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Letter to the Editor

The effects of a single dose of paracetamol in a critical phase of sepsis: a sub-analysis of the PHANTASi trial

To the Editor,

Sepsis is a life threatening syndrome in which a dysregulated host response to infection leads to life-threatening organ dysfunction [1]. In-hospital mortality for patients with sepsis is about 10% [1]. Hyperthermia is a common symptom of sepsis, but septic patients with hypothermia have higher mortality rates than patients with hyperthermia [2]. Thus, fever appears to have a protective role in patients with sepsis. In the Netherlands, some patients with sepsis receive paracetamol in the ambulances, mostly for pain management as fever is not an indication for administration of paracetamol in the Dutch Ambulance Protocol [3]. As patients with higher temperatures have lower mortality rates, it seems counterintuitive to administer antipyretic drugs.

In the last decade, a substantial amount of literature has been published on the use of antipyretics in patients with sepsis. These studies examined the use of antipyretics in different settings and different subpopulations of sepsis patients. The majority of these studies have been unable to provide an estimate of the effect, or did not find any effect, of antipyretics on mortality in sepsis [4–9], while others found significant evidence that antipyretic treatment raises mortality rates in septic patients [10–12]. As the available literature is contradictory and inconclusive, there is no general agreement or protocol about the use of paracetamol for fever control in sepsis. We aimed to determine whether patients with sepsis who are given paracetamol in the ambulance, have different mortality rates than patients with sepsis who do not receive this treatment.

To answer this question, we conducted a retrospective observational study on the database of the PHANTASi trial [13], which was a large randomized controlled trial investigating the effects of early administration of antibiotics in patients with sepsis. A detailed description of the original study design as well as the case report form are published elsewhere [13,14]. Patients in this study were randomized to receive either ceftriaxone in the ambulance (in addition to usual care) or usual care only. The latter group received their first dose of antibiotics, on average 96 min later, in the emergency department [13]. No difference in mortality was found between these groups.

In our non-randomized secondary analysis, we compared 28-day mortality rates for patients who received a dose of 1000 mg of paracetamol in the ambulance and patients who did not. Paracetamol was mostly given orally, except for a few patients who received IV paracetamol because they were unable to receive medication orally. Before paracetamol was administered, tympanic temperature was measured. This tympanic measurement was repeated at arrival in the emergency department (ED).

To minimize the likelihood of confounding, a logistic regression analysis was used to adjust the outcome for age, sex, sepsis severity, National Early Warning Score (NEWS) in the ambulance, temperature in the ambulance, source of infection and systolic blood pressure. We chose to adjust for NEWS score, as it has shown to be most accurate in predicting mortality in a general ED population [15].

In total, 254 patients received paracetamol in the ambulance and 2274 did not. See Table 1 for baseline characteristics of these groups. At 28 days, 205 patients had died (8.1%) in the complete study population. In the paracetamol group 13 (5.1%) patients had died and in the non-paracetamol group 192 (8.4%) patients had died. After adjustment for age, sex, sepsis severity, NEWS in the ambulance, temperature in the ambulance, source of infection and systolic blood pressure, there was no significant difference in 28-day mortality between the paracetamol and non-paracetamol groups (OR: 0.75 [95% CI 0.35 to 1.61]; $p = .46$).

There was a significant difference between the paracetamol and non-paracetamol groups, when the temperature measured in the ambulance and the temperature measured in the emergency department were compared. Paracetamol administration caused an average decrease in temperature of 0.49 °C. In the non-paracetamol group there was also a decrease in temperature, but to a lesser extent with 0.23 °C (mean difference: 0.26 °C (95% CI [0.15–0.36]; $p < .001$).

In this study we did not find a mortality difference between septic patients who received a single dose of paracetamol in the ambulance and patients who did not, although we confirmed that the former had a significantly larger decrease in temperature between the measurement in the ambulance and at the emergency department. These results, however circumstantial, suggest that high mortality rates in hypothermic sepsis patients are perhaps more likely to be caused by failure of the immune system, rather than by the lower temperature itself.

There are several limitations to this study. Firstly, there is no documentation of paracetamol usage prior to administration in the ambulance. The main hypothesis is that antipyretics could cause higher mortality rates in septic patients by reducing temperature, as fever is suggested to be important for both “immune function and for its bacteriostatic properties” [7]. We confirmed that paracetamol administration in our population led to the largest average difference in temperature between the groups that could be expected from a single dose of paracetamol based on the literature and therefore prior use of paracetamol was deemed irrelevant[22]. We can thus assume that a larger antipyretic and thereby more clinically relevant effect cannot be expected from paracetamol administration [7].

Secondly, assuming mortality rates of up to 10% in sepsis patients, absolute differences in mortality rates between the groups ranging from

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Table 1
Baseline characteristics paracetamol and non-paracetamol groups: percentages within patient groups (chi-square test for categorical variables and independent *t*-test for continuous variables). ED = Emergency department.

Characteristics	Categories	Non-paracetamol group (n = 2274)	Paracetamol group (n = 254)	*P*-value
Sex	Women	1309 (57.6%)	157 (61.8%)	0.19
	Men	965 (42.4%)	97 (38.2%)	
Age	(mean)	73.0 ± 13.4	70.0 ± 15.7	0.004
Sepsis severity	Sepsis	1253 (55.1%)	147 (57.9%)	0.69
	Severe sepsis	958 (42.1%)	100 (39.4%)	
	Septic shock	63 (2.8%)	7 (2.8%)	
Temperature in ambulance		38.9 ± 0.91	39.2 ± 0.79	> 0.001
Temperature difference between ambulance and ED		−0.23 ± 0.72	−0.49 ± 0.81	< 0.001
Charlison Comorbidity Score	0–3	1915 (84.2%)	205 (80.7%)	0.15
	> 3	359 (15.8%)	49 (19.3%)	
Early Warning Score	0–3	286 (17.5%)	42 (23.7%)	0.03
	4–6	482 (31.5%)	41 (23.2%)	
	> 6	781 (51.0%)	94 (53.1%)	

*For age: Levene's test for equality of variances: p < .001, therefore equal variance was not assumed.

3.1% to 4.7% could have been detected with 80% power given the current sample sizes. It is doubtful that a single prehospital dose of paracetamol, even in a critical phase of the disease, would cause this kind of a difference in 28-day mortality. However, since other studies have included much less patients and we had no estimate of what the effect could be, we argue that our results are of some value to the body of literature on this topic.

Another limitation is that there was no documentation on the use of paracetamol in the hospital. This problem was unavoidable due to the type of study we conducted. We did however show that a significant decrease in temperature was established by paracetamol in a critical phase of the illness, which is a crucial time for the immune response to function properly. Furthermore we could argue that the patients in the paracetamol group were somewhat more likely to have received paracetamol in the hospital as well, because the main indication for paracetamol would have been pain given the current protocol. This problem was likely not fixed by the single dose of paracetamol.

Lastly, as with any sub-analysis, the different study groups are not randomized. Although we adjusted the outcomes for many variables, the possibility remains that the results are influenced by confounders that were not measured in the original study.

In conclusion, administration of paracetamol in the ambulance did not lead to a detectable difference in 28-day mortality in this cohort of sepsis patients. The results of this study suggest that the single dose of paracetamol does not affect the proposed protective role of fever in sepsis, although it did lead to a significant decrease in temperature in a critical phase of the disease. As this sub-analysis was not powered to detect small differences in mortality, a randomized controlled trial is needed to finally answer the question whether antipyretic medication changes mortality rates in sepsis.

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Declaration of Competing Interest

R.S.N·P – No conflict.
M.S. – No conflict.
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