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RESEARCH

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# Cortisol total/CRP ratio for the prediction of hospital-acquired pneumonia and initiation of corticosteroid therapy in traumatic brain-injured patients

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## Abstract

**Background:** To propose a combination of blood biomarkers for the prediction of hospital-acquired pneumonia (HAP) and for the selection of traumatic brain-injured (TBI) patients eligible for corticosteroid therapy for the prevention of HAP.

**Methods:** This was a sub-study of the CORTI-TC trial, a multicenter, randomized, double-blind, controlled trial evaluating the risk of HAP at day 28 in 336 TBI patients treated or not with corticosteroid therapy. Patients were between 15 and 65 years with severe traumatic brain injury (Glasgow coma scale score  $\leq 8$  and trauma-associated lesion on brain CT scan) and were enrolled within 24 h of trauma. The blood levels of CRP and cortisol<sub>total&free</sub>, as a surrogate marker of the pro/anti-inflammatory response balance, were measured in samples collected before the treatment initiation. Endpoint was HAP on day 28.

**Results:** Of the 179 patients with available samples, 89 (49.7%) developed an HAP. Cortisol<sub>total&free</sub> and CRP blood levels upon ICU admission were not significantly different between patients with or without HAP. The cortisol<sub>total</sub>/CRP ratio upon admission was 2.30 [1.25–3.91] in patients without HAP and 3.36 [1.74–5.09] in patients with HAP ( $p = 0.021$ ). In multivariate analysis, a cortisol<sub>total</sub>/CRP ratio  $> 3$ , selected upon the best Youden index on the ROC curve, was independently associated with HAP (OR 2.50, CI95% [1.34–4.64]  $p = 0.004$ ). The HR for HAP with corticosteroid treatment was 0.59 (CI95% [0.34–1.00],  $p = 0.005$ ) in patients with a cortisol<sub>total</sub>/CRP ratio  $> 3$ , and 0.89 (CI95% [0.49–1.64],  $p = 0.85$ ) in patients with a ratio  $< 3$ .

**Conclusion:** A cortisol<sub>total</sub>/CRP ratio  $> 3$  upon admission may predict the development of HAP in severe TBI. Among these patients, corticosteroids reduce the occurrence HAP. We suggest that this ratio may select the patients who may benefit from corticosteroid therapy for the prevention of HAP.

**Keywords:** Traumatic, Brain, Injury, Pneumonia, Cortisol, CRP, Corticosteroid, Biomarkers

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## Introduction

Traumatic brain injury (TBI) is the leading cause of mortality and disability among young patients throughout the world. It is a major health and socioeconomic problem [1, 2]. Hospital-acquired pneumonia (HAP), whose incidence ranges from 40 to 60% for severe traumatic brain-injured patients [3], is associated with poor neurologic outcome and death [4]. TBI induces a disturbance of the normally balanced interplay between pro-inflammatory and anti-inflammatory mechanisms leading to a greater susceptibility to infections including HAP [5].

During the early post-traumatic period, the release of danger-associated molecular pattern by injured cells results in systemic inflammatory response syndrome (SIRS) which is characterized by increased levels of CRP and cytokines [6–8]. Elevated blood concentrations of CRP upon ICU admission are correlated with an increased risk of organ failure and death [9] and persistent systemic inflammatory response syndrome is predictive of hospital-acquired infection in trauma patients [10]. To avoid the dramatic consequences of an overwhelming SIRS such as organ failure, an anti-inflammatory response (called "compensatory anti-inflammatory response syndrome" : CARS) is rapidly triggered by the host, including cortisol secretion by adrenal glands after afferent impulses from the site of injury [11].

It is true that the administration of corticosteroids in a condition that is at risk of secondary infection may seem inappropriate. However, we have shown that low dose of hydrocortisone prevents the occurrence of hospital-acquired pneumonia in multiple trauma patients [12]. The anti-inflammatory properties of corticosteroids reduce lung inflammation secondary to trauma and enhance the functions of immune cells like dendritic cells and thus could limit secondary bacterial pneumonia [13]. The administration of corticosteroids in a context of relative immunosuppression shown after any acute condition is counter intuitive but low-dose corticosteroids may enhance immunity. Indeed, low-dose hydrocortisone improves the phagocytic abilities of neutrophils, decreases the blood concentration of anti-inflammatory cytokines such as interleukin-10, and increases the blood concentrations of interferon- $\gamma$  and interleukin-12, cytokines involved in the host defense against infections [14, 15].

We aimed to assess the predictive values of the cortisol/CRP ratio (surrogate marker of the CARS/SIRS balance) for the development of HAP in TBI patients. We also evaluated if this ratio may help to select patients who would benefit from corticosteroid therapy to prevent HAP.

## Materials and methods

### Study design

This study is a sub-study of the Corti-TC trial [3] (NCT 01093261) a multicentre, randomized, double-blind, placebo-

controlled trial of hydrocortisone and fludrocortisone in severe traumatic brain injury. Patients admitted in 19 French ICUs were enrolled in the Corti-TC trial from Sept. 1, 2010, to Nov 29, 2012. Prior to enrollment, written informed consent was obtained from a next-of-kin. Retrospective consent was obtained from patients when it was possible.

### Patients

In the Corti-TC trial, inclusion criteria were age between 15 and 65 years, severe traumatic brain injury (Glasgow coma scale score  $\leq 8$  and trauma-associated lesion on brain CT scan), and enrolment within 24 h of trauma [16, 17]. Exclusion criteria were as follows: treatment with corticosteroids in the previous 6 months, immunosuppression, pregnancy, tetraplegia, or antibiotic treatment at the time of inclusion. In this sub-study of the Corti-TC trial ( $n = 330$  patients), we included the 179 patients with available blood samples.

### Corticosteroid therapy

For the purpose of the Corti-TC trial, patients received either hydrocortisone (200 mg per day tapered) and fludrocortisone (50  $\mu\text{g}$  tablet once per day) or double placebo for 10 days. Before receiving study drug, adrenal function was assessed with a short corticotropin test. Treatment was stopped if patients had no adrenal insufficiency which was defined as basal blood cortisol concentration of less than 150  $\mu\text{g/L}$  (413 nmol/L) or a maximum increase of less than 90  $\mu\text{g/L}$  (248 nmol/L) in the 60 min after a short corticotropin test.

### Endpoints

In the Corti-TC study, the primary outcome was hospital-acquired pneumonia on day 28 of follow-up in patients with or without corticosteroid therapy. In this sub-study, the primary outcome was also the rate of hospital-acquired pneumonia in severe traumatic brain-injured patients.

### Blood samples

Blood samples were collected in the first 24 h after trauma, before any administration of the Corti-TC treatment. Sera were frozen  $-80^\circ\text{C}$  upon dosage. Concentration of CRP and plasma cortisol concentrations (free and total) were investigated in sera collected in patients from the Corti-TC study with available samples.

### Measurement of CRP, cortisol, and cortisolemia

All biochemical measurements of CRP, Transcortin, and total and free cortisol were performed at the laboratory of Clinical Biochemistry, Nantes University Hospital. The laboratory is licensed according to the ISO 15189 accreditation standard for clinical laboratories.

Serum CRP and total cortisol were determined in single measurement with an electrochemiluminescence immunoassay (C-Reactive Protein Gen.3 and Elecsys Cortisol II respectively) on the Cobas e602-module of the automated cobas®8000 system (Roche Diagnostics, Mannheim, Germany). The lower limits of detection (LoD) of the CRP and cortisol assays were 0.3 mg/L and 0.54 µg/L respectively. Each CRP and cortisol runs were validated by measuring two levels of quality control material prior to starting the experiment.

Samples for serum-free cortisol determination were prepared by equilibrating 500 µL of serum at 37 °C for 15 min in Centrifree 30,000 molecular weight cut-off Centrifugal filters (Merck Millipore, Tullagreen, Ireland) before centrifugation at 1500g for 30 min at 37 °C. Free cortisol was determined in the ultrafiltrate as previously describe for total cortisol.

Serum Transcortin concentrations were measured in duplicate using Human Corticosteroid Binding Globulin ELISA (BioVendor, Brno, Czech Republic) according to the manufacturer's instructions. Each series of assays (1 ELISA plate) was validated by two internal controls. The lower limit of detection (LoD) was 0.01 µg/mL.

#### Care of patients with severe TBI

All care provided to patients with severe TBI followed the international guidelines in effect at the time of randomization, including respiratory management, temperature management, stress ulcer prophylaxis, nutrition, fluid therapy, glucose management, intracranial pressure monitoring, and management [18] as done in our previous studies on the subject [19, 20].

#### Hospital-acquired pneumonia (HAP) definition

Pneumonia was suspected as diagnosis when at least two of the following signs: body temperature > 38 °C; leukocytosis > 12,000/mL or leukopenia < 4000/mL; purulent pulmonary secretions; were associated with the appearance of a new infiltrate or changes in an existing infiltrate on the chest X-ray. Diagnosis was confirmed by tests on a respiratory tract sample using a quantitative culture with a predefined positive threshold of 10<sup>4</sup> colony-forming units per milliliter (CFU/mL) for a bronchoalveolar lavage or nonbronchoscopic sample or 10<sup>3</sup>CFU/mL for a protected specimen brush. Respiratory samples were always obtained before starting any new antibiotic treatment. HAP was defined as pneumonia that occurred 48 h after admission [21]. All HAP recorded in the study where early-onset pneumonia (< 7 days).

#### Data collection

Overall, patient characteristics, including demographics, injury severity score and abbreviated injury score, fluid infusions, vasopressors, antibiotic prophylaxis, CRP rates,

plasma cortisol concentrations (free and total), surgery, infections, organ failures, length of ventilatory support, ICU hospitalization, and 28th day mortality, were recorded.

#### Statistical analysis

Continuous data were described as median [1st–3rd quartiles] and values were compared using the Wilcoxon-Mann-Whitney test. Categorical data were described as *N* (%) and values were compared using the chi-square test or the Fisher exact test.

The cut-off for distinguishing low versus high (cortisol<sub>total</sub>/CRP) ratio was based on logistic regression between HAP and (cortisol<sub>total</sub>/CRP) ratio. The value corresponding to the largest Youden index was selected as the cut-off. Variables that were associated with HAP at the 0.15 level in univariate analysis were included in a multiple logistic regression. Then, variables that were non-significant at the 0.05 level (Wald test) were removed one by one. Multiple logistic regressions were performed in the global sample, in the placebo group and in the corticosteroid group.

## Results

### Patients

Of the 179 analyzed patients, 89 (49.7%) developed a HAP and 90 (50.3%) did not. Table 1 shows the baseline characteristics. All cases of recorded HAP were ventilator-associated pneumonia. There were no differences in the demographics of patients (including severity scores) who developed HAP compared with those who did not develop HAP except for the body temperature > 39 °C (20% vs 5.6% respectively *p* = 0.004). Patients were equally drawn from the intervention and control arms and they do not differ in other important ways from the original study population in terms of age, sex, severity, and comorbidities (data not shown).

### Cortisol function and CRP levels

Despite a trend for higher total and free blood levels of cortisol upon ICU admission, there was no significant difference between patients with or without HAP (*p* = 0.06 and *p* = 0.26 respectively, Table 1). The delta of cortisolemia at 60 min was not different between the two groups (98 [30–161] and 84 [33–147]; *p* = 0.89). The blood level of CRP was 61 [35–98] mg/L in patients without HAP as compared to 53 [33–82] mg/L in patients with HAP (*p* = 0.20). These results demonstrate that taken separately, blood levels of cortisol and of CRP cannot predict HAP. We thus aimed to investigate the prognostic value of a ratio combining markers of CIRCI and inflammatory response.

### Combination of cortisol<sub>free</sub>, cortisol<sub>total</sub>, and CRP to predict the development of HAP

The correlation between cortisol<sub>free</sub> and cortisol<sub>total</sub> was consistent in spite of low or high CRP blood levels (Fig. 1a)

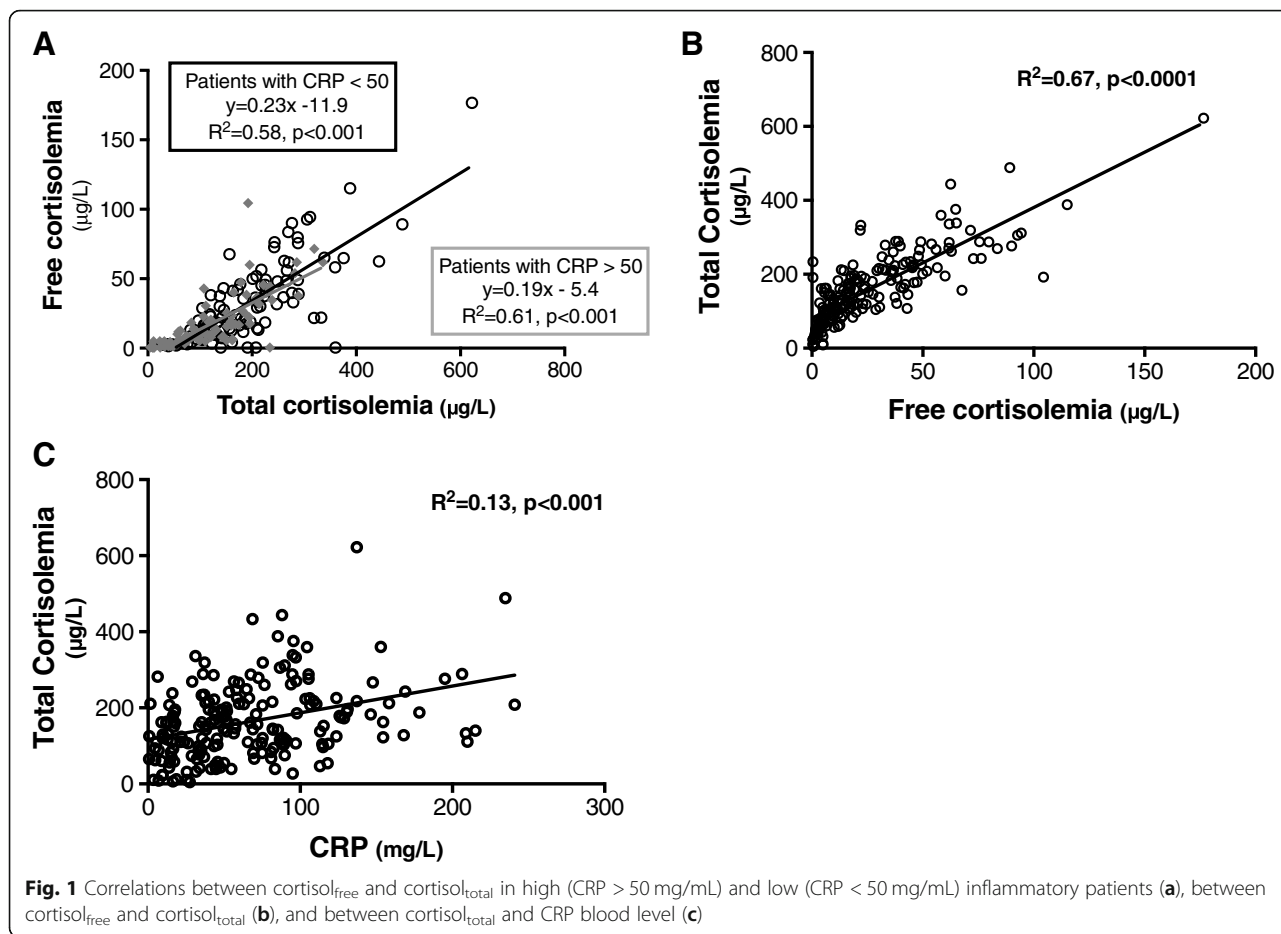
**Table 1** Baseline characteristics

	Hospital-acquired pneumonia, no <i>N</i> = 90	Hospital-acquired pneumonia, yes <i>N</i> = 89	<i>P</i> value
Age, years	34 [23–48]	31 [23–48]	0.83
Men	72 (80)	74 (83.2)	0.58
Medical history, No. (%)			
Renal insufficiency	0 (0.00)	1 (1.12)	0.49
Cardiac insufficiency	1 (1.11)	1 (1.12)	1.00
Chronic pulmonary disease	1 (1.11)	2 (2.25)	0.62
Pathological admission status, median			
SAPS II	42 [34–50]	42 [37–50]	0.29
Injury Severity Score	18 [9–29]	24 [13–30]	0.10
Glasgow coma scale	6 [4–7]	6 [4–7]	0.85
Associated Thoracic trauma (AIS $\geq$ 3)	24 (26.67)	29 (32.58)	0.38
Events prior to admission, No. (%)			
Hemorrhagic shock	5 (5.56)	5 (5.62)	0.98
Hypotension (systolic arterial pressure < 120 mmHg)	24 (26.67)	24 (26.97)	0.96
Neurosurgery	29 (32.22)	22 (24.72)	0.26
Etomidate use	62 (68.89)	64 (71.91)	0.65
Blood transfusion			
Red cell units	29 (32.22)	21 (23.60)	0.19
Frozen plasma units	29 (32.22)	23 (25.84)	0.34
Systemic inflammatory response syndrome upon admission			
Cardiac rate > 120/min	16 (17.78)	13 (14.61)	0.56
PaCO <sub>2</sub> , mmHg	38 [33–41]	37 [33–43]	0.86
Body temperature > 39.0 °C	18 (20)	5 (5.6)	0.004
Leucocytes count (g/L)	11.9 [7.8–15.9]	13.4 [10.3–16.5]	0.06
Neutrophil count (g/L)	8.4 [6–15.5]	10.6 [8–14.5]	0.19
Lymphocyt count (g/L)	1.3 [0.8–2.2]	1.2 [0.8–1.8]	0.58
C-reactive protein (mg/mL)	61 [35–98]	53 [33–82]	0.20
Short corticotropin test results			
Baseline blood cortisol <sub>total</sub> concentration, $\mu$ g/L	143 [92–201]	168 [111–225]	0.06
Baseline blood cortisol <sub>free</sub> concentration, $\mu$ g/L	16.6 [6.6–39]	21.9 [9.6–41]	0.26
Transcortin blood level, $\mu$ g/mL	21.9 [14.9–47.3]	27 [16.5–51.4]	0.12
Delta total cortisolemia after 60 min after corticotropin, $\mu$ g/L	98 [30–161]	84 [33–147]	0.89
Ratio inflammatory response/cortisol response			
Cortisol <sub>free</sub> /CRP	0.25 [0.08–0.71]	0.394 [0.17–0.80]	0.10
Cortisol <sub>total</sub> /CRP	2.30 [1.25–3.91]	3.36 [1.74–5.09]	0.021
Total Delta 60 min cortisol/CRP	1.45 [0.51–2.73]	1.55 [0.59–3.30]	0.65

CRP C reactive protein. Results expressed as median (1st–3rd quartile) or *N* (%), SAPS II Simplified Acute Physiological Score, AIS Abbreviated Injury Scale

when cortisol<sub>free</sub> and cortisol<sub>total</sub> were strongly correlated (Fig. 1b) suggesting that these two values can be used in patients with or without severe inflammatory response. Cortisol<sub>total</sub> was correlated with blood level of transcortine (Additional file 1: Figure S1). Transcortine is the major transport protein for glucocorticoids and approximately 85% of the cortisol in circulation is bound to transcortin.

We also decided to use cortisol<sub>total</sub> for subsequent analysis of the risk of HAP also because it is more available easily in clinical practice. The blood level of cortisol<sub>total</sub> increased with CRP (Fig. 1c), and the blood level of CRP alone was not able to discriminate patients at risk to develop HAP (Additional file 1: Figure S2). However, the cortisol<sub>total</sub>/CRP ratio was 2.30 [1.25–3.91] in patients



without HAP and 3.36 [1.74–5.09] in patients with HAP ( $p = 0.021$ ) (Table 1 and see Additional file 1: Figure S3). These results suggest that the combination of cortisol<sub>total</sub> and CRP could help to predict HAP.

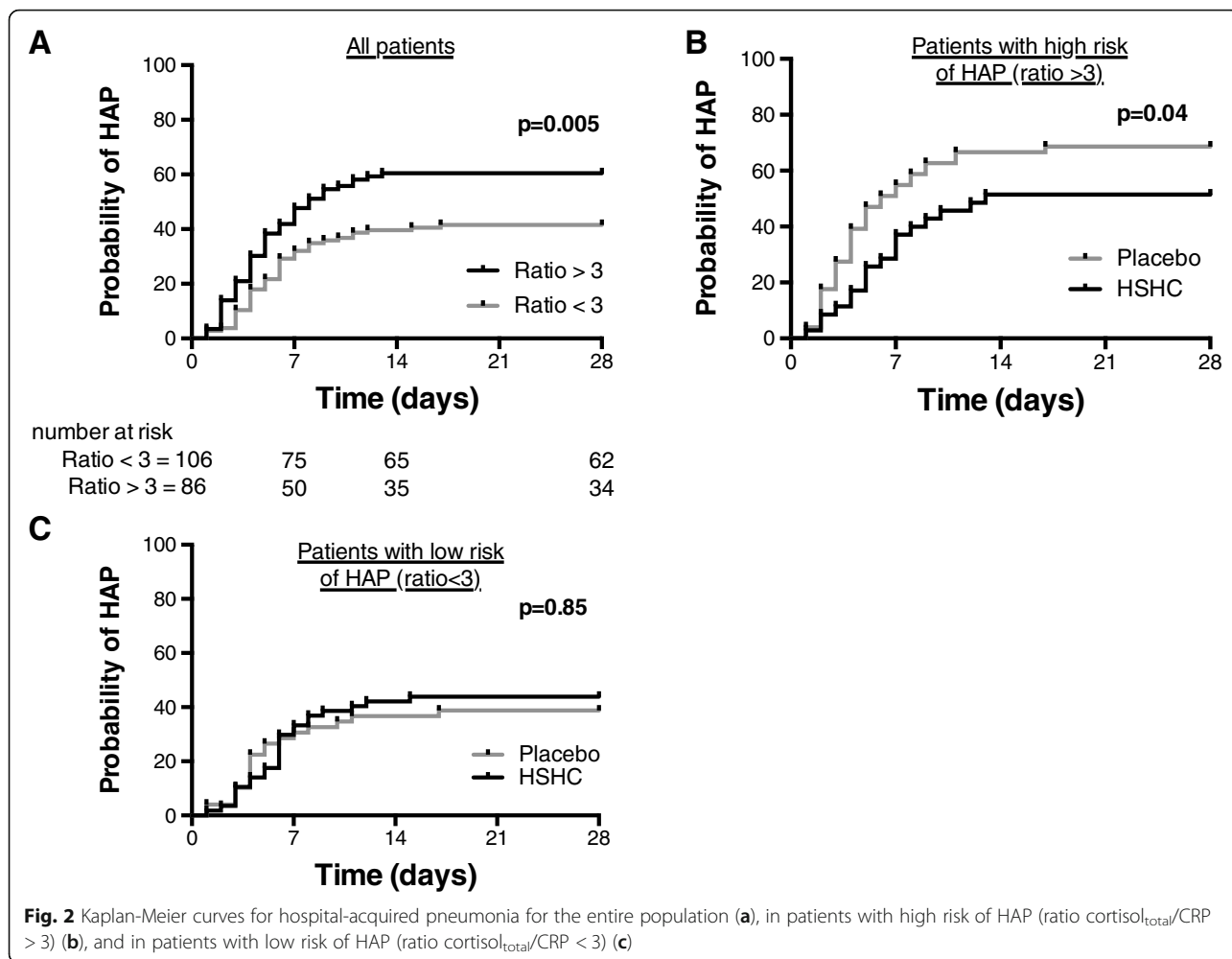
**The cortisol<sub>total</sub>/CRP ratio is an independent risk factor for HAP**

In an attempt to simplify the use of the results in clinical practice, the cortisol<sub>total</sub>/CRP ratio was dichotomized in two categories (above or below a threshold). The cut-offs of cortisol<sub>total</sub>/CRP ratio > 3 was selected because it provides the best sensitivity/specificity balance (ROC curves; Additional file 1: Figure S4) and the best calibration of the multivariate analysis (Hosmer–Lemeshow test  $p$  value > 0.05). The positive likelihood ratio was 1.66 for a cortisol<sub>total</sub>/CRP ratio > 3. In the entire population, patients with a ratio total cortisol/CRP > 3 ( $n = 88$ ) developed more HAP than those with a ratio < 3 [50 (62.50%) vs 39 (39.39%) respectively  $p = 0.002$ ] (Table 3). The Kaplan-Meier estimator for HAP at day 28 was 41.5% in the low ratio group (< 3) and 60.5% in the high ratio group (> 3), HR = 0.55 [(95% CI 0.36 to 0.84)]  $p = 0.005$  (Fig. 2a). In multivariate analysis, a ratio cortisol<sub>total</sub>/CRP > 3 was independently associated with HAP

(OR 2.50, 95% CI (1.34–4.64)  $p = 0.004$ ) (Table 2). In the entire population, there was no difference in terms of mean duration of mechanical ventilation, ICU length of stay, or in-ICU mortality between the corticosteroid-treated patient group and the placebo group (Table 3). However, this ratio also discriminates the number of antibiotic-free days with a higher “antibiotics free days at day 28” in the “low ratio” group: (21d [16–26] vs 18.5d [11–21]  $p = 0.007$ ).

**The cortisol<sub>total</sub>/CRP ratio may predict the patients who will benefit from corticosteroid therapy**

Finally, we tested the hypothesis that the ratio cortisol<sub>total</sub>/CRP has the potential to select patients who will benefit from corticosteroid therapy, and those whose risk of HAP will not be decreased by the treatment. We thus compared the relative risk of HAP in the low and the high ratio groups, according to the treatment received (placebo or corticosteroid therapy). In high-risk patients (ratio > 3), the probability of HAP at day 28 was higher in the placebo group vs corticoid group (68.6% vs 51.4% respectively,  $p = 0.04$ ) with an hazard ratio of 0.59 (CI95% [0.34–1.00],  $p = 0.005$ ) (Fig. 2b). Patients with a ratio > 3 were comparable on key demographic



characteristics in the corticosteroid and placebo groups (Additional file 1: Figure S5). In patients with low cortisol<sub>total</sub>/CRP (< 3), there was no difference between placebo and treatment groups for the development of HAP (HR = 0.89 (CI95% [0.49–1.64], *p* = 0.85)) (Fig. 2c). We conclude that the protective effect of corticosteroid in TBI patients for the risk of HAP was found mainly in the subgroup of patients with a cortisol<sub>total</sub>/CRP ratio > 3.

**Discussion**

In this sub-study of Corti-TC trial [3], we aimed to establish a correlation between the ratio “inflammatory response”/CARS and the occurrence of HAP in head trauma patients. After a TBI, pro-inflammatory cytokine secretion is a physiologic process which aims to induce damaged

tissues healing and anti-bacterial activity by activating both innate and adaptive immunity. In order to balance an excessive pro-inflammatory response, the CNS induces an important anti-inflammatory response leading to increased susceptibility to infections [5]. This anti-inflammatory response is mediated by the sympathetic nervous system [22], parasympathetic nervous system [23], and the hypothalamic-pituitary system via glucocorticoid secretion. In critically ill patients, reduced cortisol breakdown contributes to abnormal blood cortisol levels [24]. This phenomenon, called Critical Illness-Related Corticosteroid Insufficiency (CIRCI), corresponds to the impairment of the hypothalamic-pituitary axis (HPA) during critical illness resulting from inadequate anti-inflammatory response for the severity of a given patient [25].

**Table 2** Multivariate analysis of the factors associated with of hospital-acquired pneumonia (N = 179)

	Odds ratio (95% confidence interval)	P value
Body temperature > 39.0 °C	0.25 [0.09–0.72]	0.010
Cortisol <sub>total</sub> /CRP > 3	2.50 [1.34–4.64]	0.004

**Table 3** Comparison of outcomes of patients with high or low (cortisol<sub>total</sub>/CRP) ratio

	Entire population			Placebo			Hydrocortisone treatment		
	Low (cortisol <sub>total</sub> /CRP) ratio	High (cortisol <sub>total</sub> /CRP) ratio	<i>P</i> values	Low (cortisol <sub>total</sub> /CRP) ratio	High (cortisol <sub>total</sub> /CRP) ratio	<i>P</i> values	Low (cortisol <sub>total</sub> /CRP) ratio	High (cortisol <sub>total</sub> /CRP) ratio	<i>P</i> values
Hospital-acquired pneumonia	39 (39.39)	50 (62.50)	0.002	18 (37.50)	32 (65.31)	0.006	21 (41.18)	18 (58.06)	0.138
PaO <sub>2</sub> /FiO <sub>2</sub> ratio	146.5 [98–217]	175.5 [133–232]	0.147	164.5 [130–217]	175.5 [133.5–246]	0.581	122 [78–232.5]	174 [132–227]	0.156
Septic shock	5 (12.82)	2 (4.00)	0.233	2 (11.11)	0	0.125	3 (14.29)	2 (11.11)	1.00
Other infections									
Meningitis	2 (2.02)	1 (1.25)	1.000	1 (2.08)	0	0.495	1 (1.96)	1 (3.23)	1.000
Urinary tract infection	9 (9.09)	11 (13.75)	0.325	3 (6.25)	10 (20.41)	0.041	6 (11.76)	1 (3.23)	0.245
Bacteremia	8 (8.08)	5 (6.25)	0.639	4 (8.33)	3 (6.12)	0.715	4 (7.84)	2 (6.45)	1.000
Organ failures									
Duration of vasopressor support, days	4 [3–6]	4 [2–6]	0.925	4 [3–6]	5 [2–6]	0.837	4 [3–5.5]	4 [2–6]	0.787
Acute respiratory distress syndrome	18 (18.18)	16 (20.00)	0.758	5 (10.42)	9 (18.37)	0.265	13 (25.49)	7 (22.58)	0.766
Acute kidney injury	0	1 (1.25)	0.447	0	0	–	0	1 (3.23)	0.378
SOFA day 1	9 [8–10]	9 [7–10]	0.592	9 [8–9.5]	9 [7–10]	0.877	9 [7–10]	9 [7–10]	0.511
SOFA day 3	8 [6–9]	8 [5.5–9]	0.706	8 [6–9]	7 [5–9]	0.383	8 [6–9]	8 [6–10]	0.658
SOFA day 7	4 [2–7]	5 [4–6]	0.398	4 [2.5–6.5]	4 [4–6]	0.352	5 [1–8]	5 [4–6]	0.810
Outcomes									
Antibiotic-free days at day 28	21 [16–26]	18.5 [11–21]	0.007	21.5 [15.5–26.5]	19 [12–21]	0.225	21 [17–25]	18 [11–22]	0.52
Mean duration of mechanical ventilation (days)	11 [7–20]	13 [8–19.5]	0.725	11.5 [7.5–18]	12 [8–22]	0.525	11 [7–25]	13 [9–19]	0.86
Mean duration of intensive care (days)	15 [10–24]	17 [11–28]	0.288	16 [11–22]	17 [12–28]	0.167	15 [9–29]	17 [10–28]	0.867
Death in ICU									
In-ICU death	8 (8.01)	9 (11.25)	0.472	2 (4.17)	5 (10.20)	0.436	6 (11.76)	4 (12.90)	1.000

In order to correct the post-traumatic immunosuppression, many therapies have been tested in recent years. They aimed either to limit the initial SIRS (and thus the CARS) in particular by the use of low-dose glucocorticoids [3, 12] or to restore the secretion of pro-inflammatory cytokines by the use of IFN- $\gamma$ , GM-CSF [26], or interleukin 12 [27]. In a multicenter, randomized, double-blind, placebo-controlled trial, Torres et al. showed that among patients with severe community-acquired pneumonia and high initial inflammatory response (CRP > 150 mg/L), methylprednisolone (0.5 mg/kg/12 h) compared with placebo decreased treatment failure [28]. In major trauma patients, CIRCI occurs frequently and is associated with uncontrolled inflammatory response, longer vasopressors infusion and poor outcomes [29]. In a large randomized trial in multiple trauma patients, we found that hydrocortisone therapy prevented the development of hospital-

acquired pneumonia by day 28 in patients with CIRCI (defined by a change in baseline cortisol at 60 min of < 9  $\mu$ g/dl after ACTH (250  $\mu$ g) administration) [12]. However, in head trauma patients, we found no interaction between response to corticosteroid therapy and CIRCI status (using the same definition as previously described) [3]. The actualized recommendations for the diagnosis of CIRCI provide that ACTH stimulation test was not superior to random cortisol for the routine diagnosis of CIRCI [30]. Moreover, measuring plasma-free cortisol level over plasma total cortisol level was not recommended in patients with suspected CIRCI [30]. Here, the total and free cortisol blood levels were strongly correlated independently of the inflammatory status of the patient, explaining why we choose to focus on total cortisolemia.

In our study, the correlation between total cortisol and CRP levels could be explained by the early secretion of



interleukin-6 (IL-6) following trauma. Indeed, IL-6 is a pro-inflammatory cytokine known to have HPA-activating activity independent of ACTH. Thus, human IL-6 increases plasma concentrations cortisol in mice [31] and during immune system activation, such as post-traumatic inflammation or septic shock. In head-injured children, serum IL-6 and CRP levels are elevated and correlated to the severity of head trauma [32] and increased levels of IL-6 in the early phase of severe acute traumatic brain injury is associated with the high inflammatory response such as development of ARDS [33].

In association with appropriate antibiotherapy, methylprednisolone administration was also associated with a faster reduction in blood IL-6 and CRP levels in the first 24 h of treatment of community-acquired pneumonia [34]. Before initiation of glucocorticoid therapy, basal cortisol level is positively correlated with IL-6. Corticosteroids reduce the production of IL-6 and the migration of inflammatory cells into the alveolar space leading to avoid an overwhelming inflammatory response. In patients with systemic autoimmune disease, which leads to an inflammatory state, the introduction of glucocorticoid reduced the IL-6 level and contribute to the apparent suppression of the HPA axis [35]. Among patients with traumatic brain injury, IL-6 is correlated with inflammatory states, high CRP rates, and the occurrence of HAP [36].

A recent meta-analysis of corticosteroids in pneumonia found that hydrocortisone was not useful in this context, and only prednisone or methyl prednisolone was beneficial [37]. However, this meta-analysis considered community-acquired pneumonia (CAP) rather than HAP or ventilator-acquired pneumonia (VAP). The micro-organisms involved in each entity are different; in CAP, they are frequently virulent and transmitted by inhaled aerosols. Moreover, respiratory physiology and immunity is severely impaired in patients suffering from HAP or VAP and admitted in ICU. Indeed, mechanical ventilation promotes a specific histological pattern of pneumonia [38, 39]. Furthermore, comparative analysis of the host response to CAP and to HAP in patients with critical illness has revealed distinct transcriptional and plasma protein responses [40] showing the functional alterations of the immune response in patients admitted to hospital.

Here, taken separately, pro- and anti-inflammatory biomarkers (CRP and cortisol respectively) failed to predict the development of HAP. However, patients with high cortisol<sub>total</sub>/CRP ratio (> 3) have a higher susceptibility to develop HAP and for these patients, the introduction of low dose of corticosteroids is able to reduce this susceptibility. This effect of corticosteroid therapy is not found in patients with a ratio < 3. There are two means by which low-dose corticosteroids could decrease the rate of secondary pneumonia. Firstly, through an anti-inflammatory effect (patients with a low cortisol/

CRP ratio) that decrease the excessive inflammatory response and therefore the compensatory CARS response (immunosuppression). The initiation of corticosteroid therapy may for example reduce IL-6-dependent HPA stimulation, limiting the anti-inflammatory response and thus the prevalence of HAP in highly inflammatory patients. Secondly, corticosteroids may also directly enhance immunity (patients with a high cortisol/CRP ratio). Indeed, low-dose hydrocortisone improves the phagocytic abilities of neutrophils, decreases the blood concentration of anti-inflammatory cytokines such as interleukin-10, and increases the blood concentrations of interferon  $\gamma$  and interleukin-12, cytokines enhancing immunity and involved in the host defense against infections [14]. Glucocorticoids modulate dendritic cells during and after inflammation [13] allowing less tissue damage and therefore less sensitivity to bacterial infections. In septic shock or in viral pneumonia, glucocorticoids restore major histocompatibility complex class II expression on myeloid cells, suggesting a better antigen presentation by antigen-presenting cells during treatment [41, 42]. We and other groups have shown that hydrocortisone enhances immunity in the context of any acute immunosuppressive condition like severe trauma or sepsis [14, 15]. More specifically, we have demonstrated that trauma-induced immunosuppression is characterized by an interleukin-10-dependent elimination of dendritic cell by natural killer cells and that hydrocortisone improves outcome by limiting this immunosuppressive feedback loop [15].

The main strength of this ancillary study is the data from a randomized, multicentre, double-blind, controlled trial. This is the first study discriminating head injured patients at risk for developing pneumonia by using an easy-to-use anti- and pro-inflammatory factor ratio in common practice. Another strength of our study is the safety of low-dose corticosteroid use in trauma patients. Indeed, by closely monitoring patients' natriemia and glycemia, there are no serious adverse events recorded in the two large randomized trials we have conducted on the field [3, 12]. The use of low-dose corticosteroids therefore seems to us to be safe in patients suffering from severe TBI. However, high-dose corticosteroids are not recommended in this context because they provide serious safety issues [43]. Some limitations must be noted; first, it is impossible to know whether the effect of hydrocortisone is due to the restoration of post-inflammation homeostasis or the correction of the initial CIRCI although the use of a combination of a pro- and anti-inflammatory factor suggests that this effect is due to the correction of the post-inflammation disorder. However, the dosage of other more specific factors, such as IL-6 or IL-10, may help to refine the diagnosis of patients at risk of post-traumatic stress

disorder. Second, this ratio could be refined by adding other factors such as the trauma severity score (Glasgow score) or other objective variables (gender, age, medical history), but more patients are needed to implement such a score. Third, to be validated, this ratio must be the subject of a randomized controlled trial comparing management of HAP prevention by corticosteroid therapy in patients at risk (ratio > 3). Finally, our study also suffers from insufficient evidence on secondary outcomes (duration of mechanical ventilation, ICU length of stay...). This is probably due to the size of the samples under study and this issue could be improved by conducting a specific prospective study to validate the ratio.

## Conclusion

A cortisol<sub>total</sub>/CRP > 3 ratio upon admission may predict the development of HAP in patients with severe traumatic brain injury. In high-risk patients (ratio > 3), the administration of corticosteroid therapy reduces the occurrence of HAP. This ratio could be used to select patients eligible for corticosteroid therapy in prevention of HAP in patients with severe traumatic brain injury.

## Take home message

In severe traumatic brain-injured patients, the imbalance between the pro- and anti-inflammatory mechanisms leads to increased susceptibility to hospital-acquired pneumonia. We show here that cortisol and CRP blood levels together as surrogate markers of the CARS/SIRS balance upon ICU admission can accurately predict the development of hospital-acquired pneumonia and define the subgroup of patients who may benefit most from “low-dose” corticosteroid therapy.

## Supplementary information

**Supplementary information** accompanies this paper at <https://doi.org/10.1186/s13054-019-2680-6>.

**Additional file 1: Figure S1.** Correlations between transcortine blood level and cortisol<sub>total</sub> blood level in the entire population. **Figure S2.** Receiver Operating Characteristic (ROC) curve of the risk of Hospital Acquired Pneumonia in the entire population for the CRP blood levels. **Figure S3.** Comparison of the cortisol<sub>total</sub>/CRP ratio in the entire population. Results are given in median +/- SD. **Figure S4.** Receiver Operating Characteristic (ROC) curve of the risk of Hospital Acquired Pneumonia in the entire population for the cortisol/CRP ratios. **Figure S5.** Main characteristics of patients treated with corticosteroids compared to those treated with placebo amongst the subset with ratio >3.

## Abbreviations

ACTH: Adrenocorticotropic hormone; CAP: Community-acquired pneumonia; CARS: Compensatory anti-inflammatory response; CFU: Colony-forming units; CI: Confidence interval; CIRCI: Critical illness-related corticosteroid insufficiency; CNS: Central nervous system; CRP: C-reactive protein; GM-CSF: Granulocyte-macrophage colony-stimulating factor; HAP: Hospital-acquired pneumonia; HPA: Hypothalamic-pituitary axis; HR: Hazard ratio; ICU: Intensive care unit; IL-6: Interleukin 6; IL-10: Interleukin 10; IFN-γ: Interferon γ; LoD: Limit of detection; ROC: Receiver operating characteristic;

SIRS: Systemic inflammatory response syndrome; TBI: Traumatic brain injury; VAP: Ventilatory-acquired pneumonia

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## Authors' contributions

MB, KA, and AR wrote the draft. KA, PJM, and AR designed the Corti-TC trial. BP performed statistical analysis. All of the authors participated in data collection and acquisition. MB, KA, and AR did the data analysis and interpretation. All authors critically reviewed the manuscript for its important intellectual content. All the authors approved the manuscript before the submission.

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## Availability of data and materials

All data and material are available in the manuscript or are available from the corresponding author on request with justification.

## Ethics approval and consent to participate

This study is a sub-study of the Corti-TC trial (NCT 01093261). For the RCT trial, the independent Data and Safety Monitoring Board (DSMB) looked over the ethics in accordance with the Declaration of Helsinki, monitors patient safety, and reviews safety issues as the study progresses. Serious adverse events and unexpected related or possibly related serious events were reported blinded to the DSMB within respectively 24 h or 7 days.

## Consent for publication

Written informed consent for publication was obtained.

## Competing interests

The authors declare that they have no competing interests. KA declares personal fees from LSB, Fresenius and Baxter, outside the submitted work. MV declares personal fees from MSD, Pfizer, Baxter, Grants from Fisher Paykel, outside the submitted work. AR declares personal fees from Biomerieux and MSD, outside the submitted work.

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