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Antipyretic effect of dexamethasone in community-acquired pneumonia

To the Editor:

The cornerstones of treatment for community-acquired pneumonia (CAP) are early diagnosis and initiation of appropriate antibiotic therapy [1]. Despite prevention with vaccination, and optimal antibiotic treatment, CAP is associated with high mortality and morbidity and significant healthcare costs [2, 3]. Adjunctive therapy for CAP could help to reduce disease severity and, indeed, the addition of dexamethasone to antibiotic treatment in patients hospitalised with CAP has shown to reduce the length of hospital stay by 1 day [4]. Recent trials showed similar results [5, 6]. One of the comments raised to our previous study was that the antipyretic effect of dexamethasone might be the major underlying explanation for this result [7]. In patients, hospitalised with CAP, body temperature measurement is part of the standard care. Stable defervescence is one of the criteria used to define clinical stability [8]. Other clinical markers used in the decision to discharge a patient are respiratory and haemodynamic stability, the ability to maintain oral intake and a normal mental status [9–11]. Besides white cell count, C-reactive protein can be a useful marker of treatment response [10, 11].

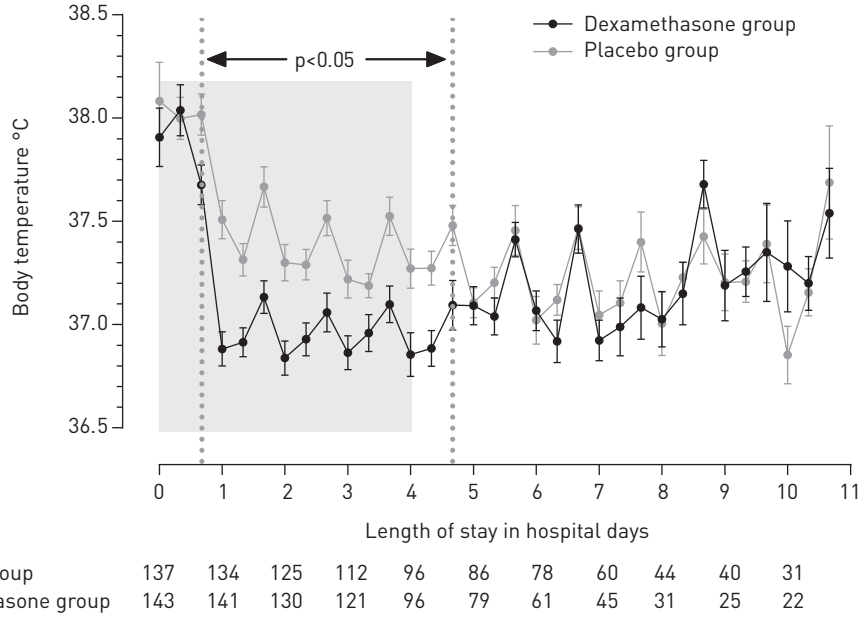
In a *post hoc* analysis, we assessed the effect of dexamethasone on body temperature in our previously conducted trial [4] and studied whether its antipyretic properties may have influenced the length of stay in hospital.

In the original clinical trial, patients, hospitalised with CAP, were randomised to a 4-day course of 5 mg intravenous dexamethasone or placebo, both in addition to standard care. More details of the study protocol are described elsewhere [4]. Retrospectively, we collected body temperature registrations from the medical charts of the study participants. Our aim was to collect three temperature measurements during each day of admission per patient. Differences in body temperature were assessed using Students' t-test. We analysed the time to persistent defervescence, defined as a body temperature <37.8°C for 8 h consecutively, with the chi-square test and with the Kaplan–Meier method and a log-rank test.

Body temperature registrations could be retrieved from 143 patients (94.7%) in the dexamethasone group and 137 patients (89.5%) in the placebo group. Baseline patient characteristics are evenly distributed over both treatment arms and reflect the characteristics in the original trial. The amount of patients that received antibiotic therapy prior to hospital admission did not differ between groups. Neither did the duration.

In the dexamethasone group, body temperature already started to decrease on the day of admission, whereas the decrease in the placebo group commenced 1 day later (fig. 1). At the end of the admission day the mean±SD for temperature was 37.68±1.04°C in the dexamethasone group and 38.0±1.072°C in the placebo group (95% CI 0.07–0.61, p=0.015,). The mean time to persistent defervescence was significantly shorter in patients treated with dexamethasone (0.97 days *versus* 1.77 days, p<0.001). The temperature difference between the dexamethasone and placebo group persisted until the end of day 4 of hospitalisation (24 h after the last administration of the study medication). Average body temperature from day 1 to day 4, during hospitalisation, was 37.3°C and 36.9°C in the placebo group and dexamethasone group, respectively. On every day from day 0 until day 4, the cumulative proportion of patients that reached defervescence was significantly higher in the dexamethasone group. By day 4, all patients in the dexamethasone group had reached stable defervescence, while 10.3% in the placebo group still had a fever (p<0.05) (table 1). The number of patients discharged did not diverge during the period that dexamethasone and placebo were given (fig. 1). Discharge rates did not start diverging until day 7 and day 8 (p<0.05) (table 1).

We found that body temperature was significantly suppressed in patients treated with dexamethasone. This resulted in a shorter time to persistent defervescence, one of the criteria used to define clinical stability [10]. There was no difference in discharge rates between the study groups during the period that a temperature difference was present. The difference in discharge rates between study groups started to occur from day 5 onwards. At that time, body temperature no longer differed between the two study groups. The most likely mechanism by which body temperature is suppressed in patients treated with dexamethasone is the suppression of pro-inflammatory and pyretic cytokines [12, 13]. The courses of



At risk n											
Placebo group	137	134	125	112	96	86	78	60	44	40	31
Dexamethasone group	143	141	130	121	96	79	61	45	31	25	22

FIGURE 1 Mean morning, afternoon and evening body temperatures from hospital admission to day 10. Dotted lines show the period during which differences in body temperature between groups are significant ($p<0.05$). Grey box indicates the period of dexamethasone or placebo administration. Error bars show standard error.

C-reactive protein, interleukin (IL)-6 and IL-10 from patients included in this study have been shown elsewhere [4]. In accordance with our findings, Snijders *et al.* [14] found that defervescence (and C-reactive protein decrease) was reached faster in hospitalised patients with CAP, treated with 40 mg of prednisolone for a total of 7 days, when compared to placebo-treated hospitalised patients (median±SD 2 ±1 days *versus* 3±2 days, $p<0.01$).

In a comment on our trial it was suggested that the "defervescence caused by the corticosteroids" might be the explanation for the reduced length of hospital stay in patients who received dexamethasone [4, 7]. The fact that discharge rates started to diverge at day 7 and that by that time temperature differences had disappeared for days (table 1), makes such an explanation unlikely. However, a delayed effect on discharge decision making cannot be ruled out. Absence of hypothermia or hyperthermia was only one of the criteria used to define clinical stability in the original trial. The other criteria that were used as a rule for hospital discharge were: improvement of shortness of breath, a consistent decrease of C-reactive protein concentrations, and adequate oral intake and gastrointestinal absorption [4]. Except for C-reactive protein concentration, daily registration of these criteria was not part of the original study protocol. It was thereby

TABLE 1 Cumulative percentages of patients free of fever per day of admission[#] and of patients discharged on each day of admission

Day	Dexamethasone n=143		Placebo n=137	
	Free of fever	Patients discharged	Free of fever	Patients discharged
0	15.9	0	6.4*	0
1	89.8	0	67.9*	0.7
2	98.9	0.7	79.5*	1.5
3	98.9	4.2	88.5*	4.4
4	100	12.6	89.7*	13.1
5	100	25.9	96.2[¶]	23.4
6	100	42	97.4	32.1[¶]
7	100	56.6	97.4	42.3*
8	100	64.3	100	52.6*
9	100	74.8	100	67.2
10	100	76.9	100	70.1

[#]: based on two consecutive readings. *: $p<0.05$; [¶]: $p<0.1$, dexamethasone *versus* placebo.

commented upon that the daily measurement of C-reactive protein may have influenced the length of stay in hospital [15]. Together with concurrent body temperature suppression, this might have favoured dexamethasone.

The main limitation of our study is that the body temperature measurements, taken during the hospital stay, were not part of the original study protocol. Consequently, body temperature values could not be retrieved for all patients at every time point. However, the occurrence of missing data can be considered fully non-differential because of the randomised nature of the trial. A point of critique to our concept of determining defervescence might be that temperature can increase again after two consecutive measures <37.8°C. Only two patients in the dexamethasone group and 11 patients in the placebo group developed fever after being labelled as having stable defervescence. Furthermore, the prescription of paracetamol, often prescribed because of its antipyretic effect, was not registered. We can, therefore, only speculate on the paracetamol effect. If any difference did occur, the prescription rate of paracetamol might be expected to be higher in the placebo group, since defervescence was more rapidly attained in patients treated with dexamethasone. It is highly unlikely that the unevenly distributed use of paracetamol would account for the faster defervescence in the dexamethasone treated patients.

In summary, our findings support the hypothesis that the reduction in length of stay in hospital was the result of a faster, overall, clinical recovery from pneumonia caused by dexamethasone, rather than a "cosmetic" suppression of fever.

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Antipyretic effect of dexamethasone in community-acquired pneumonia does not explain reduced length of hospital stay http://ow.ly/LTcST

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