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Early peak temperature and mortality in critically ill patients with or without infection

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Abstract *Purpose:* To determine whether fever is associated with an increased or decreased risk of death in patients admitted to an intensive care unit (ICU) with infection. *Methods:* We evaluated the independent association between peak temperature in the first 24 h after ICU admission and in-hospital mortality according to whether there was an admission diagnosis of infection using a database of admissions to 129 ICUs in Australia and New Zealand (ANZ) ($n = 269{,}078$). Subsequently, we sought to confirm or refute the ANZ database findings using a validation cohort of admissions to 201 ICUs in the UK ($n = 366{,}973$). *Results:* A total of 29,083/269,078 (10.8%) ANZ patients and 103,191/366,973 (28.1%) of UK patients were categorised as having an infection. In the ANZ cohort, adjusted in-hospital mortality risk progressively decreased with increasing peak temperature in patients with infection. Relative to the risk at 36.5–36.9°C, the lowest risk was at 39–39.4°C (adjusted OR 0.56; 95% CI 0.48–0.66). In patients without infection, the adjusted mortality risk progressively increased above 39.0°C (adjusted OR 2.07 at 40.0°C or above; 95% CI 1.68–2.55). In the UK cohort, findings were similar with adjusted odds ratios at corresponding temperatures of 0.77 (95% CI 0.71–0.85) and 1.94 (95% CI 1.60–2.34) for infection and non-infection groups, respectively. *Conclusions:* Elevated peak temperature in the first 24 h in ICU is associated with decreased in-hospital mortality in critically ill patients with an infection; randomised trials are needed to determine whether controlling fever increases mortality in such patients.

Keywords Infection · Fever · Body temperature · Antipyresis

Introduction

Fever is common in critically ill patients [1]. Fever may be a marker of illness severity, may be linked to a protective host response to severe illness or may represent a modifiable risk factor for morbidity and mortality. Phylogenetically, fever is a highly conserved response that may result in a survival benefit during infection [2, 3]. In the pre-antibiotic era, induction of fever was used to treat meningococcal meningitis, gonorrhoea and syphilis [4–6]. Suppression of fever with antipyretics increases mortality in viral, bacterial and parasitic infections in different mammalian species [7, 8]. Antipyretics prolong the duration of: illness in chickenpox [9], malarial parasitaemia [10] and viral shedding in rhinovirus infection [11]. Thus, there is a plausible biological rationale that fever may improve outcomes in patients with infection.

However, fever increases metabolic rate, minute ventilation and cardiac output [12–14]. Fever may be associated with increased mortality in life-threatening illnesses [1]. Observational studies suggest that maintenance of a normal body temperature after stroke and traumatic brain injury may be beneficial [15]. After out of hospital cardiac arrest [16] and following perinatal birth asphyxia [17], induced hypothermia reduces disability and death. Thus, there is a plausible biological rationale that, in critically ill patients, fever may be detrimental in patients without infection.

We hypothesised that, in contrast with all other critically ill patients, fever would have an independent association with improved outcome in the presence of infection. Specifically, we hypothesised that, after adjusting for illness severity, fever during the first 24 h after ICU admission would be associated with reduced mortality in patients admitted with an infection-related diagnosis but with increased mortality in patients admitted with other diagnoses. To investigate this hypothesis, we compared the illness-severity-adjusted association between peak temperature in the first 24 h after ICU admission and in-hospital mortality in critically ill patients with infection and non-infection-related admission diagnoses.

Methods

Study design

This study utilised a retrospective cohort design to evaluate the association between the peak temperature recorded in the first 24 h of ICU admission and in-hospital mortality among patients with and without an admission diagnosis of infection. Ethics approval was obtained from the Alfred Hospital Human Research Ethics Committee (HREC reference number 183/11).

Patients

All patients admitted to an adult ICU at one of 129 centres in Australia and New Zealand (ANZ) or one of 201 centres in the UK between 2005 and 2009 were eligible for inclusion in this study. We excluded patients admitted following a cardiac arrest due to the confounding effect of therapeutic hypothermia; patients with missing data for either temperature, admission diagnosis or vital status at hospital discharge; and patients with insufficient data to calculate an illness-severity-adjusted risk of death. Where patients were admitted to ICU more than once during a hospital admission, only the patient's first admission was included in the analysis.

Databases

ANZ data were extracted from the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS–APD) and UK data were extracted from the UK Intensive Care National Audit and Research Centre Case Mix Programme (ICNARC–CMP) database. The ANZICS–APD is an established binational voluntary database, which has been well described and contains data from more than one million ICU admissions [18]. Data are collected under the Quality Assurance Legislation of the Commonwealth of Australia (Part VC Health Insurance Act 1973, Commonwealth of Australia) which allows use of data for research purposes without individual patient consent or specific ethical approval. In New Zealand, use of anonymous quality data for research is classified as 'low risk audit activity' and is exempt from requirements for formal ethics approval. Access to the data was granted by the ANZICS Centre for Outcome and Resource Evaluation (CORE) Management Committee in accordance with standing protocols.

The ICNARC–CMP database is a trinational, representative database with coverage of adult general critical care units in England (92%), Wales (100%) and Northern Ireland (100%). The ICNARC–CMP database contains over one million adult critical care admissions and has been described in detail [19]. The ICNARC–CMP has support for the collection and use of patient identifiable data without consent under Section 251 of the NHS Act 2006 (approval number PIAG 2–10(f)/2005).

Data extraction and categorisation of patients into infection and non-infection groups

The following variables were extracted from the databases: age, gender, co-morbidities, physiological measures in the first 24 h, ICU admission source and vital status at hospital discharge. Additionally, illness severity was determined using the APACHE III risk prediction

model for the ANZ data [20] and the ICNARC model for the UK data [21]. In both cases, the temperature component of the model was removed.

Patients in the ANZ database were categorised into the infection and non-infection groups using APACHE III codes as shown in the "Electronic supplementary material" (ESM). Patients in the UK database were categorised into the infection and non-infection groups using the ICNARC coding method (ICM) [22]. The ICM is used to categorise up to two 'reason for admission' fields, namely the primary and secondary reason(s) for admission to the ICU. The ICM code is hierarchical with each reason for admission being coded as type (surgical/non-surgical); body system (e.g. respiratory, etc.); anatomical site (e.g. lungs, etc.); physiological or pathological process (e.g. inflammation, infection, etc.); and, finally the condition being coded. Infection is one of 105 processes. All admissions coded as infection in either the primary or secondary 'reason for admission' were categorised into the infection group; all other admissions were categorised as non infection.

Outcomes

The primary outcome was illness-severity-adjusted in-hospital mortality associated with peak documented temperature in the first 24 h following admission to ICU. For patients in the ANZ database, vital status was determined at the time of discharge from the acute hospital housing the ICU to which the patient was admitted. For patients in the UK database, vital status was determined at the time the patient was ultimately discharged from acute hospital. For example, if a patient was transferred from one acute hospital to another, their vital status would be determined at the time of discharge from the final acute hospital.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) and median ± interquartile range [IQR] for parametric and non-parametric data, respectively. We report categorical variables as counts and percentages. We considered temperature as a categorical variable, divided into 0.5°C increments and report odds ratios relative to a normal temperature defined as a range from 36.5 to 36.9°C.

First, we tested our hypothesis using the ANZ database. After this analysis was completed, providing an initial confirmation of our hypothesis, we performed an independent analysis to further test our hypothesis using the UK database.

We calculated odds ratios (95% CI) for the risk of in-hospital mortality associated with peak temperature for the infection and non-infection groups. We performed multivariate analysis using logistic regression adjusting for the patient's severity of illness. To establish if the relationship between temperature and hospital mortality differed between the infection and non-infection groups, we fitted an interaction between temperature and group. Given the established association between fever and poor outcome in neurologically injured patients [15, 23], we performed a post hoc analysis of the non-infection group which excluded neurologically injured patients. A two-sided p value of 0.05 was considered to be statistically significant.

Results

Over the study period from 2005 to 2009, 405,359 patients were included in the ANZICS–APD and 399,827 patients where included in the ICNARC–CMP. Of these, 269,078 (66.4%) of patients in the ANZICS–APD and 366,973 (91.8%) of the patients in the ICNARC–CMP were included in the analysis (see ESM). Among included patients, 29,083/269,078 (10.8%) (ANZ) and 103,191/366,973 (28.1%) UK patients, respectively, were categorised as having an infection-related admission diagnosis.

Admissions included in the ANZ database were drawn from 129 hospitals (26% rural, 22% metropolitan, 24% tertiary and 28% private). The majority of hospitals (61%) had less than 300 beds, with 24% of hospitals having between 300 and 500 beds and 15% having more than 500 beds. Admissions included in the UK database were pooled from 201 adult critical care units. Of the 201 critical care units, 50 are in university hospitals, 31 are university-affiliated and 120 non-university (district general) hospitals.

Table 1 (and the ESM) presents the baseline characteristics, physiological data and outcomes for patients in the infection and non-infection groups. In both cohorts, the infection group were more likely to be immunosuppressed ($P < 0.0001$), had more co-morbidities, including cancer ($P < 0.0001$), and had higher illness severity scores than patients in the non-infection group ($P < 0.0001$). The infection group had a significantly higher temperature, heart rate, respiratory rate and mean arterial pressure than the non-infection group ($P < 0.0001$). The infection group had higher ICU and in-hospital mortality than the non-infection group ($P < 0.0001$).

Illness-severity-adjusted associations between peak temperature recorded in the first 24 h of ICU admission and in-hospital mortality, relative to the risk at a normal temperature between 36.5 and 36.9°C, are presented in Tables 2, 3 and Figs. 1 and 2. In the development (ANZ) cohort, there was a highly significant interaction between peak temperature and infection ($P < 0.0001$) indicating

Table 1 Baseline characteristics, physiology and outcomes of study patients

	ANZ cohort		UK cohort	
	Infection (n = 29,083)	Non-infection (n = 239,995)	Infection (n = 103,191)	Non-infection (n = 263,782)
Age, mean (SD)	62.0 (18.2)	60.9 (18.9)	62.4 (17.7)	59.0 (19.2)
Male gender, number (%)	16,242 (56)	140,595 (59)	54,533 (53)	150,232 (57)
ICU admission source, number (%)				
Operating room	3,462 (12)	140,791 (59)	32,824 (32)	130,121 (49)
Emergency department	12,353 (42)	55,399 (23)	15,008 (15)	58,428 (22)
Hospital ward	8,966 (31)	26,644 (11)	49,021 (48)	61,105 (23)
Other hospital	4,265 (15)	16,696 (7)	6,338 (6)	14,128 (5)
Illness severity scores				
APACHE III, mean (SD)	66.2 (31.2)	48.0 (25.3)	N/A	N/A
SAPS II, mean (SD)	38.1 (17.5)	28.6 (15.0)	N/A	N/A
ICNARC physiology score, mean (SD)	N/A	N/A	21.7 (9.4)	15.6 (8.7)
Estimated risk of death based on ICNARC model with temperature component removed, median [IQR]	N/A	N/A	31.8% [14.1–54.0]	8.8% [3.2–26.2]
Estimated risk of death based on APACHE III with temperature component removed, median [IQR]	16.9% [5.8–40.2]	3.0% [1.0–10.7]	N/A	N/A
Physiological variables for first 24 h in ICU				
Highest temperature, mean (SD)	37.7 (1.0)	37.3 (0.7)	37.5 (0.9)	37.3 (0.8)
Highest MAP, median [IQR]	93 [85–105]	97 [87–108]	95 [86–105]	98 [88–110]
Highest heart rate, mean (SD)	111.7 (24.9)	98.8 (21.5)	116.2 (23.8)	105.1 (23.1)
Highest respiratory rate, mean (SD)	27.3 (9.0)	22.1 (6.6)	27.0 (11.4)	24.0 (8.1)
Mortality				
Died in ICU, number (%)	4,354 (15)	13,020 (5)	27,081 (26)	30,702 (12)
Died in hospital, number (%)	6,284 (22)	21,675 (9)	38,591 (37)	51,151 (19)
ICU-free survival days to day 28, median [IQR]	23.6 [6.8–26.2]	26.2 [24.1–27.1]	18 [0–24]	25 [18–26]
Hospital length of stay for survivors median, median [IQR]	12.7 [7.0–24.1]	9.24 [5.9–16.8]	14 [7–29]	9 [5–19]

APACHE acute physiology and chronic health evaluation, *SAPS* simplified acute physiology score, *ICNARC* Intensive Care National Audit & Research Centre, *MAP* mean arterial pressure
$P < 0.0001$ for all comparisons between 'infection' and 'non-infection'

Table 2 In-hospital mortality relative to normothermia (36.5–36.9°C) in ANZ patients

Temperature (°C)	Number in category	In-hospital mortality no. (%)	Odds ratio for in-hospital mortality (±95% CI)	Adjusted odds ratio for in-hospital mortality (±95% CI)[a]
Infection group				
<36	480	279 (58.1)	4.84 (3.99–5.89)	3.01 (2.37–3.82)
36–36.4	1,782	536 (30.1)	1.50 (1.33–1.70)	1.42 (1.23–1.65)
36.5–36.9	4,387	978 (22.3)	1	1
37–37.4	6,345	1,282 (20.2)	0.88 (0.80–0.97)	0.83 (0.74–0.92)
37.5–37.9	5,180	1,031 (19.9)	0.87 (0.79–0.96)	0.78 (0.7–0.87)
38–38.4	4,241	806 (19.0)	0.82 (0.74–0.91)	0.69 (0.61–0.78)
38.5–38.9	2,911	594 (20.4)	0.90 (0.80–1.01)	0.69 (0.61–0.79)
39–39.4	1,924	358 (18.6)	0.80 (0.69–0.91)	0.56 (0.48–0.66)
39.5–39.9	1,099	221 (20.1)	0.88 (0.75–1.03)	0.62 (0.51–0.74)
≥40	734	200 (27.2)	1.31 (1.09–1.56)	0.77 (0.63–0.94)
Non-infection group				
<36	3,791	1,346 (35.5)	6.72 (6.24–7.24)	3.60 (3.26–3.98)
36–36.4	19,070	2,079 (10.9)	1.5 (1.42–1.58)	1.34 (1.26–1.44)
36.5–36.9	51,318	3,900 (7.6)	1	1
37–37.4	73,767	5,311 (7.2)	0.95 (0.91–0.99)	0.87 (0.83–0.92)
37.5–37.9	50,473	3,987 (7.9)	1.04 (0.99–1.09)	0.83 (0.79–0.88)
38–38.4	25,862	2,638 (10.2)	1.38 (1.31–1.46)	0.89 (0.84–0.95)
38.5–38.9	10,233	1,269 (12.4)	1.73 (1.62–1.86)	0.91 (0.84–0.98)
39–39.4	3,709	675 (18.2)	2.72 (2.48–2.97)	1.16 (1.05–1.29)
39.5–39.9	1,206	274 (22.7)	3.59 (3.12–4.12)	1.19 (1.01–1.41)
≥40	566	230 (40.6)	8.36 (7.04–9.92)	2.07 (1.68–2.55)

[a] Odds ratios adjusted for illness severity using APACHE III predicted log odds risk of death with the temperature component removed

Table 3 In-hospital mortality relative to normothermia (36.5–36.9°C) in UK patients

Temperature (°C)	Number in category	In-hospital mortality no. (%)	Odds ratio for in-hospital mortality (±95% CI)	Adjusted odds ratio for in-hospital mortality (±95% CI)[a]
Infection group				
<36	2,874	2,091 (72.8)	3.99 (3.54–4.48)	3.04 (2.67–3.46)
36–36.4	6,971	3,511 (50.4)	1.52 (1.42–1.61)	1.37 (1.28–1.48)
36.5–36.9	16,812	6,743 (40.1)	1	1
37–37.4	24,957	8,820 (35.3)	0.82 (0.78–0.85)	0.84 (0.80–0.89)
37.5–37.9	21,692	7,225 (33.3)	0.75 (0.71–0.79)	0.77 (0.72–0.82)
38–38.4	14,509	4,695 (32.4)	0.71 (0.67–0.76)	0.72 (0.67–0.77)
38.5–38.9	7,931	2,636 (33.2)	0.74 (0.69–0.80)	0.75 (0.69–0.81)
39–39.4	4,175	1,478 (35.4)	0.82 (0.75–0.89)	0.77 (0.71–0.85)
39.5–39.9	1,936	754 (38.9)	0.95 (0.85–1.07)	0.90 (0.79–1.02)
≥40	1,334	638 (47.8)	1.37 (1.20–1.56)	1.09 (0.94–1.26)
Non-infection group				
<36	7,425	3,799 (51.2)	4.32 (3.98–4.69)	2.80 (2.61–3.01)
36–36.4	20,496	5,360 (26.2)	1.46 (1.39–1.53)	1.31 (1.24–1.38)
36.5–36.9	50,346	9,823 (19.5)	1	1
37–37.4	72,398	12,183 (16.8)	0.83 (0.81–0.87)	0.85 (0.82–0.89)
37.5–37.9	58,458	9,217 (15.8)	0.77 (0.73–0.81)	0.77 (0.73–0.80)
38–38.4	32,966	5,604 (17.0)	0.84 (0.79–0.90)	0.78 (0.74–0.83)
38.5–38.9	13,722	2,797 (20.4)	1.06 (0.98–1.14)	0.84 (0.78–0.90)
39–39.4	5,205	1,339 (25.7)	1.43 (1.30–1.57)	1.04 (0.95–1.14)
39.5–39.9	1,831	573 (31.3)	1.88 (1.67–2.12)	1.11 (0.96–1.27)
≥40	935	456 (48.8)	3.93 (3.34–4.61)	1.94 (1.60–2.34)

[a] Odds ratios adjusted for illness severity using ICNARC (2009) model predicted log odds of acute hospital mortality with temperature component removed

that the nature of the relationship between in-hospital mortality and peak temperature differed between the infection and non-infection groups. For peak temperatures below 38.0°C, the pattern of risk was similar for the infection and non-infection groups. In all patients, increasing degrees of hypothermia were associated with progressively increasing mortality. In the infection group, increasing peak temperature was associated with a progressively decreasing risk of in-hospital mortality until temperature reached 39.0–39.4°C and, even when peak temperature exceeded 40.0°C, there was a significantly reduced risk of in-hospital mortality. In the non-infection group, increasing peak temperature above 39.0°C was associated with a progressively increasing risk of in-hospital mortality.

Similar findings were observed in the UK validation cohort. There was a highly significant interaction between peak temperature and infection ($P < 0.0001$). For peak temperatures below 38.0°C, in-hospital mortality risk rose progressively in the infection and non-infection groups. In the infection group, increasing peak temperature was associated with reducing in-hospital mortality until peak temperature exceeded 38.4°C and, even when peak temperature exceeded 40.0°C, there was no significant increased risk of in-hospital mortality. However, in the non-infection group, peak temperatures of greater than 40.0°C were associated with a significantly increased risk of in-hospital mortality.

In both datasets, the association between elevated peak temperature and increased mortality risk persisted in the non-infection group when neurologically injured patients were excluded from the analysis (see ESM).

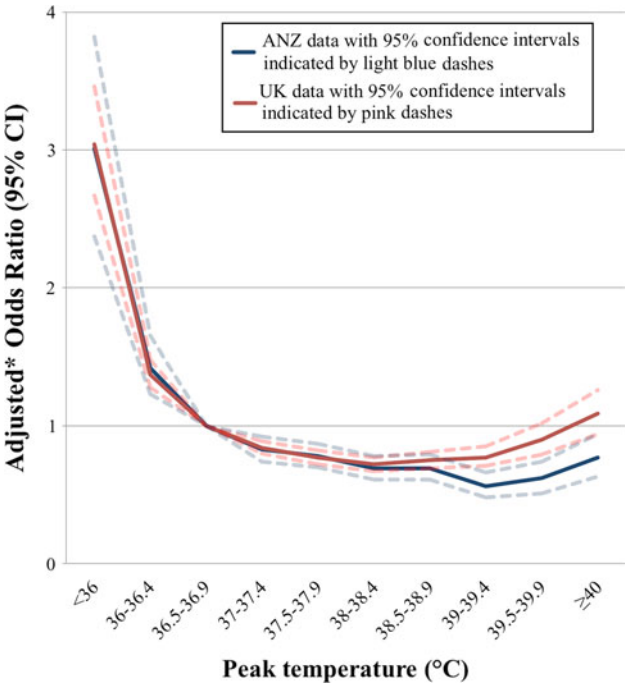

Fig. 1 Adjusted odds ratios (see Tables 2, 3) for in-hospital mortality versus peak temperature in the first 24 h in ICU for patients in the infection group

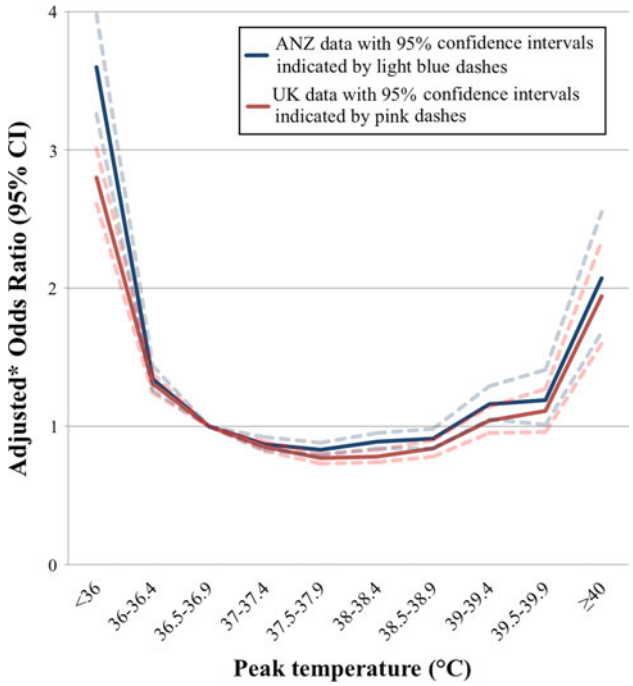

Fig. 2 Adjusted odds ratios (see Tables 2, 3) for in-hospital mortality versus peak temperature in the first 24 h in ICU for patients in the non-infection group

Discussion

Statement of principal findings

Using two very large, independent, multicentric, geographically distinct and representative databases and employing different risk prediction models to adjust for illness severity and different methods to classify patients into infection and non-infection groups, we found that peak temperatures above 39.0°C in the first 24 h after ICU admission were generally associated with a reduced risk of in-hospital mortality in patients with an admission diagnosis of infection. Conversely, higher peak temperatures were associated with an increased risk of in-hospital mortality in patients with a non-infection diagnosis. In both the infection and non-infection groups, increasing degrees of hypothermia were associated with progressively increasing in-hospital mortality.

Study significance

Our findings are consistent with previous animal studies which suggest that fever, in the setting of an infective illness, may be a beneficial physiological response [2, 3]. One potential explanation for the association between fever and reduced risk of mortality in patients with infective illness is that patients who fail to mount a febrile response are at increased risk of dying due to a relatively reduced production of pyrogenic cytokines linked to a blunted immunological response that predisposes to overwhelming infection. Alternatively, it is possible that patients with lower temperatures, either due to administration of antipyretics or to physical cooling, are at increased risk. The only study investigating the effect of acetaminophen on infective complications in ICU was stopped by the Data Safety Monitoring Board after an interim analysis identified a trend towards increased risk of infection and death in patients being cooled more aggressively [24]. However, two other studies investigating the use of ibuprofen, administered as an anti-inflammatory rather than antipyretic agent, reported no significant effect on mortality in critically ill patients with sepsis [25, 26]. Our findings raise the possibility that fever itself may be protective in critically ill patients with infection. This explanation is plausible because temperatures in the febrile range cause direct inhibition of a number of viral and bacterial organisms which are common causes of life-threatening illnesses such as *Streptococcus pneumoniae* [27], influenza [28] and *Neisseria meningitides* [29]. For influenza, the degree of heat sensitivity is a determinant of virulence, such that strains with a shut-off temperature of no greater than 38.0°C cause mild symptoms, whereas strains with a shut-off temperature of at least 39.0°C cause severe symptoms [28]. Temperatures within the physiological febrile range have also been shown to increase in vitro antibiotic activity [30].

Our finding that high fever in the early stages of critical illness is associated with increased risk of mortality in patients without an infection diagnosis on admission is similarly biologically plausible. It is consistent with previous studies in neurologically injured and general ICU patients that have shown that the presence of fever is associated with an increased risk of death [1, 23]. There is a marked metabolic cost associated with fever [12]. Patients who develop fever in the absence of infection are exposed to these deleterious effects without the potential benefit of fever-related suppression of an invading pathogen.

Another observation is that infection and non-infection patients demonstrated a similar pattern of increased risk with hypothermia. This finding is consistent with previous data indicating that hypothermia is associated with increased risk of mortality in patients with sepsis [31]. It is also consistent with data indicating that avoiding hypothermia in the perioperative period may reduce the incidence of cardiac events [32], the incidence of surgical wound infection [33] and the duration of hospitalization [33].

Strengths and limitations

Our study has several strengths. It used two large, independent, multinational databases and included 636,051

critically ill patients. It used one database to test the hypothesis and the second database to validate the initial findings. This approach increases the external validity of our findings. The data were independently collected by multiple trained data collectors for the purpose of audit and are unlikely to be subject to bias in relation to the recording of body temperature in the different groups of patients studied. The outcome (in-hospital mortality) is objective and easily verifiable, thus unlikely to be affected by ascertainment error or bias. Collection of validated markers for severity of illness allowed the adjusted odds ratio for the risk of mortality to be calculated by multivariate analysis. Finally, the differential association of fever with outcome in the two groups is statistically strong.

There are a number of limitations. First, the study was retrospective; however, the data were collected prospectively and the analysis was undertaken independent of the study hypothesis. Second, some patients were excluded from the analysis due to missing data points. It is likely that these data were missing at random. Third, our categorisation of patients into infection and non-infection groups was based on either APACHE III admission diagnostic codes [20] or the ICNARC coding method [22]. The infection group for the ANZ data was defined using those APACHE diagnostic codes which included infectious diseases exclusively. As a result, there are some infectious diseases (such as 'endocarditis' which can fall under a generic cardiology code) which might have been counted in the non-infection group in this dataset. This type of error, however, would bias the findings against our initial hypothesis. The UK data are categorised by organ system and by disease process with infection being one such disease process defined in the dataset. All patients who had an infection listed as either a primary or secondary reason for admission were categorised in the infection group. This method of categorisation is likely to be more sensitive than the method used for the ANZ data although less specific. Thus, a number of patients may have been classified into the infection group even where infection was only a relatively minor factor in their illness. Microbiological data to confirm the presence of infection in patients allocated to the infection group are not routinely collected as part of the audits and were not available. Because the diagnostic categories only related to the main admission diagnosis, there were additional confounding influences of subsequent or associated diagnoses that may not be accounted for. Fourth, it was not possible to control for antipyretic use in the multivariate analyses or to assess the time course of the febrile response, because the databases do not contain data on the treatment or duration of fever. Fifth, there was no standardisation in the methods used to measure temperature by the ICUs contributing data to this analysis. It is therefore possible that the sickest patients, at greatest risk of mortality, were more likely to have had invasive measurements of core temperature, resulting in relatively higher values. However, this bias should not have influenced the observed differences between the infection and non-infection groups. Sixth, adjustments for illness severity were based on data collected concurrently with the peak temperature data. While it would be preferable to have determined the illness severity prior to the collection of the temperature data, this was not possible using these databases and, in any case, the differential association between early peak temperature and outcome for infection and non-infection groups was evident in the unadjusted analysis. Finally, data accuracy was not independently monitored. However, given that errors in recording temperature are likely to be random, any such effect should be small given the size of the dataset.

Conclusions

The association between fever early in the course of critical illness and in-hospital mortality is different in patients with an infection admission diagnosis compared with those with a non-infection admission diagnosis. In the infection group, fever was associated with a decreased risk of death raising the possibility that the febrile response may be protective in infective illnesses and that reducing temperature in this context may be harmful.

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