European Journal of Pediatrics (2025) 184:419
https://doi.org/10.1007/s00431-025-06248-9

RESEARCH

Prophylactic hydrocortisone and the risk of sepsis in neonates born extremely preterm

Olivier Baud[1,2,3] · Philippe Lehert[4,5] · on behalf of the PREMILOC study group

Received: 1 April 2025 / Revised: 19 May 2025 / Accepted: 1 June 2025

Abstract

Bronchopulmonary dysplasia (BPD) is a serious complication of extreme prematurity and has few treatment options. The postnatal use of steroids to prevent BPD remains controversial, but prophylactic low-dose hydrocortisone (HC) has been shown to improve survival without BPD. However, an increased risk of late-onset sepsis (LOS) was also reported in extremely preterm neonates exposed to prophylactic HC treatment. Because its causal link remains unclear, our objective was to assess the effect of prophylactic HC exposure on LOS risk, adjusted for perinatal risk factors of LOS. We re-analyzed the PREMILOC trial to investigate the postnatal factors influencing the incidence of LOS occurring after day 3 from baseline conditions and to evaluate the potential interaction produced by prophylactic HC exposure. We used three different statistical models (poisson, Cox regression, competing risks) to test the effect of HC on LOS occurrence. LOS was reported in 64/264 (24%) and 77/255 (30%) in the placebo and HC groups, respectively ($P=0.12$). A decreasing risk of LOS was observed with increasing gestational age ($P<0.001$), vaginal delivery ($P=0.005$), and supplemental corticosteroids given after a 10-day treatment with prophylactic HC but before the LOS ($P<0.001$). A trend of higher risk of LOS was noted in infants exposed to perinatal asphyxia ($P=0.065$). Adjusted for these covariates, we found a non-significant association between HC exposure and risk of LOS (relative risk, 1.041 (95% CI, 0.738 to 1.471]), $P=0.817$). Using a survival competing risk analysis, we confirmed the lack of significant effect of HC on LOS (hazard risk ratio, 1.105 [95% CI, 0.787 to 1.552], $P=0.560$), while competing death was significantly reduced by the treatment (hazard risk ratio, 0.427 [95% CI, 0.259 to 0.707], $P<0.001$).
Conclusion: The effect of prophylactic HC compared with placebo on LOS is summarized by a risk ratio varying within the interval [0.90–1.10] and this effect was never significant.
Trial registration: EudraCT number 2007–002041-20, ClinicalTrials.gov number NCT00623740.

What is Known:
- *Prophylactic hydrocortisone improves survival without bronchopulmonary dysplasia in extremely preterm neonates.*
- *It increases the risk of late-onset sepsis in the most immature infants.*
- *Causality remains unclear.*

What is New:
- *A lower risk of late-onset sepsis was observed with higher gestational age at birth, vaginal delivery, and, more surprisingly, with supplemental corticosteroids administration after day 10.*
- *Competing survival by Fine and Gray analysis suggests that death was reduced by prophylactic hydrocortisone, without a significant effect of treatment on the risk of late-onset sepsis.*

Keywords Hydrocortisone · Outcome · Prematurity · Chronic lung disease

Introduction

Neonatal sepsis remains a major cause of neonatal morbidity and mortality, particularly in very preterm neonates [1]. Late-onset sepsis (LOS), defined as the presence of positive blood or cerebrospinal fluid cultures on or after postnatal day

Communicated by Emma Elizabeth Williams

Extended author information available on the last page of the article

Published online: 14 June 2025

3, usually results from the transmission of pathogens from the postnatal environment, facilitated by intravascular catheters or other invasive procedures that disrupt mucosal membranes. The increased susceptibility to infection in preterm infants is primarily due to a deficient immune system, an immature epithelial barrier, and an increased need for invasive devices [1, 2]. Therefore, the extremely low gestational age neonate (ELGAN) population is at particularly high risk for LOS, with approximately 20% of neonates experiencing at least one culture-proven episode prior to discharge [3].

Quality improvement processes aim to reduce the burden of LOS in ELGANs [4], and LOS should therefore be considered in the risk–benefit balance of any new intervention in ELGANs. While some systematic reviews support benefits from early HC treatment [5, 6], particularly in infants with gestational age at birth above 25 weeks, concerns regarding safety remain [7]. Although some neonatal centers have incorporated the PREMILOC regimen into local practice [8], prophylactic hydrocortisone is not currently recommended as standard of care. As prophylactic administration of low-dose hydrocortisone (HC) in ELGANs improves survival without BPD, reduces the need for treatment of patent ductus arteriosus, and reduces pre-discharge mortality, it is increasingly being introduced as standard treatment in neonatal intensive care units [5]. However, an individual patient data (IPD) meta-analysis of the main trials using prophylactic HC to prevent BPD or neonatal death showed an increased risk of LOS (OR, 1.34 [95% CI, 1.02 to 1.75], $P = 0.04$) [5], particularly in the subgroup of infants born at 24–25 weeks' gestation (OR, 1.87 [95% CI, 1.09 to 3.21], $P = 0.02$) [9]. This adverse event is undoubtedly a barrier to further implementation of this prophylactic strategy. Surprisingly, this potential adverse event did not result in additional risk for neonatal mortality, mortality at discharge, or neurodevelopmental disorders at 2 or 5 years of age [10, 11], and its incidence varied widely between centers.

Real-world data come from single-center retrospective cohorts in the UK [12], Canada [13], the USA [14], and, more recently, Sweden [15]. After risk adjustment, the potential negative effect of prophylactic HC on LOS incidence in these cohorts was not confirmed. In the present study, we therefore re-analyzed the PREMILOC dataset to first predict LOS incidence from baseline conditions, examine the perinatal factors influencing LOS incidence, and assess the potential interaction arising from prophylactic HC exposure.

Methods

Study population and database

We performed a post hoc analysis of the PREMILOC trial, which was a double-masked, placebo-controlled, multicenter randomized trial that enrolled extremely preterm infants delivered before 28 weeks of gestation from 21 perinatal centers in France. Eligible infants were randomly assigned to receive either prophylactic low-dose prophylactic HC or placebo within 24 h after birth and for 10 days. The trial was approved by the national ethics committee in accordance with the Declaration of Helsinki (Comité de Protection des Personnes (CPP), Ile-de-France II, Necker), the French National Drug Safety Agency (ANSM, EudraCT number 2007–002041-20), and the French data protection authority (Commission Nationale de l'Informatique et des Libertés; CNIL). Written informed consent was obtained from parents of all eligible infants before randomization. The trial was registered at ClinicalTrials.gov (NCT00623740, first recorded version on February 25, 2008) before the first patient was enrolled. The study protocol and principal analyses have been previously reported [16]. The primary endpoint of the PREMILOC trial was a composite endpoint defined as survival without BPD at 36 weeks of post-menstrual age (PMA). The neurodevelopmental outcomes of recruited infants were assessed both at 2 and 5 years of age [11, 17].

Outcomes

The primary outcome of this study was the risk of late-onset sepsis (LOS) as defined by a positive blood culture or a diagnosis of pneumonia with significant clinical deterioration detected after day 3 (according to the international definition of LOS). Pneumonia was defined as chest radiography showing pulmonary opacities associated with the presence of microbes in the airway spaces and clinical deterioration occurring after day 3. LOS occurring after day 7 or day 10 (i.e., after the end of HC exposure) was considered as an endpoint for sensitivity analyses only. Maternal and neonatal characteristics included perinatal variables and respiratory support at baseline (RSB). RSB was classified according to the highest required respiratory support before 24 postnatal hours into 3 categories: RSB-mild: noninvasive ventilation with an $FiO_2 < 30\%$; RSB-moderate: mechanical ventilation with an $FiO_2 < 30\%$; and RSB-severe: mechanical ventilation with an $FiO_2 \geq 30\%$. Secondary neonatal outcomes specifically included the total number of days the infant was mechanically ventilated, age at weaning from respiratory support, and patent ductus arteriosus (PDA), which was treated both medically and surgically. Safety outcomes included severe neonatal morbidities occurring before 36 weeks of PMA, including spontaneous intestinal perforation, necrotizing enterocolitis, insulin treatment, treatment of retinopathy of prematurity (ROP), pulmonary hemorrhage, grade 3–4 intraventricular hemorrhage, and cystic periventricular leukomalacia.

Statistical analysis

A statistical plan was agreed by the authors and locked before the analysis. Our objective was to identify baseline and perinatal factors associated with LOS and to assess the effect of prophylactic hydrocortisone exposure on LOS risk, adjusted for these factors. By using sepsis occurrence as the dependent variable and all the available baseline characteristics as independent variables, we extracted the significant predictors through a stepwise strategy, sequentially adding the covariate while simultaneously minimizing the Akaike information criterion (AIC) with a significant χ^2 deviance change and significant Net Reclassification Index (NRI, sum of the changes in sensitivity and specificity). To provide an easier clinical interpretation, we conducted a Poisson regression producing risk ratios.

The used dataset benefited from careful monitoring, having minimized the missing data: All the baseline covariates were available except for vaginal delivery ($n = 2$), perinatal asphyxia ($n = 1$), and epidural analgesia ($n = 2$). These very rare missing data were imputed by the maximum likelihood technique. Aware of the methodological limits of the stepwise strategy, we prioritized covariates found in previously published research. For sensitivity purposes, we (i) compared results with backward and forward elimination, (ii) compared the results on the whole population with the placebo subgroup, (iii) tested the optimized model considering the center as a fixed or random factor, and (iv) completed these results by comparing time to LOS event using a Cox proportional hazard applied to competing risks.

All statistical tests were performed at a two-sided significance level of 0.05. The statistical analyses were carried out using R release 4.1.0 for Windows (R Core team, 2021).

Results

Population description

Of the 523 extremely preterm infants recruited in the PREMILOC trial, a total of 519 infants were included for this exploratory analysis, as the parents of one infant in the HC group and three infants in the placebo group withdrew their consent. Baseline and neonatal characteristics of the population are described in the Supplementary Table 1. A relative difference of more than 15% between the compared groups was found for general anesthesia and gestational hypertension only. No significant difference was found for the other variables.

Overall, the proportion of LOS reported in the total population after day 3, day 7, and day 10 was 27.2%, 23.1%, and 17.9%, respectively, with a slightly higher proportion in the HC treatment group (Table 1). The case fatality rate likely attributable to LOS was 23% and 26% in the placebo and HC groups, respectively.

Table 1 Incidence of late-onset sepsis after day 3 (primary outcome), day 7, or day 10 and case fatality rate according to the treatment group

Variable	Placebo ($n = 264$)	Hydrocortisone ($n = 255$)
Late-onset sepsis after day 3 (primary outcome)	64 (24%)	77 (30%)
Late-onset sepsis after day 7	54 (21%)	66 (26%)
Late-onset sepsis after day 10	45 (17%)	56 (22%)
Case fatality rate	15/64 (23%)	20/77 (26%)

Table 2 Predictive covariates of LOS (poisson regression)

	Effect	95% CI	*P*-value
Proportion of LOS[a]	0.245	0.204 to 0.294	< 0.001
Vaginal delivery	0.611	0.433 to 0.861	0.005
Gestational age (week)	0.772	0.671 to 0.888	< 0.001
Perinatal asphyxia	1.660	0.970 to 2.843	0.065
SCS[b]	0.484	0.310 to 0.756	< 0.001

[a]Proportion of LOS for patients with vaginal delivery, without perinatal asphyxia and mean gestational age of 26.4 weeks

[b]SCS means supplemental corticosteroid administered after day 10 and before LOS occurrence

LOS predictors at baseline and time occurrence of LOS

Using a stepwise strategy to study the occurrence of LOS occurring after day 3, our main analysis provided 3 main predictors at baseline (Table 2). A decreasing risk of LOS was observed with increasing gestational age (RR = 0.772 per week, [95% CI, 0.671 to 0.888], $P < 0.001$), vaginal delivery (RR = 0.611, 95% CI [0.433 to 0.861], $P = 0.005$), and perinatal asphyxia (RR = 1.660 [95% CI, 0.970 to 2.843], $P = 0.065$). Among covariates occurring during the first postnatal weeks, supplemental steroids given after 10-day treatment with prophylactic HC but before the LOS occurrence (SCS) were found to be associated with a decreased risk of LOS (RR = 0.484, [95% CI, 0.310 to 0.756], $P < 0.001$).

Effect of hydrocortisone treatment on the risk of LOS

The model predicting the occurrence of LOS found in the previous section was used to assess the HC effect in adjusting the risk of LOS for gestational age, vaginal delivery, perinatal asphyxia, and supplementary corticosteroid (SCS) (Table 3). The proportion of LOS was 24.5% (20.4 to 29.4),

Table 3 Risk of LOS diagnosed after day 3 in infants exposed to prophylactic hydrocortisone adjusted for baseline predictors of LOS (Poisson's stepwise regression)

	Effect	95% CI	*P*-value
Proportion of LOS[a]	0.245	0.204 to 0.294	0.001
Vaginal delivery	0.615	0.434 to 0.871	0.006
Gestational Age	0.775	0.671 to 0.895	0.001
Perinatal asphyxia	1.666	0.972 to 2.854	0.063
SCS[b]	0.486	0.311 to 0.758	0.001
HC treatment	1.041	0.738 to 1.471	0.817

[a]Proportion of LOS for patients with vaginal delivery, without perinatal asphyxia and mean gestational age of 26.4 weeks

[b]SCS means supplemental corticosteroid administered after day 10 and before LOS occurrence

with a standard deviation of 9.8% across the centers (variation coefficient = 0.33). The effects of the 3 main adjustment variables did not change, and adjusted for these covariates, we found a non-significant HC effect of RR = 1.041 (95% CI, 0.738 to 1.471, $P = 0.817$).

By using a supportive model excluding the use of supplemental corticosteroids after day 10 (SCS), we found similar results (Supplementary Table 2).

Lastly, we investigated LOS occurring between day 3 and the end of the prophylactic HC time exposure (day 10). By adjusting for the same model, we found a treatment effect of RR = 0.968 (95% CI, 0.796 to 1.173, $P = 0.741$).

As the treatment effect might be higher in some subgroups defined by the main predictors, we repeated our analysis assuming the interaction of treatment with gestational age, vaginal delivery, asphyxia, and SCS (Supplementary Table 3). None of these terms was significant, and the treatment main effect remained non-significant (RR = 1.058, [95% CI, 0.734 to 1.525], $P = 0.764$). As a lack of interaction when using a continuous term does not preclude meaningful differences between clinically relevant gestational age groups, we repeated the same analysis in testing the effect of gestational age transformed into a dichotomized variable (< 26 weeks, ≥ 26 weeks), which confirmed the non-significance of this interaction (Supplementary Table 4).

By adjusting for baseline characteristics according to the same model, we finally found a non-significant effect of hydrocortisone on the occurrence of death attributable to sepsis (RR = 0.772, [95% CI, 0.366 to 1.628], $P = 0.496$).

Time to LOS occurrence: Cox proportional hazard regression

A Cox proportional hazard regression for competing risks (death, LOS) has compared time to LOS occurrence between treatment groups. The effect of the 4 adjustment factors (gestational age, asphyxia, vaginal delivery, and SCS) was confirmed, and the treatment effect adjusted for these three covariates was characterized by a HR = 0.903 (95% CI, 0.637 to 1.279, $P = 0.566$) (Supplementary Table 5). The Cox proportional hazard regression was repeated in using center as a random factor, in which a HC treatment effect was estimated to HR = 1.03 (SE = 0.17, $P = 0.86$).

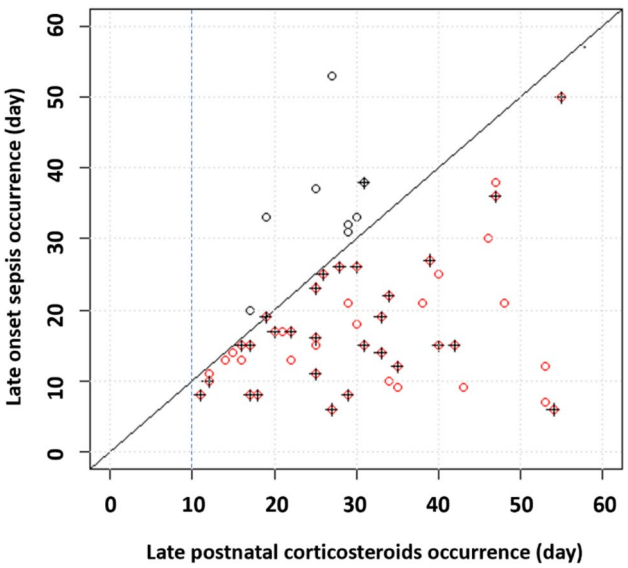

Fig. 1 Time interval between the onset of LOS and supplemental late postnatal corticosteroids exposure after day 10 (63 infants with both events). Black dots represent patients who received steroids before LOS time, and red dots represent patients who received steroids later than LOS occurrence (all these dots are on the right side of the straight line representing equal time of LOS occurrence and selective steroids start). Patients treated with HC have a " + " sign superimposed. This figure suggests that a majority of late (> day 10) postnatal steroid exposure was decided after the LOS has occurred and that the distribution of patients is similar across the two treatment groups

An unexpected negative association between exposure to postnatal steroids after day 10 (but before LOS occurrence, SCS) was observed with a HR = 0.904 (95% CI, 0.860 to 0.951, $P < 0.001$). This association between SCSs (excluding prophylactic HC, but including late parenteral steroids and inhaled steroids) was further investigated. Figure 1 illustrates the time lag between the onset of LOS and the timing of late steroid exposure, suggesting that the majority of late steroids were administered after LOS diagnosis, with a similar distribution of patients in the two treatment groups.

Competing survival by Fine and Gray analysis

We performed a competing survival analysis (Fine and Gray model) considering death and LOS as competing endpoints. After adjustment for baseline covariates associated with LOS risk (gestational age at delivery, vaginal delivery, and perinatal asphyxia), the effect of prophylactic HC on LOS was found not statistically significant (HR = 1.105 [95%

Table 4 Results of the Fine and Gray competing survival model, considering death and LOS as competing endpoints

	HR	95% CI	*P*-value
Gestational age at birth	0.787	0.686 to 0.904	< 0.001
Vaginal delivery	0.610	0.432 to 0.861	0.005
Perinatal asphyxia	1.939	1.071 to 3.513	0.029
Hydrocortisone effect			
LOS	1.105	0.787 to 1.552	0.560
Death	0.427	0.259 to 0.707	< 0.001

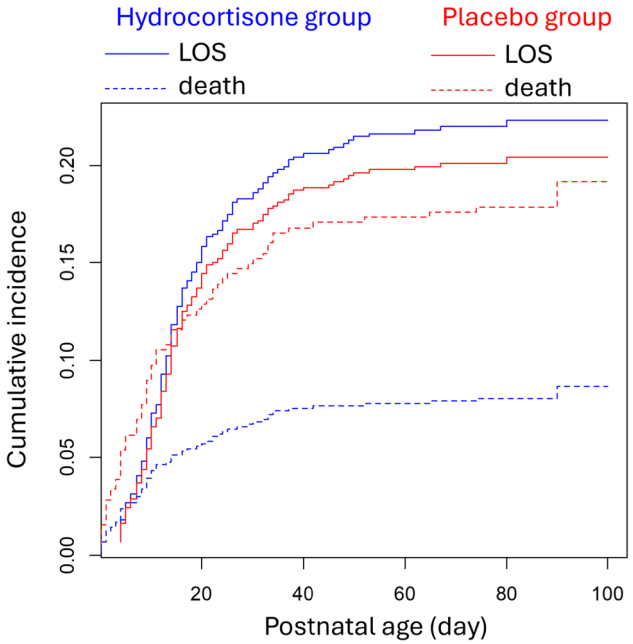

Fig. 2 Cumulative incidence diagram of LOS and death according to the treatment group, adjusted for baseline characteristics (gestational age at birth, vaginal delivery and perinatal asphyxia). Curves reflect adjusted cumulative incidences (and not raw event data) using the model investigated in the study

CI, 0.787 to 1.552], $P = 0.560$), while competing death was reduced by the treatment (HR = 0.427 [95% CI, 0.259 to 0.707], $P < 0.001$) (Table 4, Fig. 2).

Discussion

The present study refined the potential association between LOS and early low-dose HC exposure in extremely preterm infants. While the effect of HC on LOS occurrence, without adjusting for baseline conditions, was found with an odds ratio of 1.3 (95% CI, 0.94 to 1.81, $P = 0.12$), this re-analysis provides evidence of important baseline variables that influence LOS: gestational age, vaginal delivery, and perinatal asphyxia. By adjusting for these factors, we were able to confirm the non-significance of the HC effect on LOS occurrence and case fatality rate in the overall population of enrolled patients and the absence of subgroups for whom prophylactic HC may have a particular effect. For the main endpoint, defined as LOS at or later than 3 days of age, the incidence of LOS was found to be 4% higher in the HC treatment group than in the placebo group.

In the original PREMILOC report [9], the effect of prophylactic HC on the subgroup born at 24–25 weeks gestational age who were treated with prophylactic HC was shown to be significant (30 [40%] of 83 vs. 21 [23%] of 90 infants; sub-hazard ratio, 1.87 [95% CI, 1.09 to 3.21], $P = 0.02$). In adjusting for baseline covariates, we found a significant effect of gestational age, where low gestational ages are characterized by a higher rate of LOS; however, this observed difference is not confirmed by the interaction of treatment with age. By adjusting for the effects of baseline covariates, the odds ratio of the subgroup born at 24–25 weeks gestational age becomes OR = 1.26 (95% CI, 0.54 to 2.95, $P = 0.60$) and equivalent to a risk ratio RR = 1.13 (95% CI, 0.56 to 2.25, $P = 0.74$). Furthermore, the Cox proportional hazard regression for competing risks analysis investigated time to LOS occurrence and confirmed the previous results for LOS. Overall, based on three different statistical models (Poisson, Cox regression, competing risks), the effect of prophylactic HC compared to placebo on LOS is summarized by a risk ratio that varies within the interval [0.90–1.10], and this effect was never significant.

Owing to the immunosuppressive effect of hydrocortisone, a higher LOS incidence could be expected in the HC group; thus, the question is to estimate the non-inferiority margin of the risk ratio of HC. This margin was not a priori fixed; however, the 100*(1-α) one-sided upper limit of the confidence interval provides this estimate. Based on the main analysis, the HR was 1.04 (SE = 0.17), meaning the 95% or 90% one-sided upper limits are 31% and 25% more in the HC group, respectively. Further evidence provided by the lack of interaction of baseline characteristics and the HC treatment, including the suspected effect on the subgroup of patients with a gestational age at birth < 26 weeks as previously reported, indicates that these non-inferiority estimates can be considered homogeneous across the whole studied population.

Our results are not fully consistent with the individual meta-analysis of controlled trials, reporting a significant effect of HC on LOS incidence [5]. Nevertheless, the causal relationship between prophylactic HC and LOS was challenged by the fact that HC was not associated with an increased risk of neonatal mortality, BPD, or neurodevelopmental disorders, all recognized consequences of LOS. Furthermore, our findings are consistent with recent real-world data. In the first report from a retrospective cohort from a single center in the UK, the incidence of LOS after

the introduction of HC was found to be similar to that before the introduction of HC (34.0% vs. 30.6%, $P = 0.63$) [12]. In North America cohorts, no significant adverse effect, in particular, no increase in LOS incidence, was reported [13, 14], even in neonates born before 24 weeks. More recently, in a Swedish cohort [15], LOS incidence was not available, but in a larger population-based cohort, LOS was found to be more common in HC-exposed than unexposed newborns, but the difference was not significant after adjustment for covariates or in propensity score 1:1 matched analysis. Thus, while HC was associated with LOS in studies completed 10 to 25 years ago, recent advances in neonatal care for ELGANs may have reduced this risk.

The apparent negative association between postnatal steroid exposure after day 10 and the onset of LOS should be viewed with caution because postnatal steroids after day 10 were not a controlled intervention and were likely administered based on individual clinical need. In addition, LOS occurrence after day 10 may be strongly influenced by the number of confounding factors, including nutritional strategies, duration of central line, policy for central line insertion, maintenance and substitution, and policy for weaning from mechanical ventilation.

To our knowledge, this is the first analysis to examine the causality of prophylactic HC exposure for the occurrence of LOS in extremely preterm infants. Another strength of this study is the homogeneous and prospective recording of LOS diagnosis in each patient included in the PREMILOC study. Finally, the timing of the onset of each episode was accurately recorded without missing data.

However, it is important to recognize some limitations of our study, including the fact that in our analysis there is no difference between a single or multiple episodes of LOS in each patient. Another major limitation is the lack of recording of the microbial pathogen that was responsible for the LOS episode. However, the randomized controlled design of the trial should minimize the risk of imbalance in pathogen exposure between the two intervention groups (HC vs. placebo). This exploratory study used a relatively "old" dataset collected from 2008 to 2014, with a relatively high incidence of LOS. Our findings might therefore not be necessarily applicable to current NICU practices. Finally, due to the relatively small number of events, it was not possible to stratify the analysis by gestational age at birth, although the incidence of LOS was particularly high in infants born at 24 or 25 weeks of gestation.

In conclusion, considering baseline risk factors, the risk of LOS was not significantly different between prophylactic HC and placebo. Competing survival by Fine and Gray analysis suggests that death was reduced by prophylactic hydrocortisone, without a significant effect of treatment on the risk of late-onset sepsis. These results should be confirmed in larger real-world population-based cohort studies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00431-025-06248-9.

Acknowledgements Consortium author list (PREMILOC study group):
Valérie Biran, MD-PhD[6], Aline Rideau Batista-Novais, MD-PhD[6], Caroline Farnoux, MD[6], Sophie Soudée, MD[6], Laure Maury, MD[6]
Michèle Granier, MD[7], Florence Lebail, MD[7]
Duksha Ramful, MD[8], Sylvain Samperiz, MD[8]
Alain Beuchée, MD-PhD[9], Karine Guimard, MD[9]
Fatima El Moussawi, MD[10], Pascal Boileau, MD-PhD[10], Florence Castela, MD[10]
Claire Nicaise, MD[11], Renaud Vialet, MD[11]
Pierre Andrini, MD[12], Thierry Debillon, MD-PhD[12]
Véronique Zupan-Simunek, MD[13], Hasinirina Razafimahefa, MD[13]
Anne Coursol, MD[14], Saïd Merbouche, MD[14]
Pascal Bolot, MD[15], Jean-Marc Kana, MD[15]
Julie Guichoux, MD[16], Olivier Brissaud, MD-PhD[16]
Gérard Thiriez, MD-PhD[17], Olivier Schulze, MD[17]
Mickael Pomedio, MD[18], Patrice Morville, MD-PhD[18]
Thierry Blanc, MD[19], Stéphane Marret, MD-PhD[19]
Bernard Guillois, MD-PhD[20], Cénéric Alexandre, MD[20]
Stéphane Le Bouëdec, MD[21], Bertrand Leboucher, MD[21]
Umberto Simeoni, MD-PhD[22], Valérie Lacroze, MD[22]
Pierre Kuhn, MD-PhD[23], Stéphanie Litzler-Renaud, MD[23]
Elodie Zana-Taïeb, MD-PhD[24], Pierre-Henri Jarreau, MD-PhD[24]
Sylvain Renolleau, MD-PhD[25], Virginie Meau-Petit, MD[25]
Gilles Cambonie, MD-PhD[26]
Corinne Alberti, PhD[27], Aurélie Bourmaud, PhD[27]
Affiliations (all in France):
[6]Neonatal Intensive Care Unit, University Hospital Robert Debré, Assistance Publique – Hôpitaux de Paris, Paris
[7]Neonatal Intensive Care Unit, General Hospital, Corbeil-Essonnes
[8]Neonatal Intensive Care Unit, Regional Hospital Saint-Denis, La Réunion
[9]Neonatal Intensive Care Unit, University Hospital, Rennes
[10]Neonatal Intensive Care Unit, General Hospital, Poissy
[11]Neonatal Intensive Care Unit, University Hospital, Hôpital Nord, Assistance Publique – Hôpitaux de Marseille, Marseille
[12]Neonatal Intensive care unit, University Hospital, Grenoble
[13]Neonatal Intensive Care Unit, University Hospital Antoine Béclère, Assistance Publique – Hôpitaux de Paris, Clamart
[14]Neonatal Intensive Care Unit, General Hospital, Pontoise
[15]Neonatal Intensive Care Unit, General Hospital Saint-Denis
[16]Neonatal Intensive Care Unit, University Hospital, Bordeaux
[17]Neonatal Intensive Care Unit, University Hospital Besançon
[18]Neonatal Intensive Care Unit, University Hospital, Reims
[19]Neonatal Intensive Care Unit, University Hospital, Rouen
[20]Neonatal Intensive Care Unit, University Hospital, Caen
[21]Neonatal Intensive Care Unit, University Hospital, Angers
[22]Neonatal Intensive Care Unit, University Hospital La Conception, Assistance Publique – Hôpitaux de Marseille, Marseille
[23]Neonatal Intensive Care Unit, University Hospital Strasbourg
[24]Neonatal Intensive Care Unit, University Hospital Cochin-Broca-Hôtel Dieu, Assistance Publique – Hôpitaux de Paris, Paris
[25]Neonatal Intensive Care Unit, University Hospital Armand Trousseau, Assistance Publique – Hôpitaux de Paris, Paris
[26]Neonatal Intensive Care Unit, University Hospital Montpellier
[27]Unit of Clinical Epidemiology, Assistance Publique-Hôpitaux de Paris, CHU Robert Debré, University Paris Diderot, Sorbonne Paris-Cité, Inserm U1123 and CIC-EC 1426, Paris.

Author Contributions O.B. and P.L. wrote the main manuscript P.L. performed statistical analyses Study group reviewed the manuscript.

Funding This work was supported by a research grant from the French Ministry of Health and sponsored by the Département de la Recherche Clinique et du Développement, Assistance Publique-Hôpitaux de Paris (AOM 06 025 and AOM 11 129). French Ministry of Health has no role in the design and conduct of this study.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interest The authors thank Aguettant Pharma for a provided unconditional grant. This financial sponsor had no implication in study design, data collection, analysis, decision to publish or preparation of the manuscript.

References

1. Shane AL, Sanchez PJ, Stoll BJ (2017) Neonatal sepsis. Lancet 390:1770–1780
2. El Manouni El Hassani S et al (2019) Risk factors for late-onset sepsis in preterm infants: a multicenter case-control study. Neonatology 116**:**42–51
3. Bell EF et al (2022) Mortality, in-hospital morbidity, care practices, and 2-year outcomes for extremely preterm infants in the US, 2013–2018. JAMA 327:248–263
4. Kaplan HC, Lannon C, Walsh MC, Donovan EF, Ohio Perinatal Quality C (2011) Ohio Statewide quality-improvement collaborative to reduce late-onset sepsis in preterm infants. Pediatrics 127**:**427–435
5. Shaffer ML et al (2019) Effect of prophylaxis for early adrenal insufficiency using low-dose hydrocortisone in very preterm infants: an individual patient data meta-analysis. J Pediatr 207**:**136–142 e135
6. Morris IP, Goel N, Chakraborty M (2019) Efficacy and safety of systemic hydrocortisone for the prevention of bronchopulmonary dysplasia in preterm infants: a systematic review and meta-analysis. Eur J Pediatr 178:1171–1184
7. van de Loo M et al (2024) Corticosteroids for the prevention and treatment of bronchopulmonary dysplasia: an overview of systematic reviews. Cochrane Database Syst Rev 4**:**CD013271
8. Iacobelli S et al (2023) Postnatal corticosteroid exposure in very preterm infants: a French cohort study. Front Pharmacol 14:1170842
9. Baud O et al (2016) Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial. Lancet 387:1827–1836
10. Trousson C, Toumazi A, Bourmaud A, Biran V, Baud O (2022) Neurocognitive outcomes at age 5 years after prophylactic hydrocortisone in infants born extremely preterm. Dev Med Child Neurol 65(7):926–932
11. Baud O et al (2017) Association between early low-dose hydrocortisone therapy in extremely preterm neonates and neurodevelopmental outcomes at 2 years of age. JAMA 317:1329–1337
12. Briscoe A, Piyasena C, Meau-Petit V (2022) Tolerance of hydrocortisone prophylaxis administration in extreme preterm neonates: experience of a single UK level III neonatal unit. Early Hum Dev 171:105630
13. de Souza M et al (2024) Effects of prophylactic hydrocortisone in a tertiary Canadian NICU. Arch Dis Child Fetal Neonatal Ed 109:342
14. Shah SD et al (2024) Prophylactic early low-dose hydrocortisone and survival without bronchopulmonary dysplasia among extremely preterm infants born at 22–27 weeks' gestation. J Perinatol 44(7):947–952
15. Petrishka-Lozenska M et al (2025) Association between early postnatal hydrocortisone and retinopathy of prematurity in extremely preterm infants. Neonatology 122(3):329–338
16. Baud O, Alberti C, Mohamed D, Watterberg K (2016) Low-dose hydrocortisone in extremely preterm infants - authors' reply. Lancet 388:1158–1159
17. Baud O et al (2018) Two-year neurodevelopmental outcomes of extremely preterm infants treated with early hydrocortisone: treatment effect according to gestational age at birth. Arch Dis Child Fetal Neonatal Ed 104(1):F30–F35

Authors and Affiliations

Olivier Baud[1,2,3] · Philippe Lehert[4,5] · on behalf of the PREMILOC study group

✉ Olivier Baud
olivier.baud@aphp.fr

[1] Obstetric, Perinatal, Paediatric and Life Course Epidemiology Team (OPPaLE), Center for Research in Epidemiology and StatisticS (CRESS), Alimentation Et L'Environnement (INRAe), Institut National Pour La Santé Et La Recherche Médicale (INSERM, French Institute for Health and Medical ResearchInstitut National de Recherche Pour L'Agriculture, l'Paris Cité University, Paris, France

[2] Department of Neonatal Medicine, FHU Prem'Impact, Cochin-Port Royal Hospital, Assistance Publique–Hôpitaux de, Paris Cité University, 123 Bd de Port-Royal, 75014 Paris, France

[3] Paris Cité University, Neuro-Diderot, INSERM, Paris, France

[4] Faculty of Medicine, University of Melbourne, Melbourne, Australia

[5] Faculty of Economics School of Management, University of Louvain, Louvain, Belgium