	0.62 (0.35–1.09)	0.095
Dexamethasone, adjusted effect[a]	0.82 (0.53–1.26)	0.364	0.84 (0.56–1.27)	0.415
Starting GCS <12 ($n = 153$)[b]				
Dexamethasone, unadjusted effect	0.87 (0.60–1.24)	0.435	1.12 (0.66–1.89)	0.669
Dexamethasone, adjusted effect[c]	1.11 (0.79–1.56)	0.544	0.99 (0.65–1.50)	0.947
Starting GCS ≥12 ($n = 151$)[b]				
Dexamethasone, unadjusted effect	1.18 (0.22–6.20)	0.847	0.91 (0.75–1.10)	0.324
Dexamethasone, adjusted effect[c]	0.84 (0.23–3.00)	0.786	0.92 (0.77–1.10)	0.348
Symptoms-Atb[d] ≤24 h ($n = 203$)				
Dexamethasone, unadjusted effect	1.58 (0.71–3.55)	0.264	0.85 (0.70–1.04)	0.110
Dexamethasone, adjusted effect[e]	0.90 (0.44–1.85)	0.800	0.95 (0.79–1.14)	0.584
Symptoms-Atb[d] >24 h ($n = 101$)				
Dexamethasone, unadjusted effect	0.91 (0.62–1.34)	0.643	0.87 (0.36–2.11)	0.759
Dexamethasone, adjusted effect[e]	0.93 (0.67–1.31)	0.688	0.81 (0.38–1.74)	0.591
Greater CSF inflammation ($n = 86$)[f]				
Dexamethasone, unadjusted effect	0.93 (0.52–1.68)	0.815	1.23 (0.67–2.26)	0.500
Dexamethasone, adjusted effect[g]	1.39 (0.87–2.23)	0.166	1.23 (0.77–1.98)	0.383
Lesser CSF inflammation ($n = 218$)[f]				
Dexamethasone, unadjusted effect	1.25 (0.73–2.14)	0.415	0.79 (0.61–1.01)	0.058
Dexamethasone, adjusted effect[g]	0.84 (0.55–1.28)	0.419	0.93 (0.76–1.14)	0.503
Atb before admission (dexa) ($n = 102$)[h]				
Dexamethasone, unadjusted effect	1.55 (0.74–3.23)	0.243	0.64 (0.42–0.97)	0.037
Dexamethasone, adjusted effect[g]	1.14 (0.61–2.10)	0.685	0.75 (0.54–1.03)	0.079
No Atb before admission (dexa) ($n = 202$)				
Dexamethasone, unadjusted effect	1.09 (0.67–1.76)	0.726	0.88 (0.67–1.16)	0.358
Dexamethasone, adjusted effect[g]	0.93 (0.63–1.36)	0.701	1.11 (0.89–1.39)	0.349

Relative risks (RR) are given with 95% confidence interval (CI)

GCS Glasgow Coma Scale, *Atb* antibiotic, *CSF* cerebrospinal fluid, *dexa* dexamethasone

[a] Adjustments for GOS = 1: age, worst GCS score within 24 h since admission, meningitis following septicaemia, immunodeficiency, malignancy or diabetes, appropriate antibiotic treatment within 24 since the onset of consciousness disturbance or other overt meningitis symptoms. Adjustment for GOS = 5: the same, except immunodeficiency, malignancy or diabetes replaced by "other serious comorbidity"

[b] Worst GCS score within 24 h since admission

[c] Adjustments as in [a], except that "starting GCS" replaced with "proven bacterial meningitis"

[d] Timing of appropriate antibiotic treatment relative to the onset of overt meningitis symptoms (see footnote to Table 2 and "Patients and methods")

[e] Adjustments as in [a], but "antibiotic timing" replaced with "proven bacterial meningitis"

[f] Clusters based on CSF markers of inflammation (see footnote to Table 1)

[g] Adjustments as in [a] plus "proven bacterial meningitis"

[h] Any antibiotic (oral, parenteral) before admission/verification of diagnosis and, when used, dexamethasone commencement

Croatia is very low even in vulnerable populations. The cumulative prevalence for the period 1985–2005 is 553 patients, which is negligible for a country with a population of 4.4 million that has been stable at this level over the past 15–20 years [20, 21]. In this respect, Croatia is more similar to countries in which benefits of adjunctive dexamethasone are expected than to the "low-income countries" in which benefits are not expected [5, 9, 10]. In line with this, the mortality (24% overall, 27.1% in pneumococcal disease) and full recovery rates (54% overall, 49.6% in pneumococcal disease) in the current cohort (39.1% patients received adjunctive dexamethasone) (Table 2) greatly overlap with the observational Dutch data where mortality and full recovery rates in *S. pneumoniae* BM were 30 and 50%, respectively, in the 1998–2002 cohort (17% received adjunctive dexamethasone), or 20 and 61%, respectively, in the 2006–2009 cohort (92% received adjunctive dexamethasone) [7]. Definitions of "adult" and "community-acquired" BM were practically identical in the present report as in the published European trial and observational data [6, 7]. Also, proportions of patients with malignancy, immunodeficiency (by the same criteria) or diabetes were similar in the present (18.4% overall, 26% in pneumococcal disease) and the published cohorts (23%) [7]. In the current cohort, 52% of all patients and 70% of those with pneumococcal disease where admitted to the hospital within 30 h since the onset of any (including mild, atypical) symptoms, which compares well with the reported 50% of patients admitted within the first 24 h in the Dutch pneumococcal cohorts [7]. Finally, as in the published reports, *S. pneumoniae* was the most prevalent single causative agent in the current cohort, found in 43.1% of the overall patients and in 55% of those with bacteriologically proven disease [6, 7]. This is in agreement with the European trial (36 and 46%, respectively) and observational data (62 and 69%, respectively) [6, 7]. Of note, *Neisseria meningitidis*, which was the causative agent in one-third of the patients in the European trial and for which the beneficial effect of dexamethasone was clearly lacking, was found in only 6.3% of the current patients (7.9% of those with bacteriologically proven disease) [6]. Because of the long observational period, some of the overall socio-economic factors probably have changed. Nevertheless, all relevant factors regarding the accessibility and the quality of medical care, as well as the prevalence of HIV infection remained very similar. Hence, it seems unlikely that the patient and causative agent characteristics could account for the discrepancy between the current and published results [6, 7].

Antibiotic treatment and dexamethasone regimen

There is no substantial difference between antibiotic regimens applied in the current cohort (see "Patients and methods") and those applied in the European trial and observational reports, which is understandable since they were developed based on the same common knowledge and developments in the field over the observed time [6, 7]. Also, considering the data on lag-times between (any) symptom onset and admissions (see above) and the fact that 66.8% of the current patients (67.2% of those with the pneumococcal disease) received appropriate treatment within 24 h since the onset of more specific symptoms, it seems unlikely that the observed discrepancy between the current and published results is generated by a discrepancy in the basic therapy [6, 7].

The European trial evaluated a specific dexamethasone regimen (4 × 10 mg/day over 4 days, started before or with the first antibiotic dose) and subjects who received antibiotics prior to assessment of eligibility were not enrolled [6]. In the Dutch cohort of patients with pneumococcal disease and better outcomes (2006–2009), 77% of patients received this particular regimen and a further 15% received dexamethasone with variations in dose, duration and commencement relative to commencement of antibiotics, whereas in the cohort with poorer outcomes (1998–2002), 3% received this particular regimen, and a further 14% received variable dexamethasone treatments [7]. Clearly, the current cohort differs regarding the dexamethasone treatment: the entire regimen varied from a (theoretical) minimum of 4 × 8 mg/day over 2 days to a maximum of 4 × 12 mg/day over 4 days, and 33.6% patients had received some form of antibiotic treatment before hospital admission, verification of diagnosis and commencement of the appropriate antibiotic (and dexamethasone) treatment (exactly the same proportion of patients with "prior" antibiotic therapy was seen among patients not treated with dexamethasone). Hence, one cannot rule out this disagreement as a potential source of discrepancy between the current and published results, although it does not seem likely that it could completely account for it [6, 7]. First, two recent meta-analyses of placebo-controlled trials demonstrated that commencing dexamethasone before (or with) the first antibiotic dose or after antibiotic treatment had already started had no impact on its effects [8, 9]. In the present analysis, dexamethasone had no effect on mortality or full recovery in the entire cohort, but also in the subgroup of patients who received antibiotics before dexamethasone, as well as in the subgroup in which dexamethasone was started immediately before or with the first antibiotic dose. Theoretically, the rationale of timing dexamethasone before (or with) the antibiotic seems reasonable, as it should suppress the potential pro-inflammatory effects of bacterial lysis. However, it does not seem likely that a few doses of oral antibiotic treatment (for example, at the early stage of the disease with no evident meningitis symptoms) would

induce such damage that a consequent dexamethasone would be useless.

Second, in the Dutch 2006–2009 cohort of patients with the pneumococcal meningitis, the rate of full recovery was 42% in patients who received no dexamethasone (8%), 64% in patients who received the exact 4-day regimen as in the European trial (77%), 53% in patients who received other dexamethasone treatment (different from that one) (15%), and 61% in patients who received any dexamethasone regimen (92%) [6, 7]. Therefore, even a regimen discrepant from the one proposed by the European trial resulted in an absolute risk increase of 11%, and "any dexamethasone regimen" (as opposed to no dexamethasone) resulted in an absolute risk increase of 19% [6]. Therefore, "any" or even "erroneous" dexamethasone regimen would be expected to yield at least some benefit. In the current subgroup with pneumococcal disease, the rate of full recovery with "any dexamethasone" regimen was 42.3%, whereas it was 51.7% with no dexamethasone treatment. The unadjusted and adjusted RR were 0.82 (95% CI 0.57–1.18) and 1.12 (95% CI 0.83–1.50), respectively. Furthermore, in the current subgroup of patients who did not receive antibiotics prior to verification of diagnosis and commencement of appropriate antibiotic and, where applicable, dexamethasone, i.e., in patients where the disagreement between the current dexamethasone regimen and the one proposed by the European trial was confined to dose (4×8 to 4×12 mg/day vs. 4×10 mg/day) and duration (2–4 vs. 4 days) ($n = 94$), the rate of full recovery with dexamethasone was 26/54 (48.2%) and with no dexamethasone treatment it was 21/40 (52.5%) [6]. Therefore, even if, in a way, stratified in respect to dexamethasone treatment schedule, current results on dexamethasone effects are in discrepancy with the published ones and disagreements related to dexamethasone regimen cannot account (or, at least, cannot fully account) for it [7].

Accounting for confounders

The present analysis accounted for all relevant confounders known to affect mortality or full recovery in adult community-acquired BM as suggested by the literature (e.g., age, severity of consciousness disturbance, presence of immunodeficiency, malignancy, diabetes mellitus and other serious comorbidity, *S. pneumoniae* as a causative agent) and as indicated by the imbalances in baseline characteristics of dexamethasone-treated and not treated patients [5–10]. Naturally, adjustments can hardly compensate for randomization (in terms of having "patients comparably susceptible to treatment in the treatment and control groups"). In the current cohort, dexamethasone-treated patients presented with, on average, somewhat more difficult disease (illustrating physicians' tendency to introduce dexamethasone in more difficult patients), but the two groups largely overlapped in respect to all relevant diseases features. Under such circumstances, adjustments in multivariate models may greatly straighten the situation. For example, the crude rate of full recovery in the dexamethasone-treated patients was statistically significantly lower than in the non-treated patients, but multivariate analysis revealed that dexamethasone treatment is not harmful in this respect. Additionally, the present analysis adjusted for another effect that turned out to be consistently very important regarding both analyzed outcomes: timing of appropriate antibiotic treatment relative to the onset of consciousness alteration or other overt meningitis symptoms. A delay in antibiotic treatment has a considerable unfavourable effect in adult BM and timing relative to the onset of more specific (and not "any") meningitis symptoms seems to be particularly important [17, 18, 22]. In the European trial, no adjustments were made for "timing of antibiotic treatment" and no data on this variable were provided [6]. One could assume that randomization ascertained a fair balance between the dexamethasone and placebo groups in this respect. But this does not mean that adjusting for this variable could not have changed the estimate of the size of the dexamethasone effect (antibiotic timing not as a confounding, but as an "effect-modifying" variable).

Conclusions

Our 20-year experience in the treatment of adult community-acquired BM caused by *S. pneumoniae* or other common agents suggests no benefit of adjunctive iv dexamethasone treatment in terms of reduced mortality (GOS = 1) and increased likelihood of full recovery (GOS = 5). These observations are in discordance with the results of a randomized, placebo-controlled European trial and observational data [6, 7]. Potential methodological differences, socio-economic circumstances and patient characteristics do not seem to explain this discrepancy. Hence, although the specific dexamethasone regimen evaluated in the European trial might indeed be beneficial in some patients and is a part of the recommended treatment of adult BM, empirical use of adjunctive dexamethasone in this setting remains controversial [5, 6, 10, 23].

Acknowledgments We are thankful to all the present and past staff members at the Department of Intensive Care Medicine and Neuroinfectology for their dedication and expertise. We thank Mrs. Arijana Pavelić and Mrs. Marija Fijucek for their help in the preparation of the manuscript. There was no financial support for this study.

Conflict of interest None.

References

1. Scheld WM, Koedel U, Nathan B, Pfister HW (2002) Pathophysiology of bacterial meningitis: mechanism(s) of neuronal injury. J Infect Dis 186(suppl. 2):S225–S233
2. Koedel U, Scheld WM, Pfister HW (2002) Pathogenesis and pathophysiology of pneumococcal meningitis. Lancet Infect Dis 2:721–736
3. Koedel U, Klein M, Pfister HW (2010) New understandings on the pathophysiology of bacterial meningitis. Curr Opin Infect Dis 23:217–223
4. Weber JR, Tuomanen EI (2007) Cellular damage in bacterial meningitis: an interplay of bacterial and host driven toxicity. J Neuroimmunol 184:45–52
5. Greenwood BM (2007) Corticosteroids for acute bacterial meningitis. N Engl J Med 357:2507–2509
6. de Gans J, van de Beek D (2002) Dexamethasone in adults with bacterial meningitis. N Engl J Med 347:1549–1556
7. Brouwer MC, Heckenberg SG, de Gans J, Spanjaard L, Reitsma JB, van de Beek D (2010) Nationwide implementation of adjunctive dexamethasone therapy for pneumococcal meningitis. Neurology 75:1533–1539
8. van de Beek, Farrar JJ, de Gans J et al (2010) Adjunctive dexamethasone in bacterial meningitis: a meta-analysis of individual patient data. Lancet Neurol 9:254–263
9. Brouwer MC, McIntyre P, de Gans J, Prasad K, van de Beek D (2010) Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev 9:CD004405. doi:10.1002/14651858.CD004405.pub.3
10. McIntyre P (2010) Adjunctive dexamethasone in meningitis: does value depend on clinical setting? Lancet Neurol 9:229–231
11. Flores-Cordero JM, Amaya-Villar R, Rincon-Ferrari MD et al (2003) Acute community-acquired bacterial meningitis in adults admitted to the intensive care unit: clinical manifestations, management and prognostic factor. Intensive Care Med 29:1967–1973
12. Girgis NI, Farid Z, Mikhail IA, Farrag I, Sultan Y, Kilpatrick ME (1989) Dexamethasone treatment for bacterial meningitis in children and adults. Pediatr Infect Dis J 8:848–851
13. Odio CM, Faingezicht I, Paris M et al (1991) The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis. N Engl J Med 324:1525–1531
14. Jennett B, Bond M (1975) Assessment of outcome after severe brain damage. Lancet 1:480–484
15. McNutt LA, Wu Ch, Xue X, Hafner PP (2003) Estimating relative risk in cohort studies and clinical trials of common outcomes. Am J Epidemiol 157:940–943
16. Teasdale G, Jennett B (1974) Assessment of coma and impaired consciousness. A practical scale. Lancet 2(7872):81–84
17. Koster Rasmussen R, Korshin A, Meyer N (2008) Antibiotic treatment delay and outcome in acute bacterial meningitis. J Infect 57:449–454
18. Lepur D, Baršić B (2007) Community-acquired bacterial meningitis in adults: antibiotic timing in disease course and outcome. Infection 35:225–231
19. World Bank. World Development Indicators database. http://databank.worldbank.org/ddp/home.do?Step=12&id=4&CNO=2. Accessed 10 Jan 2001
20. Croatian Bureau of Statistics. Census of population, households and dwellings, March 31, 2001. http://www.dzs.hr/default_e.htm. Accessed 10 Jan 2001
21. Begovac J, Zekan A, Skoko-Poljak D (2006) Twenty years of human immunodeficiency virus infection in Croatia—an epidemic that is still in an early stage. Coll Antropol 30(2):17–23
22. Proulx N, Frechette D, Toye B, Chan J, Kravick S (2005) Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. Q J Med 98:291–298
23. Tunkel AR, Harman BJ, Kaplan SL et al (2004) Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 39:1267–1284