

Improving the outcomes in children with bacterial meningitis

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Current Opinion in Infectious Diseases 2009, 22:250–255

Purpose of review

Intravenous dexamethasone (DXM) is used as adjuvant medication in bacterial meningitis of childhood, although no single study has proven its efficacy against death, severe neurological sequelae, or hearing impairment. Meta-analyses do not facilitate interpretation, because they combine profoundly dissimilar populations and neglect the child's presenting condition. Important new information was revealed by a large double-blind, prospective study from Latin America in which the effects of oral glycerol (GLY) were compared with those of DXM.

Recent findings

Of 654 children, mainly with *Haemophilus influenzae* type b or pneumococcal meningitis, 166 received DXM, 159 DXM and GLY, 166 GLY, and 163 placebo. Neither of the adjuvants prevented hearing impairment, regardless of agent or timing of antibiotic. Instead of the causative agent, the presenting status was the only characteristic that associated with all three outcomes. GLY, but not DXM, prevented neurological sequelae, especially in *Haemophilus influenzae* type b meningitis. The likely mechanism of GLY is the increase in plasma osmolality. Cerebrospinal fluid genome counts differ enormously and predict death in pneumococcal but not *Haemophilus influenzae* type b meningitis.

Summary

Being the first adjuvant in childhood meningitis with documented clinically meaningful benefits, GLY seriously challenges the position of DXM as adjuvant medication. Severe neurological sequelae are relieved by GLY, whereas no current medication prevents hearing impairment.

Keywords

adjuvant treatments, bacterial meningitis, dexamethasone, glycerol

Curr Opin Infect Dis 22:250–255
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0951-7375

Introduction

As the outcomes of bacterial meningitis of childhood have essentially not improved since the advent of chloramphenicol and ampicillin more than 40 years ago, adjuvant medications have been tried. Shown by biochemical markers, dexamethasone (DXM) dampens the massive inflammatory reaction, but not a single, prospective, randomized, double-blind study has documented any major clinical benefit. The only exception was one trial on 100 children treated suboptimally with cefuroxime [1] in which statistical significance was meagerly reached. All other studies had to combine different outcomes to show any effectiveness. Still, Cochrane analysis [2] recommends early DXM, at least in high-income countries and for *Haemophilus influenzae* type b (Hib) meningitis. DXM should preferably be instituted prior to antibiotic.

Several major problems load these recommendations. First, all data have been derived from small retrospective and prospective studies in which the conditions and

populations have varied enormously. Second, leaving, the three relevant outcomes of bacterial meningitis – death, severe neurological sequelae, and hearing impairment – unanalyzed separately is not justified because the pathogenesis is likely different. Obtaining an overall picture is interesting, but composite endpoints should be examined only after the primary, outcome-wise analysis. Third, hearing impairment has been measured using different methodology, dissimilar thresholds, and sometimes leaving the smallest children unanalyzed. Fourth, as if these issues are not sufficient to prevent a well balanced interpretation, the biggest problem is that no analysis has taken into account the child's presenting condition, assuming that the causative agent *per se* associates with outcome. Total neglect of the presenting status in such a variable disease as bacterial meningitis is a major shortcoming. This view is underlined by the results of recent research.

Realizing the above-listed problems, it was not surprising that the first sufficiently powered pediatric study in

Malawi [3] did not find DXM beneficial, no matter which outcome, cause, or relation to the institution of antibiotic. However, economic constraints hindered routine use of third-generation cephalosporins in this pivotal trial. A retrospective cohort study from the USA [4] agreed with the African data: DXM did not reduce mortality or shorten the hospital stay. A special committee of the American Academy of Pediatrics virtually recommends DXM at least in Hib meningitis [5], but doubts prevail even in the USA [6]. As the clinically meaningful benefits of DXM in childhood bacterial meningitis are far from documented, new paths should be explored.

New information from Latin America

The largest to date prospective, randomized double-blind study was carried out in six countries of Latin America in 1996–2003 [7•]. On the basis of a few case reports, a pilot study [8], and decades long experience in the reduction of increased tissue pressure in neurology, neurosurgery, otology, and ophthalmology [7•], oral glycerol (1, 2, 3-propanetriol, GLY) was compared vis-a-vis DXM intravenously (i.v.). The endpoints were death, severe neurological sequelae, and hearing impairment (measured at three threshold levels), but a post-hoc analysis was done for the combination of severe neurological sequelae or death. The setup offered an opportunity to examine bacterial meningitis in its complex entirety and from a considerably wider angle than in any earlier study.

Children of age 2 months to 15 years in 10 institutions constituted the series. The trial was designed, conducted, and analyzed independently of any companies. The protocol was approved by ethical committees and legal guardians' consent was requested. Bacterial meningitis was defined with strict criteria [7•] and the outcomes were assessed at discharge from hospital. Severe neurological sequelae were defined as blindness, quadriplegia or plegia, hydrocephalus requiring a shunt, or severe psychomotor retardation (does not sit or walk, speak, or establish contact, or requires institutionalization). Hearing was usually measured with brainstem-evoked audiometry response (BERA). All test results were read independently by an experienced audiologist. Age-adjusted Glasgow Coma Scale was used to quantify the child's condition on admission. Double blinding was ensured as all children received an adjuvant or placebo in an indistinguishable form i.v. and orally.

Ceftriaxone (80–100 mg/kg once daily i.v. for 7–10 days) was given to all children who were randomized to receive one of the following four adjuvant medications: DXM i.v. 15 min before ceftriaxone + placebo orally; DXM i.v. + GLY orally; GLY orally + placebo i.v.; placebo i.v. + placebo orally. Both adjuvants were administered for 48 h, DXM at a dose of 0.6 mg/kg/day i.v. divided in four

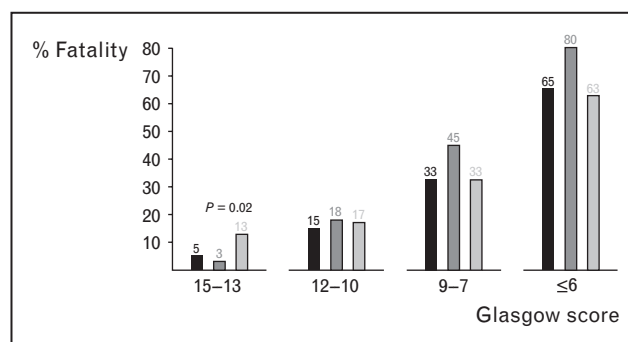
doses and 85% GLY (1 ml contains 1 g of GLY) at 6.0 g (6.0 ml) per kg/day orally divided in four doses up to 25 ml per dose. Often a nasogastric tube was used. If the child vomited (rarely), the same dose was repeated immediately. Normal maintenance fluids with isotonic crystalloids were used routinely. In hypovolemia, all deficits were first replaced. Sample size calculation assumed at least 88 patients in each arm. The outcomes in the three adjuvant groups were compared with the placebo group by logistic regression and the results were expressed as odds ratio (OR) with 95% confidence intervals (95%CI). The final analysis was done on intention-to-treat basis.

Death vs. other outcomes

Of the 654 analyzed children, 87 (13%) died. An agent was disclosed in 74% ($n=484$) of cases, of which Hib caused 221, pneumococcus 132, meningococcus 110, and other bacteria 21 cases. One hundred and sixty-six children received DXM, 159 DXM + GLY, 166 GLY only, and 163 placebo only. The on-admission characteristics of the four groups did not differ.

In univariate analysis, the risks of death, severe neurological sequelae, either of these two, or being left deaf (better ear's threshold >80 dB) were associated, not unexpectedly, with several factors [9•]: young age, seizures, late arrival, low scoring in the Glasgow Coma Scale, slow capillary filling time, low glucose or high protein concentration of cerebrospinal fluid (CSF), low blood hemoglobin or leukocyte count, and a pneumococcal cause. However, when this information was submitted to logistic regression [9•], only one factor remained significant across all the outcomes: scoring in the Glasgow Coma Scale. Notably, this characteristic was more important than the cause *per se* (Fig. 1), the only exception being

Figure 1 The risk of death in bacterial meningitis was independently associated with the child's clinical condition on admission



Only if the patient was not very ill, scoring 15–13 in the Glasgow Coma Scale, was the risk of death higher in pneumococcal than *Haemophilus influenzae* type b (Hib) meningitis. ■, All; ■, Hib; ■, pneumococcus.

the situation in which the child presented not very ill (score 15–13), in which case the risk of death was higher in pneumococcal than Hib meningitis.

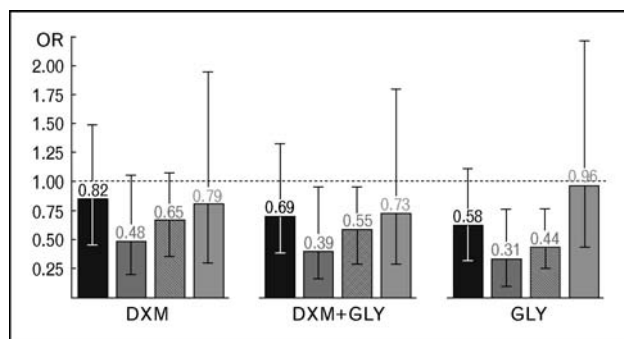
This clear-cut and new information was underscored once the risks of death or severe neurological sequelae were projected against the lowering Glasgow Coma score. Regardless of the causative agent, the risk increased 3.5-fold at the score 12–10, 11-fold at 9–7, and almost 30-fold at the score of 6 or less [9**]. This association, so easily understandable to clinicians – that the child's presenting status predicts survival or nonsurvival – was so straightforward that any analysis that compares different patient series remains severely impaired unless this characteristic is included as cofactor. Neither DXM nor GLY (or their combination) prevented death, but a trend in favor of GLY prevailed in non-Hib meningitis ($n = 433$; OR 0.49; 95%CI 0.21–1.13) [7**].

Severe neurological sequelae

GLY, in contrast to DXM, significantly prevented severe neurological sequelae (Fig. 2). The effect was clearest in Hib meningitis and almost significant in other types of bacterial meningitis. Overall, OR in patients receiving only GLY was 0.31 (95%CI 0.13–0.76) compared with 0.39 (0.17–0.93) in the DXM + GLY and 0.48 (0.21–1.07) in the DXM-only groups [7**].

Examining the composite endpoint of severe neurological sequelae or death, the picture was much the same and the DXM-only group remained nonsignificant. OR in the GLY-only group was 0.44 (95%CI 0.25–0.76) compared with 0.55 (0.32–0.93) in the DXM + GLY and 0.65 (0.39–1.09) in the DXM-only group [7**].

Figure 2 Compared with the placebo group, the risk of death, severe neurological sequelae, either of these two, or deafness among children who received adjuvant dexamethasone (DXM), glycerol (GLY), or DXM+GLY varied, but the GLY-only group benefited most



Horizontal line depicts the 1.00 odds ratio (OR) level, vertical lines the 95% confidence intervals. The salutary effect of an adjuvant is significant only if both ends of the vertical lines are under the horizontal line. SeNeSe, severe neurological sequelae. ■, Death; ■, SeNeSe; ■, SeNeSe/death; ■, deafness.

Associations between nutritional status and outcomes have not been well described in bacterial meningitis. A retrospective study from Angola [10] showed that being severely underweight increased death and severe neurological sequelae. Whether this effect extends to hearing impairment and what is the role of the mild-to-moderate malnutrition are now questions under scrutiny.

Deafness

Neither GLY nor DXM, or their combination, prevented profound hearing loss (better ear's threshold ≥ 80 dB) significantly (Fig. 2). Even when Hib meningitis was examined separately and only children without prior antibiotics and an adjuvant instituted before ceftriaxone were analyzed, no major benefit of DXM was observed. Compared with the placebo group, OR among the GLY recipients was 0.48 (95%CI 0.08–2.89) compared with 0.23 (0.02–2.21) in the DXM + GLY and 0.19 (0.02–1.86) in the DXM-only groups [7**].

Table 1 summarizes a few essential findings of the Latin American study. First, the child's presenting status, measured with the Glasgow Coma score, was the single most important cofactor through all three outcomes of death, severe neurological sequelae, and deafness. Second, the causative agent *per se* was of lesser importance, but associated with deafness in Hib but not pneumococcal or meningococcal meningitis. Third, death or severe neurological sequelae followed meningococcal meningitis less frequently than Hib or pneumococcal meningitis. Fourth, and most importantly, oral GLY significantly prevented neurological sequelae. Finally, deafness was relieved by neither DXM nor GLY, but a positive trend in the DXM group hinted that there is a subgroup of patients who sometimes benefit from DXM. However, it is equally clear that these children are not just those with Hib meningitis with no pretreatment antibiotics and who start the DXM treatment prior to antibiotic. No currently known characteristic identifies these few individuals.

How does glycerol work?

The mechanisms of GLY in childhood bacterial meningitis were scrutinized in Chandigarh, India [11**]. The setup was identical to the Latin American trial, but the study was powered to investigate the effects of GLY and DXM on plasma osmolality and urine output, not to examine their clinical impact [12].

In all, the series consisted of 36 children of age 2 months to 12 years, mostly with pneumococcal, Hib, or staphylococcal meningitis. The effect of GLY was clear: it increased plasma osmolality [11**]. The increase was only by a few per cent, but very constant among the GLY recipients during the first 6 h, that is, at the critical

Table 1 Effects of some essential patient characteristics on the outcome of bacterial meningitis of childhood (binominal logistic regression analysis)

	Death (n = 612)			Severe neurological sequelae (n = 520)			Deafness ^a (n = 355)		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Scoring on Glasgow Coma Scale ^b	1.44	1.32–1.57	<0.0001	1.47	1.30–1.66	<0.0001	1.18	1.04–1.33	0.008
Cause									
<i>Haemophilus influenzae</i> type b	1.12	0.58–2.15	0.74	0.51	0.22–1.20	0.12	2.70	1.13–6.43	0.03
<i>Streptococcus pneumoniae</i>	1.37	0.69–2.73	0.37	0.72	0.30–1.72	0.46	2.16	0.80–5.83	0.13
<i>Neisseria meningitidis</i>	0.10	0.01–0.79	0.03	0.10	0.01–0.75	0.03	–	–	–
Adjuvant treatment									
Dexamethasone	0.77	0.38–1.58	0.48	0.48	0.19–1.19	0.11	0.40	0.14–1.12	0.08
Dexamethasone + glycerol	0.75	0.36–1.57	0.44	0.37	0.14–0.98	0.04	0.89	0.35–2.21	0.79
Glycerol	0.70	0.33–1.47	0.34	0.29	0.10–0.78	0.01	1.15	0.48–2.73	0.75

CI, confidence interval; OR, odds ratio.

^a Better ear's hearing ≥ 80 dB.

^b Each lowering score starting from the highest (normal) of 15.

time when antibiotic treatment was instituted. The effect lasted less than 24 h. The DXM + GLY group showed the same effect, but to a lesser extent, whereas the DXM-only and the placebo-only groups remained totally unaffected. Urine output did not increase nor was blood pressure affected.

These observations on osmolality fully agree with the old ophthalmological and otological data [11^{••}], which demonstrate that oral GLY is a well tolerated agent and acts quickly. Animal data [13] have shown that a tiny 1% increase in osmolality decreases the CSF excretion by 7% and an 18% increase blocks it entirely. Furthermore, human [14] data show that a single dose of 0.5–1.5 g/kg of GLY orally induces a small increase in osmolality but a major decrease in raised intracranial pressure.

Combining this information with the data from India [11^{••}], it is likely that up to 3% increase in plasma osmolality in bacterial meningitis decreased the CSF excretion by 20–30%. This occurred at the time when intracranial edema was likely to increase. Details remain to be unveiled as to the mechanisms of GLY, but probably, intracranial hypovolemia is relieved by water removal back to the plasma by osmosis and the cerebral blood flow is increased. Hence, brain oxygenation likely improves as a result of the GLY-induced increase in plasma osmolality.

Cerebrospinal fluid genome counts vs. the outcome

Extremely wide bacterial loads in CSF are characteristic of bacterial meningitis, but with the exception of young age, no consistent associations with outcomes have been documented. Quantification occurs usually by counting bacterial colony-forming units on media, but this methodology probably underestimates the load for reasons such as prior pretreatment antibiotics and that only viable

organisms are detected. Real-time PCR offers a tool to examine potential associations more closely.

A Malawian group investigated 82 children with bacterial meningitis and 13 with pneumonia, all caused by pneumococci [15]. In addition to measuring cytokines [tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , IL-6, and IL-10], pneumococcal bacterial DNA was quantified with real-time PCR. The CSF cytokine levels in bacterial meningitis were significantly higher than the plasma concentrations in pneumonia. The correlations were not uniform, but generally, cytokine activity was greater in HIV-infected than noninfected patients and lower in nonsurvivors than survivors. The CSF bacterial load was associated with IL-1 β and IL-10, but not with TNF- α or IL-6. Regardless of the HIV status, no difference prevailed between survivors and nonsurvivors in the median CSF cytokine concentrations, or between the CSF bacterial loads and the CSF total leukocyte or neutrophil counts. Interestingly, the duration of symptoms and signs was not much different between survivors and nonsurvivors, and between HIV-positive and HIV-negative children.

A Finnish group [16^{*}] applied real-time PCR in 85 cases of Hib and 36 of pneumococcal meningitis, aimed at finding a correlation between CSF counts and the outcomes. The counts varied million-fold (from 0 to 9.250 000/ μ l), but again, no clear-cut associations with outcomes were found, except that high counts predicted severe neurological sequelae (OR 1.36; 95%CI 1.09–1.69) and death in pneumococcal (OR 2.05; 95%CI 1.08–3.87), but not Hib meningitis. Hearing impairment was not predicted by the CSF genome counts. This finding adds to the view [7^{••}, 9^{••}] that meningitis treatments should primarily be examined by outcome because the mechanism of hearing impairment appears to be different from that of death or neurological sequelae, these two outcomes probably forming a continuum. Future meta-analyses should take this into account better than do those of today, which are used as basis for recommendations.

Childhood vs. adulthood meningitis

That pediatric diseases are not just those of adults but occurring at young age has been demonstrated recently also in bacterial meningitis. A prospective study in Europe showed adjuvant DXM to be beneficial in adult pneumococcal meningitis [17], but comparison with childhood bacterial meningitis is difficult as the end-points differed. Also in Vietnam, DXM was salutary [18], but only if the causative agent was confirmed; otherwise, DXM was deleterious. As primarily a pig pathogen *Streptococcus suis* was common in this series, the information may not apply easily outside south-east Asia. In Malawi [19], DXM showed no benefit, as was earlier the case in children in the same country [3].

Conclusion

The potential of oral GLY [7**] is undoubtedly the greatest news of the past many years in the treatment of childhood bacterial meningitis. The information arises from only one study, but except for the Malawian trial [3], it was overwhelmingly the largest in pediatrics. These two studies, which consist of no less than 1252 children, fully agreed with regard to the negative results for DXM.

The attitude of the medical community, at least of some prominent persons, to this novel approach has been unexpectedly belittling. The Latino study was said to have problems in ethics [20*] and although the main results were significant [7**,9**], their 'reliable interpretation' [20*] was declared difficult. These emotional statements are odd and entirely unjustified in light of the vague information on which the current DXM recommendations are based, starting from the serious lack of power of all those trials. The GLY vs. DXM study [7**,9**] was a major undertaking, addressed several unanswered questions [21*], and for the first time, was sufficiently powered to do so in a scientifically solid way.

A rather common thinking among clinicians is that although adjuvant DXM might not necessarily be of much benefit, the short 2–4-day course is not likely to harm the patient. This is not necessarily so. A dose of corticosteroid potentiates neuronal toxicity in the dentate gyrus, rich in corticoid receptors, in pneumococcal meningitis of rabbits [22]. In an infant rat model, adjuvant DXM increases hippocampal cell injury, reduces learning capacity [23], and does not prevent hearing loss better than isotonic saline [24*].

Many (in one series in 90% [3,25]) children with bacterial meningitis present with high serum cortisol levels. Because of the vulnerability in neurons possessing a high concentration of corticosteroid receptors, adding

exogenous steroids in this common situation may not be a good idea, unless some clinically meaningful benefits of adjuvant DXM are proven [26*]. So far, this has not been the case.

Conjugate vaccines have a great potential to decrease the burden of childhood bacterial meningitis worldwide. Unfortunately, the progress has been slow in the less privileged countries where one-third of patients still die [27] and survivors are often left with serious sequelae. The incidence of hearing impairment is mostly unknown. Modern technology [28] has, however, brought new tools for better elucidation of this problem, too.

Acknowledgements

We are indebted to the following colleagues who, besides the authors, constituted the LatAm Meningitis Study Group:

Antonio Arbo, Asunción, Paraguay,
Rosa Bologna, Buenos Aires, Argentina,
Solange Dourado de Andrade, Manaus, Brazil,
Josefina Fernández, Santo Domingo, Dominican Republic,
José Goyo, Mérida, Venezuela,
Silvia González Ayala, La Plata, Argentina,
Antonio González Mata, Barquisimeto, Venezuela,
Eduardo López, Buenos Aires, Argentina,
Greta Miño, Guayaquil, Ecuador, and
Inés Zavala, Guayaquil, Ecuador.

Partial funding for the accomplishment of the studies in Latin America and India was obtained from the GlaxoSmithKline company, and the Funds of Alfred Kordelin, Päivikki and Sakari Sohlberg, and Sigfrid Jusélius, and Paediatric Research of Finland.

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- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 328).

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