

A SURVEY ON FEVER MONITORING AND MANAGEMENT IN PATIENTS WITH ACUTE BRAIN INJURY: THE SUMMA STUDY

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1 **ABSTRACT**

2 **BACKGROUND:** Fever is common in patients with acute brain injury (ABI) and worsens
3 secondary brain injury and outcome. Currently, there is a lack of consensus on the definition of
4 fever and temperature management. The aims of the survey were to explore: a) fever definitions, b)
5 temperature thresholds to trigger management and c) therapeutic strategies to control temperature.

6 **METHODS:** A questionnaire (26 items) was available on the European Society of Intensive Care
7 Medicine website between July 2016 and December 2016.

8 **RESULTS:** Among 231 respondents, 193 provided complete responses to the questionnaire (84%);
9 mostly intensivists [n=124, (54%)]. Body temperature was more frequently measured using a
10 bladder probe [n=93, (43%)]. A large proportion of respondents considered fever as a body
11 temperature > 38.3 °C [n=71, (33%)]. The main thresholds for antipyretic therapy were considered
12 37.5°C [n=74, (34%)] and 38.0°C [n=86, (40%)]; however, the thresholds were deemed lower (i.e.
13 37.0-37.5°C) in case of intracranial hypertension and cerebral ischemia. Among first-line methods
14 to treat fever, ice packs were the most frequently utilized physical method [n=90, (47%)], external
15 non-automated systems were the most frequent utilized device [n=49, (25%)] and paracetamol was
16 the most frequently utilized drug [n=135, (70%)]. Among second-line methods, intravenous cold
17 fluids were the most frequently utilized physical method [n=68, (35%)], external computerized
18 automated systems were the most frequently utilized device [n=75, (39%)] and diclofenac was the
19 most frequently utilized drug [n=62, (32%)]. Protocols for fever control and shivering management
20 were available for 83 (43%) and 54 (28%) of respondents.

21 **CONCLUSIONS:** We identified substantial variability regarding fever definition and application
22 of temperature management in ABI patients. Consensus recommendations are needed to improve
23 clinical use of targeted temperature management in this setting and to optimize the design of future
24 trials.

25

26 **Keywords:** fever, acute brain injury, temperature, management

Introduction

Fever is generally defined in the intensive care unit (ICU) setting as a core body temperature of at least 38°C,¹⁻² and is present in almost 70 % of patients suffering from an acute brain injury (ABI) who are admitted to the neuro-ICU (NICU).³ Fever is known to play a detrimental key role in worsening secondary brain injury⁴ and febrile ABI patients have a higher likelihood of poor outcomes when compared to others, as demonstrated in a meta-analysis pooling 14431 subjects suffering from different neurological injuries⁵. Fever exerts several deleterious effects in the acute stage of brain injury, such as exacerbations of intracranial hypertension, breakdown of the blood-brain barrier (BBB) and increased release of excitatory amino acids and free radicals.^{4,6-8} Moreover, it remains unclear whether fever is a prognostic factor or a marker of severity (or both), considering that the thermoregulatory centre is located inside the brain (i.e. the target of the primary insult).⁸ No prospective randomized controlled study exploring the optimal strategies to monitor and manage fever in NICU patients have been published yet. Moreover, the definition of fever and the optimal temperature to initiate active antipyretic therapies are frequently debated in this setting.

Considering all these issues, we conducted a survey to explore practices of fever monitoring and management in ABI patients admitted to the ICU. Specifically, we aimed to evaluate a) fever definitions commonly used in clinical practice, b) thresholds and triggers to start intervention and c) methods for temperature modulation.

1 **Materials and Methods**

2 The international **SURvey on Fever Monitoring and Management in Patients with Acute**
3 Brain Injury (SUMMA) was promoted and endorsed by the European Society of Intensive Care
4 Medicine (ESICM). The questionnaire was composed of 26 items and available on the ESICM
5 website from July 2016 to December 2016 [www.surveymonkey.com/r/SUMMAfever - Appendix
6 1 in Supplemental Material (SM)]. The survey was developed by three investigators (EP, FST, MO)
7 after a recent **non-systematic** review of the literature on temperature management in neurocritical
8 care. **Questions were formulated considering some factors related to different issues concerning this**
9 **topic, such as low levels of evidence, lack of good quality studies and controversial results from**
10 **observational trials.**

11 The items of the survey explored: a) characteristics of the participants, such as
12 demographics and type of hospital and specialty (items 1-9), b) temperature monitoring (items 10-
13 13), c) fever definition (item 14), d) triggers to start antipyretic therapy (items 15-19), e) fever
14 management (items 20-22 and 24), f) shivering management (items 23 and 25) and g) rewarming
15 (item 26).

16 The sample targeted included ESICM members who agreed to participate in Society surveys
17 at the time of their membership registration **and who treat patients with at least one form of ABI**
18 **(traumatic brain injury and/or subarachnoid hemorrhage and/or intracerebral hemorrhage and/or**
19 **acute ischemic stroke and/or status epilepticus) in their practice.** The investigators invited the target
20 participants to involve more respondents locally. Participants did not **receive** compensation and the
21 survey was disseminated via the ESICM office, thus protecting data confidentiality and anonymity.
22 The survey was registered within the ESICM Survey portfolio and no ethical approval was required.
23 The questionnaire was not specifically tested in a pilot cohort of potential respondents but
24 underwent a peer-review process within the ESICM Research Committee.

25

26 *Statistics*

1 Data from the questionnaire have been exported as CSV (Comma Separated Value) report
2 from the Surveymonkey software package and subsequently stored as Excel file (Microsoft Corp,
3 Redmond, WA). Descriptive statistics were computed for all study variables. The results are
4 presented as counts (percentage). Differences between groups (i.e. neuro-ICU vs. general ICU and
5 european vs. non-european respondents) were assessed using a chi-square test for binary variable or
6 by multinomial logistic regression for more than two categories per variable. A $p < 0.05$ was
7 considered as statistically significant. Stata software release 13.0 was used for the statistical
8 analysis (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp
9 LP).

1 **Results**

2 Out of 231 respondents to the survey, 193 (coming from 144 centers) completed the
3 questionnaire (84%). Figure S1 (Supplemental Material, SM) shows the numbers of respondents in
4 relation to completed items. Most of the respondents [$n = 138$ (60%)] were from Europe. The
5 highest number of respondents was from Italy ($n = 69$), United States of America ($n = 34$), France
6 ($n = 18$) and Australia ($n = 15$) (SM: Figure S2). Baseline characteristics of participants are reported
7 in Table 1. The majority of respondents were intensivists [$n = 124$ (54%)], working in mixed
8 medical-surgical ICUs [$n = 120$ (52%)]. Sites of preferred measurement of body temperature are
9 reported in Figure 1. Body temperature was monitored more frequently with a bladder probe [$n =$
10 93 (43%)] and multiple sites of measurement at the same time were often used [$n = 120$ (56%)].
11 Only some respondents reported to monitor brain temperature [$n = 47$ (22%)]. For most
12 respondents, temperature was monitored continuously [$n = 145$ (67%)]. The definition of fever
13 commonly used by participants is reported in Figure 2. A large proportion of respondents
14 considered fever as a body temperature greater than 38.3 °C [$n = 71$ (33%)]. Temperature triggers
15 to start fever management are illustrated in Figure 3. Antipyretic therapy was mainly started for
16 body temperature $> 38.0^{\circ}\text{C}$ [$n = 86$ (40%)] and $> 37.5^{\circ}\text{C}$ [$n = 74$ (34%)]. The majority of
17 respondents changed threshold for antipyretic treatment if intracranial hypertension [$n = 142$
18 (66.7%)] or cerebral ischemia [$n = 144$ (75%)] were present; in particular, these thresholds were
19 lower in case of intracranial hypertension [37.0°C - $n = 42$ (30%)] and cerebral ischemia [37.5°C -
20 $n = 40$ (28%)]. The main preferred methods for fever management (first-line and second-line
21 treatment) are shown in Figure 4. Among the first-line methods, ice packs were the most frequently
22 utilized physical method [$n = 90$ (47%)], external non-automated systems were the most frequent
23 utilized device [$n = 49$ (25%)], and paracetamol was the most frequently utilized drug [$n = 135$
24 (70%)]. Amongst the second-line methods intravenous (IV) cold fluids were the most frequently
25 utilized physical method [$n = 68$ (35%)], external computerized automated system were the most
26 frequently utilized device [$n = 75$ (39%)], and diclofenac was the most frequently utilized drug [$n =$

62 (32%)). Fever was generally treated during the entire ICU stay [$n = 64$ (33%)] or until intracranial hypertension is resolved or cerebral ischemia treated [$n = 61$ (32%)] (Table 2). Written protocols for fever and shivering were available respectively for 83 (43%) and 54 (28%) of respondents. Shivering was mainly treated with opiates [$n = 115$ (60%)] (SM: Table S1). The preferred strategy for rewarming was controlled (0.1-0.4 °C/h) to predefined temperature target for 75 (39%) of responders and titrated to intracranial pressure for 55 (28%) (SM: Table S2).

Data regarding comparison between european vs. non-european respondents as well as general vs. neuro-ICU are reported in Table S3. European respondents were more prone to change their threshold to treat fever in case of elevated ICP and would use more frequently, among available drugs, diclofenac, both as first or second-line therapy, than non-european respondents. Respondents from neuro-ICU would consider more often the 38.3°C threshold to define fever, use less physical device as first or second-line therapy and more paracetamol as first-line drug to control fever in ABI patients.

1 Discussion

2 This international survey provided some important data regarding practices on fever
3 monitoring and management in ABI patients admitted to the ICU. In relation to these results, future
4 studies in this setting will need to consider this heterogeneity found in clinical practice, i.e. what
5 threshold and which therapy should be used in ABI febrile patients.

7 *Fever definition and triggers for antipyretic therapy*

8 Fever in ICU patients has been defined by the American College of Critical Care
9 Medicine and Infectious Diseases Society of America guidelines as a core body temperature ≥ 38.3
10 $^{\circ}\text{C}$.¹ This definition is generally accepted by the majority of respondents to our survey. The second
11 most frequent definition of fever is a temperature $> 38^{\circ}\text{C}$. This could be related to the historical
12 definition of sepsis.² Surprisingly, 41% of respondents used other unconventional body temperature
13 values to define fever. This finding indicates that educational projects promoted by scientific
14 international societies should be encouraged to develop homogenous and clear definition of fever in
15 this setting. Moreover, although fever might be defined at a high body temperature, many
16 pathological processes underlying most of acute brain injuries are temperature-dependent and the
17 active modulation of this parameter in ABI patients might contribute to reduce the burden of
18 secondary brain damage.^{4-6,8} This concept is also highlighted by the discrepancy between the
19 definition of fever (i.e. body temperature $> 38.3^{\circ}\text{C}$) and the threshold to initiate therapy (i.e. 37.5 -
20 38.0°C) in ABI patients. Furthermore, the treatment thresholds are even lower in case of
21 intracranial hypertension or cerebral ischemia. In recent trials evaluating the impact of hypothermia
22 in ABI patients,⁹⁻¹¹ the control group was strictly maintained at normothermia (i.e. 37°C),
23 reinforcing the attention of physicians for narrow temperature control in this setting. It is also
24 possible that ICU physician would consider a potential gradient between core and brain temperature
25 that might justify initiation of therapy at lower thresholds. As such, Rossi et al.⁷ analysed nearly
26 2000 paired measurements (blood temperature measured by a pulmonary artery catheter and brain

temperature by a ventricular probe) in 20 neurosurgical patients and demonstrated that brain temperature was higher by a mean of 0.16°C before febrile episodes (defined as blood temperature $\geq 38^\circ\text{C}$) and of 0.41°C during febrile events, with the highest gradient recorded of 2.3°C. Other studies,¹²⁻¹³ employing rectal and brain probes, led to similar results. In daily clinical practice, few centers have the possibility to monitor brain temperature, as confirmed by the results of our survey. This would justify why many of the respondents would begin antipyretic strategies for body temperature values $> 37.5^\circ\text{C}$. Brain temperature monitoring and its influence on the management of fever in ABI patients represents an important field of research for the future.

Sites of fever monitoring

In the previous cited guidelines¹ the methods for the measurement of body temperature were classified, in order of accuracy, in 3 groups: 1) most accurate, 2) acceptable and 3) less desirable. Most accurate methods were considered respectively: pulmonary artery thermistor, urinary bladder catheter thermistor, oesophageal and rectal probes. Acceptable methods were considered oral probe and infrared ear thermometry. Temporal artery thermometer, axillary thermometer and chemical dot were regarded as less desirable methods. The majority of respondents in this survey used bladder probes embedded in urinary catheter. However, the second most utilized site remains skin measurements. This latter approach could lead to misinterpretation and underestimation of body and brain temperature. Indeed, during the initial phase of fever generation, to raise body temperature to the “new” hypothalamic set-point, an important cutaneous vasoconstriction is carried out to retain heat.¹⁴⁻¹⁶ In this situation, core temperature is greater than skin temperature¹⁴⁻¹⁵ and the use of skin measurements could significantly delay the recognition of fever and related treatments.

Fever, shivering and rewarming management

1 In general, fever in ICU is treated by pharmacological and/or physical means.¹⁷⁻¹⁸ The
2 most frequently drugs used in the NICU to control fever are paracetamol¹⁹⁻²¹ and diclofenac.²²⁻²⁴
3 Accordingly, these are the most frequent drugs proposed by the respondents, paracetamol as first-
4 line and diclofenac as second-line. The choice of diclofenac as a second line method, in particular
5 for resistant fever, could be related to the fact that this drug, contrary to paracetamol, can be also
6 administered by continuous infusion. This approach could be associated with better control of
7 temperature and a lower rate of adverse events, such as hypotension.²² No prospective randomized
8 controlled trial comparing paracetamol and diclofenac has been performed in this setting and this
9 could also explain the different approaches between european and non-european centers or general
10 and neuroICUs. This issue represents, in our opinion, an interesting topic of research for the future.
11 Ice packs are the most frequently method chosen by respondents as first-line physical therapy of
12 fever; this is probably related to their ease of use, availability and low cost.¹⁸ Nevertheless, ice
13 packs can be associated with skin lesions and burns and the control or reduction of body
14 temperature is unpredictable.¹⁸ The second most utilized physical method are intravenous (IV) cold
15 fluids. Indeed, they can rapidly decrease body temperature,^{18, 28} although large amounts of fluid are
16 generally necessary (i.e. 20-30 ml/kg),²⁸ which may result in fluid overload and pulmonary
17 edema.^{18,28} Moreover, both ice packs and IV cold fluids are not effective in maintaining a strict
18 control of normothermia and are labour intensive.^{18,29} In the last years, a large number of automated
19 devices have been produced and commercialized in association with the widespread use of targeted
20 temperature management (TTM) in cardiac arrest patients.³⁰⁻³¹ Usually, these devices are generally
21 either surface or intravascular cooling systems^{18, 29}. Our respondents used, as device for first-line
22 control of fever, mainly external (surface) non-automated systems, generally represented by
23 blankets with circulating cold fluid or air, wrapped around the patient.^{18,29} These devices are
24 generally easy to apply and effective in lowering body temperature but, being not computerized and
25 automated, not ideal for maintaining a tight temperature control.¹⁸⁻¹⁹ In case of resistant fever the
26 most frequently used device chosen by our respondents was an external computerized automated

1 system. This tool has a computerized loop control to allow a set target temperature to be strictly
2 maintained by the system by changing the water temperature and using the feedback from patient's
3 core temperature sensors.^{18,29} Endovascular computerized automated devices (CADs) have been
4 chosen by 20% of our respondents as second line method for fever management. The largest study
5 published **to date**,³² comparing endovascular vs. external CADs, is a retrospective analysis of data
6 from the **TTM** trial involving 934 patients [240 (26%) intravascular and 694 (74%) surface]. This
7 research shows that: a) surface and intravascular devices are equally effective during induction of
8 mild hypothermia, b) surface devices are associated with less precision during the maintenance
9 phase and c) there is no difference in adverse events (such as shivering, bleeding, sepsis, etc.),
10 mortality or poor neurological outcome.³¹ It is likely that the preference of our respondents towards
11 external CADs is **related** to their less invasiveness and ease of use compared to endovascular
12 devices. **To date**, no prospective randomized trial comparing intravascular vs. external CADs has
13 been performed; this adds to the key future research areas to explore.

14 Shivering is a **well-known** side effect of therapeutic hypothermia and temperature
15 management, with potentially dangerous consequences on cardiorespiratory system and ICP of **ABI**
16 patients. Shivering may be present even to a greater extent during fever management.^{18,33} While
17 body counter-regulatory mechanisms decrease significantly at lower temperatures, they **are**
18 **extremely effective when temperature is within** normal ranges.¹⁸ **In this survey, most of** respondents
19 would treat shivering mainly with opiates, propofol, benzodiazepines and/or neuromuscular
20 blocking agents. **To our knowledge, none of these drugs is officially approved for shivering**
21 **management.** The utilization of these interventions, although useful, could expose the patients to
22 more complications, such as delirium and critical illness acquired weakness, potentially resulting in
23 greater morbidity and mortality.³⁴⁻³⁵ Prevention and management of shivering with interventions
24 with no or minimal side effects should be **the** objective of future studies.

25 On rewarming, many respondents prefer a controlled and slow procedure (0.1-0.4 °C/h)
26 to predefined temperature target or titrated to ICP control. This approach seems to be very

important for the severe patients and can probably be achieved in an accurate and easy way with CADs. Less than 50% and 30% of respondents have respectively a written protocol for fever and shivering management. We hope this will change in the future as more evidence and consensus guidelines become available.

This survey has several limitations. First, response rate could not be calculated as the survey was sent to all ESICM members via a link to the ESICM website and participants could represent more respondents from the same center. Moreover, as not all ESICM members would take care of ABI patients, having the total number of ESICM members as denominator to calculate the response rate would also be biased. Compared to other surveys endorsed by ESICM,³⁶ the number of respondents was slightly lower and with discrepancies in geographical distribution. Second, respondents from specialized NICUs were included in this survey together with those coming from general ICUs. This might be considered as a significant limitation in the methodology of center eligibility and selection. Nevertheless, patients with ABI are treated worldwide not only in specialized and dedicated NICUs; therefore, our approach resulted in more generalizable findings. Moreover, we observed no significant differences regarding intensity and thresholds for fever treatment between neuro-intensive and general ICUs. Third, this survey was developed only by three investigators, without a systematic review of the literature and a pilot testing in a smaller sample of participants, which would further limit the quality of the questionnaire. Fourth, in the survey we did not consider the underlying cause or diagnosis for fever, such as non-infectious vs. infectious fever, as well as additional diagnostic tests (i.e. blood cultures, antibiotics, imaging) that would normally be used in this setting.

In conclusion, this survey shows a wide variability regarding definition, monitoring and management of fever in ABI patients admitted to ICU. These findings may be helpful in promoting educational intervention and defining future investigations on this topic.

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Acknowledgments: We would like to acknowledge the support of ESICM and all the participants to the survey.

Authors' Contributions: EP and FST were involved in the study design, acquisition of data, analysis and interpretation of data, drafting of manuscript and critical revision. MO was involved in study design, analysis and interpretation of data, drafting of manuscript and critical revision. LP and RH were involved in study design, drafting of manuscript and critical revision.

Conflict of interest: FST is a lecturer for BARD. FST is the Chair of the Neuro-Intensive Care (NIC) section of the European Society of Intensive Care Medicine (ESICM). RH is a lecturer and received congress support from Bard and Zoll. RH is a steering committee member for the INTREPID study supported by Bard. LP is the Deputy Chair of the NIC section of the ESICM.

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1 **FIGURES LEGENDS**

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3 **Figure 1.** Sites of measurement of body temperature. The number of respondents is shown in
4 brackets.

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6 **Figure 2.** Definition of fever. The number of respondents is shown in brackets.

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8 **Figure 3.** Temperature triggers to start fever management.

9 Abbreviations: ABI = acute brain injury, IH = intracranial hypertension, CI = cerebral ischemia.

10 * to IH or CI.

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12 **Figure 4.** Use of physical methods, cooling devices or antipyretic drugs as first-line or second-line
13 therapy.

14 Abbreviations: EN = endovascular computerized automated devices; Ext-AD = external
15 computerized automated devices; Ext-NonAD = external non-automated devices; DCF = diclofenac
16 sodium; Comb = combination of drugs

17 * = Others.

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1 **TABLE LEGENDS**

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3 **Table 1.** Baseline characteristics of **the** population.

4 Abbreviations: n = number, ICU = intensive care unit, ABI = acute brain injury, TBI = traumatic
5 brain injury, SAH = subarachnoid hemorrhage, ICH = intracerebral hemorrhage, AIS = acute
6 ischemic stroke.

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8 **Table 2.** Duration of fever management (numbers of respondents = 193).

9 Abbreviations: ICU = intensive care unit, IH = intracranial hypertension, CI = cerebral ischemia,
10 ABI = acute brain injury.

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1 **ABSTRACT**

2 **BACKGROUND:** Fever is common in patients with acute brain injury (ABI) and worsens
3 secondary brain injury and outcome. Currently, there is a lack of consensus on the definition of
4 fever and temperature management. The aims of the survey were to explore: a) fever definitions, b)
5 temperature thresholds to trigger management and c) therapeutic strategies to control temperature.

6 **METHODS:** A questionnaire (26 items) was available on the European Society of Intensive Care
7 Medicine website between July 2016 and December 2016.

8 **RESULTS:** Among 231 respondents, 193 provided complete responses to the questionnaire (84%);
9 mostly intensivists [n=124, (54%)]. Body temperature was more frequently measured using a
10 bladder probe [n=93, (43%)]. A large proportion of respondents considered fever as a body
11 temperature > 38.3 °C [n=71, (33%)]. The main thresholds for antipyretic therapy were considered
12 37.5°C [n=74, (34%)] and 38.0°C [n=86, (40%)]; however, the thresholds were deemed lower (i.e.
13 37.0-37.5°C) in case of intracranial hypertension and cerebral ischemia. Among first-line methods
14 to treat fever, ice packs were the most frequently utilized physical method [n=90, (47%)], external
15 non-automated systems were the most frequent utilized device [n=49, (25%)] and paracetamol was
16 the most frequently utilized drug [n=135, (70%)]. Among second-line methods, intravenous cold
17 fluids were the most frequently utilized physical method [n=68, (35%)], external computerized
18 automated systems were the most frequently utilized device [n=75, (39%)] and diclofenac was the
19 most frequently utilized drug [n=62, (32%)]. Protocols for fever control and shivering management
20 were available for 83 (43%) and 54 (28%) of respondents.

21 **CONCLUSIONS:** We identified substantial variability regarding fever definition and application
22 of temperature management in ABI patients. Consensus recommendations are needed to improve
23 clinical use of targeted temperature management in this setting and to optimize the design of future
24 trials.

25

26 **Keywords:** fever, acute brain injury, temperature, management

1 **Introduction**

2 Fever is generally defined in the intensive care unit (ICU) setting as a core body temperature
3 of at least 38°C,¹⁻² and is present in almost 70 % of patients suffering from an acute brain injury
4 (ABI) who are admitted to the neuro-ICU (NICU).³ Fever is known to play a detrimental key role in
5 worsening secondary brain injury ⁴ and febrile ABI patients have a higher likelihood of poor
6 outcomes when compared to others, as demonstrated in a meta-analysis pooling 14431 subjects
7 suffering from different neurological injuries⁵. Fever exerts several deleterious effects in the acute
8 stage of brain injury, such as exacerbations of intracranial hypertension, breakdown of the blood-
9 brain barrier (BBB) and increased release of excitatory amino acids and free radicals.^{4,6-8} Moreover,
10 it remains unclear whether fever is a prognostic factor or a marker of severity (or both), considering
11 that the thermoregulatory centre is located inside the brain (i.e. the target of the primary insult).⁸ No
12 prospective randomized controlled study exploring the optimal strategies to monitor and manage
13 fever in NICU patients have been published yet. Moreover, the definition of fever and the optimal
14 temperature to initiate active antipyretic therapies are frequently debated in this setting.

15 Considering all these issues, we conducted a survey to explore practices of fever monitoring
16 and management in ABI patients admitted to the ICU. Specifically, we aimed to evaluate a) fever
17 definitions commonly used in clinical practice, b) thresholds and triggers to start intervention and c)
18 methods for temperature modulation.

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1 **Materials and Methods**

2 The international **SURvey on Fever Monitoring and Management in Patients with Acute**
3 **Brain Injury (SUMMA)** was promoted and endorsed by the European Society of Intensive Care
4 **Medicine (ESICM)**. The questionnaire was composed of 26 items and available on the ESICM
5 website from July 2016 to December 2016 [www.surveymonkey.com/r/SUMMAfever - Appendix
6 1 in Supplemental Material (SM)]. The survey was developed by three investigators (EP, FST, MO)
7 after a recent non-systematic review of the literature on temperature management in neurocritical
8 care. Questions were formulated considering some factors related to different issues concerning this
9 topic, such as low levels of evidence, lack of good quality studies and controversial results from
10 observational trials.

11 The items of the survey explored: a) characteristics of the participants, such as
12 demographics and type of hospital and specialty (items 1-9), b) temperature monitoring (items 10-
13 13), c) fever definition (item 14), d) triggers to start antipyretic therapy (items 15-19), e) fever
14 management (items 20-22 and 24), f) shivering management (items 23 and 25) and g) rewarming
15 (item 26).

16 The sample targeted included ESICM members who agreed to participate in Society surveys
17 at the time of their membership registration and who treat patients with at least one form of ABI
18 (traumatic brain injury and/or subarachnoid hemorrhage and/or intracerebral hemorrhage and/or
19 acute ischemic stroke and/or status epilepticus) in their practice. The investigators invited the target
20 participants to involve more respondents locally. Participants did not receive compensation and the
21 survey was disseminated via the ESICM office, thus protecting data confidentiality and anonymity.
22 The survey was registered within the ESICM Survey portfolio and no ethical approval was required.
23 The questionnaire was not specifically tested in a pilot cohort of potential respondents but
24 underwent a peer-review process within the ESICM Research Committee.

25

26 *Statistics*

1 Data from the questionnaire have been exported as CSV (Comma Separated Value) report
2 from the Surveymonkey software package and subsequently stored as Excel file (Microsoft Corp,
3 Redmond, WA). Descriptive statistics were computed for all study variables. The results are
4 presented as counts (percentage). Differences between groups (i.e. neuro-ICU vs. general ICU and
5 european vs. non-european respondents) were assessed using a chi-square test for binary variable or
6 by multinomial logistic regression for more than two categories per variable. A $p < 0.05$ was
7 considered as statistically significant. Stata software release 13.0 was used for the statistical
8 analysis (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp
9 LP).

1 **Results**

2 Out of 231 respondents to the survey, 193 (coming from 144 centers) completed the
3 questionnaire (84%). Figure S1 (Supplemental Material, SM) shows the numbers of respondents in
4 relation to completed items. Most of the respondents [$n = 138$ (60%)] were from Europe. The
5 highest number of respondents was from Italy ($n = 69$), United States of America ($n = 34$), France
6 ($n = 18$) and Australia ($n = 15$) (SM: Figure S2). Baseline characteristics of participants are reported
7 in Table 1. The majority of respondents were intensivists [$n = 124$ (54%)], working in mixed
8 medical-surgical ICUs [$n = 120$ (52%)]. Sites of preferred measurement of body temperature are
9 reported in Figure 1. Body temperature was monitored more frequently with a bladder probe [$n =$
10 93 (43%)] and multiple sites of measurement at the same time were often used [$n = 120$ (56%)].
11 Only some respondents reported to monitor brain temperature [$n = 47$ (22%)]. For most
12 respondents, temperature was monitored continuously [$n = 145$ (67%)]. The definition of fever
13 commonly used by participants is reported in Figure 2. A large proportion of respondents
14 considered fever as a body temperature greater than 38.3 °C [$n = 71$ (33%)]. Temperature triggers
15 to start fever management are illustrated in Figure 3. Antipyretic therapy was mainly started for
16 body temperature $> 38.0^{\circ}\text{C}$ [$n = 86$ (40%)] and $> 37.5^{\circ}\text{C}$ [$n = 74$ (34%)]. The majority of
17 respondents changed threshold for antipyretic treatment if intracranial hypertension [$n = 142$
18 (66.7%)] or cerebral ischemia [$n = 144$ (75%)] were present; in particular, these thresholds were
19 lower in case of intracranial hypertension [37.0°C - $n = 42$ (30%)] and cerebral ischemia [37.5°C -
20 $n = 40$ (28%)]. The main preferred methods for fever management (first-line and second-line
21 treatment) are shown in Figure 4. Among the first-line methods, ice packs were the most frequently
22 utilized physical method [$n = 90$ (47%)], external non-automated systems were the most frequent
23 utilized device [$n = 49$ (25%)], and paracetamol was the most frequently utilized drug [$n = 135$
24 (70%)]. Amongst the second-line methods intravenous (IV) cold fluids were the most frequently
25 utilized physical method [$n = 68$ (35%)], external computerized automated system were the most
26 frequently utilized device [$n = 75$ (39%)], and diclofenac was the most frequently utilized drug [$n =$

62 (32%)]]. Fever was generally treated during the entire ICU stay [$n = 64$ (33%)] or until intracranial hypertension is resolved or cerebral ischemia treated [$n = 61$ (32%)] (Table 2). Written protocols for fever and shivering were available respectively for 83 (43%) and 54 (28%) of respondents. Shivering was mainly treated with opiates [$n = 115$ (60%)] (SM: Table S1). The preferred strategy for rewarming was controlled (0.1-0.4 °C/h) to predefined temperature target for 75 (39%) of responders and titrated to intracranial pressure for 55 (28%) (SM: Table S2).

Data regarding comparison between european vs. non-european respondents as well as general vs. neuro-ICU are reported in Table S3. European respondents were more prone to change their threshold to treat fever in case of elevated ICP and would use more frequently, among available drugs, diclofenac, both as first or second-line therapy, than non-european respondents. Respondents from neuro-ICU would consider more often the 38.3°C threshold to define fever, use less physical device as first or second-line therapy and more paracetamol as first-line drug to control fever in ABI patients.

1 **Discussion**

2 This international survey provided some important data regarding practices on fever
3 monitoring and management in ABI patients admitted to the ICU. In relation to these results, future
4 studies in this setting will need to consider this heterogeneity found in clinical practice, i.e. what
5 threshold and which therapy should be used in ABI febrile patients.

7 *Fever definition and triggers for antipyretic therapy*

8 Fever in ICU patients has been defined by the American College of Critical Care
9 Medicine and Infectious Diseases Society of America guidelines as a core body temperature ≥ 38.3
10 °C.¹ This definition is generally accepted by the majority of respondents to our survey. The second
11 most frequent definition of fever is a temperature > 38 °C. This could be related to the historical
12 definition of sepsis.² Surprisingly, 41% of respondents used other unconventional body temperature
13 values to define fever. This finding indicates that educational projects promoted by scientific
14 international societies should be encouraged to develop homogenous and clear definition of fever in
15 this setting. Moreover, although fever might be defined at a high body temperature, many
16 pathological processes underlying most of acute brain injuries are temperature-dependent and the
17 active modulation of this parameter in ABI patients might contribute to reduce the burden of
18 secondary brain damage.^{4-6,8} This concept is also highlighted by the discrepancy between the
19 definition of fever (i.e. body temperature $> 38.3^{\circ}\text{C}$) and the threshold to initiate therapy (i.e. 37.5 -
20 38.0°C) in ABI patients. Furthermore, the treatment thresholds are even lower in case of
21 intracranial hypertension or cerebral ischemia. In recent trials evaluating the impact of hypothermia
22 in ABI patients,⁹⁻¹¹ the control group was strictly maintained at normothermia (i.e. 37°C),
23 reinforcing the attention of physicians for narrow temperature control in this setting. It is also
24 possible that ICU physician would consider a potential gradient between core and brain temperature
25 that might justify initiation of therapy at lower thresholds. As such, Rossi et al.⁷ analysed nearly
26 2000 paired measurements (blood temperature measured by a pulmonary artery catheter and brain

temperature by a ventricular probe) in 20 neurosurgical patients and demonstrated that brain temperature was higher by a mean of 0.16°C before febrile episodes (defined as blood temperature $\geq 38^{\circ}\text{C}$) and of 0.41°C during febrile events, with the highest gradient recorded of 2.3°C. Other studies,¹²⁻¹³ employing rectal and brain probes, led to similar results. In daily clinical practice, few centers have the possibility to monitor brain temperature, as confirmed by the results of our survey. This would justify why many of the respondents would begin antipyretic strategies for body temperature values $> 37.5^{\circ}\text{C}$. Brain temperature monitoring and its influence on the management of fever in ABI patients represents an important field of research for the future.

Sites of fever monitoring

In the previous cited guidelines¹ the methods for the measurement of body temperature were classified, in order of accuracy, in 3 groups: 1) most accurate, 2) acceptable and 3) less desirable. Most accurate methods were considered respectively: pulmonary artery thermistor, urinary bladder catheter thermistor, oesophageal and rectal probes. Acceptable methods were considered oral probe and infrared ear thermometry. Temporal artery thermometer, axillary thermometer and chemical dot were regarded as less desirable methods. The majority of respondents in this survey used bladder probes embedded in urinary catheter. However, the second most utilized site remains skin measurements. This latter approach could lead to misinterpretation and underestimation of body and brain temperature. Indeed, during the initial phase of fever generation, to raise body temperature to the “new” hypothalamic set-point, an important cutaneous vasoconstriction is carried out to retain heat.¹⁴⁻¹⁶ In this situation, core temperature is greater than skin temperature¹⁴⁻¹⁵ and the use of skin measurements could significantly delay the recognition of fever and related treatments.

Fever, shivering and rewarming management

1 In general, fever in ICU is treated by pharmacological and/or physical means.¹⁷⁻¹⁸ The
2 most frequently drugs used in the NICU to control fever are paracetamol¹⁹⁻²¹ and diclofenac.²²⁻²⁴
3 Accordingly, these are the most frequent drugs proposed by the respondents, paracetamol as first-
4 line and diclofenac as second-line. The choice of diclofenac as a second line method, in particular
5 for resistant fever, could be related to the fact that this drug, contrary to paracetamol, can be also
6 administered by continuous infusion. This approach could be associated with better control of
7 temperature and a lower rate of adverse events, such as hypotension.²² No prospective randomized
8 controlled trial comparing paracetamol and diclofenac has been performed in this setting and this
9 could also explain the different approaches between european and non-european centers or general
10 and neuroICUs. This issue represents, in our opinion, an interesting topic of research for the future.
11 Ice packs are the most frequently method chosen by respondents as first-line physical therapy of
12 fever; this is probably related to their ease of use, availability and low cost.¹⁸ Nevertheless, ice
13 packs can be associated with skin lesions and burns and the control or reduction of body
14 temperature is unpredictable.¹⁸ The second most utilized physical method are intravenous (IV) cold
15 fluids. Indeed, they can rapidly decrease body temperature,^{18, 28} although large amounts of fluid are
16 generally necessary (i.e. 20-30 ml/kg),²⁸ which may result in fluid overload and pulmonary
17 edema.^{18,28} Moreover, both ice packs and IV cold fluids are not effective in maintaining a strict
18 control of normothermia and are labour intensive.^{18,29} In the last years, a large number of automated
19 devices have been produced and commercialized in association with the widespread use of targeted
20 temperature management (TTM) in cardiac arrest patients.³⁰⁻³¹ Usually, these devices are generally
21 either surface or intravascular cooling systems^{18, 29}. Our respondents used, as device for first-line
22 control of fever, mainly external (surface) non-automated systems, generally represented by
23 blankets with circulating cold fluid or air, wrapped around the patient.^{18,29} These devices are
24 generally easy to apply and effective in lowering body temperature but, being not computerized and
25 automated, not ideal for maintaining a tight temperature control.¹⁸⁻¹⁹ In case of resistant fever the
26 most frequently used device chosen by our respondents was an external computerized automated

1 system. This tool has a computerized loop control to allow a set target temperature to be strictly
2 maintained by the system by changing the water temperature and using the feedback from patient's
3 core temperature sensors.^{18,29} Endovascular computerized automated devices (CADs) have been
4 chosen by 20% of our respondents as second line method for fever management. The largest study
5 published to date,³² comparing endovascular vs. external CADs, is a retrospective analysis of data
6 from the TTM trial involving 934 patients [240 (26%) intravascular and 694 (74%) surface]. This
7 research shows that: a) surface and intravascular devices are equally effective during induction of
8 mild hypothermia, b) surface devices are associated with less precision during the maintenance
9 phase and c) there is no difference in adverse events (such as shivering, bleeding, sepsis, etc.),
10 mortality or poor neurological outcome.³¹ It is likely that the preference of our respondents towards
11 external CADs is related to their less invasiveness and ease of use compared to endovascular
12 devices. To date, no prospective randomized trial comparing intravascular vs. external CADs has
13 been performed; this adds to the key future research areas to explore.

14 Shivering is a well-known side effect of therapeutic hypothermia and temperature
15 management, with potentially dangerous consequences on cardiorespiratory system and ICP of ABI
16 patients. Shivering may be present even to a greater extent during fever management.^{18,33} While
17 body counter-regulatory mechanisms decrease significantly at lower temperatures, they are
18 extremely effective when temperature is within normal ranges.¹⁸ In this survey, most of respondents
19 would treat shivering mainly with opiates, propofol, benzodiazepines and/or neuromuscular
20 blocking agents. To our knowledge, none of these drugs is officially approved for shivering
21 management. The utilization of these interventions, although useful, could expose the patients to
22 more complications, such as delirium and critical illness acquired weakness, potentially resulting in
23 greater morbidity and mortality.³⁴⁻³⁵ Prevention and management of shivering with interventions
24 with no or minimal side effects should be the objective of future studies.

25 On rewarming, many respondents prefer a controlled and slow procedure (0.1-0.4 °C/h)
26 to predefined temperature target or titrated to ICP control. This approach seems to be very

important for the severe patients and can probably be achieved in an accurate and easy way with CADs. Less than 50% and 30% of respondents have respectively a written protocol for fever and shivering management. We hope this will change in the future as more evidence and consensus guidelines become available.

This survey has several limitations. First, response rate could not be calculated as the survey was sent to all ESICM members via a link to the ESICM website and participants could represent more respondents from the same center. Moreover, as not all ESICM members would take care of ABI patients, having the total number of ESICM members as denominator to calculate the response rate would also be biased. Compared to other surveys endorsed by ESICM,³⁶ the number of respondents was slightly lower and with discrepancies in geographical distribution. Second, respondents from specialized NICUs were included in this survey together with those coming from general ICUs. This might be considered as a significant limitation in the methodology of center eligibility and selection. Nevertheless, patients with ABI are treated worldwide not only in specialized and dedicated NICUs; therefore, our approach resulted in more generalizable findings. Moreover, we observed no significant differences regarding intensity and thresholds for fever treatment between neuro-intensive and general ICUs. Third, this survey was developed only by three investigators, without a systematic review of the literature and a pilot testing in a smaller sample of participants, which would further limit the quality of the questionnaire. Fourth, in the survey we did not consider the underlying cause or diagnosis for fever, such as non-infectious vs. infectious fever, as well as additional diagnostic tests (i.e. blood cultures, antibiotics, imaging) that would normally be used in this setting.

In conclusion, this survey shows a wide variability regarding definition, monitoring and management of fever in ABI patients admitted to ICU. These findings may be helpful in promoting educational intervention and defining future investigations on this topic.

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Acknowledgments: We would like to acknowledge the support of ESICM and all the participants to the survey.

Authors' Contributions: EP and FST were involved in the study design, acquisition of data, analysis and interpretation of data, drafting of manuscript and critical revision. MO was involved in study design, analysis and interpretation of data, drafting of manuscript and critical revision. LP and RH were involved in study design, drafting of manuscript and critical revision.

Conflict of interest: FST is a lecturer for BARD. FST is the Chair of the Neuro-Intensive Care (NIC) section of the European Society of Intensive Care Medicine (ESICM). RH is a lecturer and received congress support from Bard and Zoll. RH is a steering committee member for the INTREPID study supported by Bard. LP is the Deputy Chair of the NIC section of the ESICM.

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FIGURES LEGENDS

Figure 1. Sites of measurement of body temperature. The number of respondents is shown in brackets.

Figure 2. Definition of fever. The number of respondents is shown in brackets.

Figure 3. Temperature triggers to start fever management.

Abbreviations: ABI = acute brain injury, IH = intracranial hypertension, CI = cerebral ischemia.

* to IH or CI.

Figure 4. Use of physical methods, cooling devices or antipyretic drugs as first-line or second-line therapy.

Abbreviations: EN = endovascular computerized automated devices; Ext-AD = external computerized automated devices; Ext-NonAD = external non-automated devices; DCF = diclofenac sodium; Comb = combination of drugs

* = Others.

1 **TABLE LEGENDS**

2

3 **Table 1.** Baseline characteristics of the population.

4 Abbreviations: n = number, ICU = intensive care unit, ABI = acute brain injury, TBI = traumatic
5 brain injury, SAH = subarachnoid hemorrhage, ICH = intracerebral hemorrhage, AIS = acute
6 ischemic stroke.

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8 **Table 2.** Duration of fever management (numbers of respondents = 193).

9 Abbreviations: ICU = intensive care unit, IH = intracranial hypertension, CI = cerebral ischemia,
10 ABI = acute brain injury.

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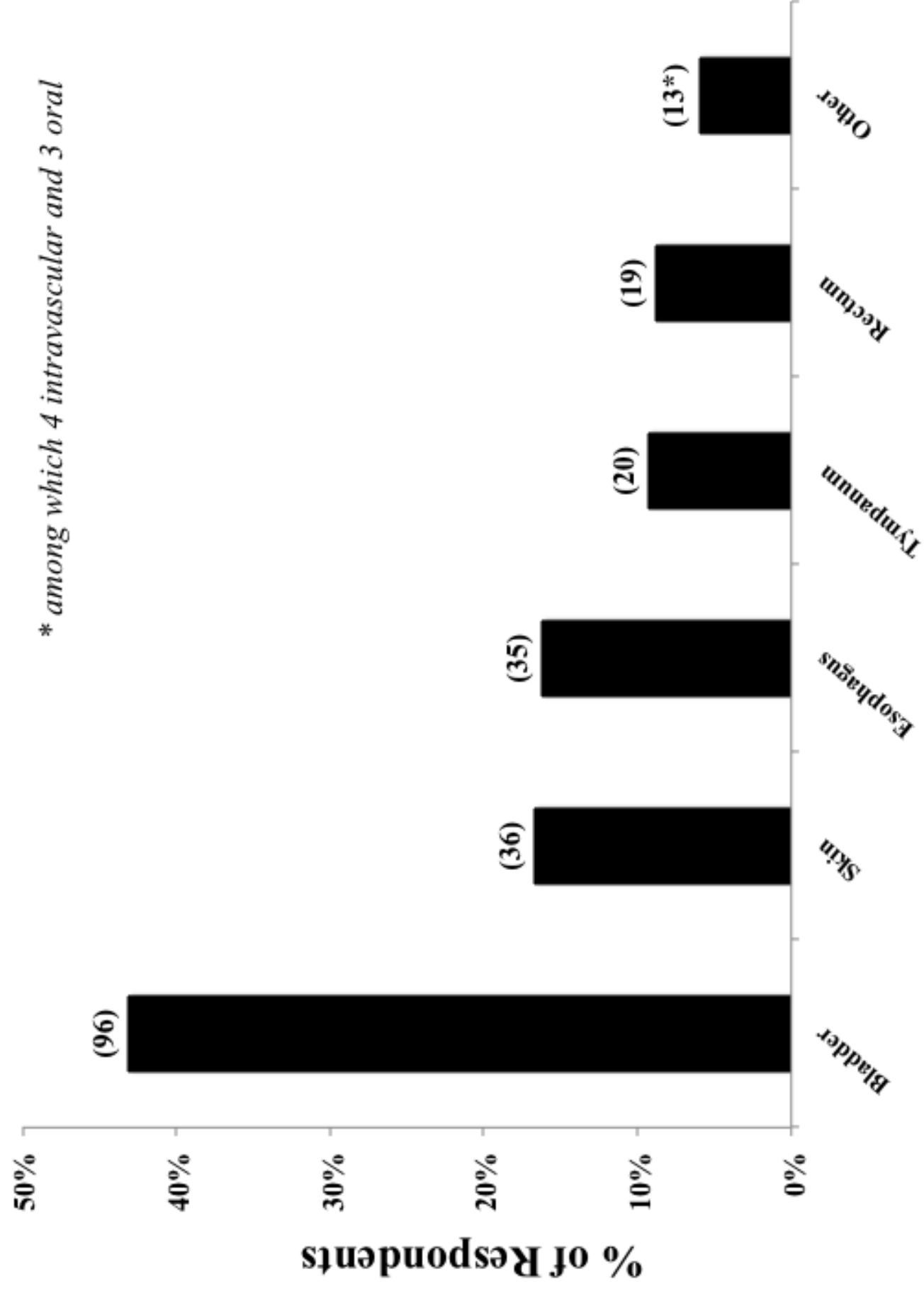


Figure 1

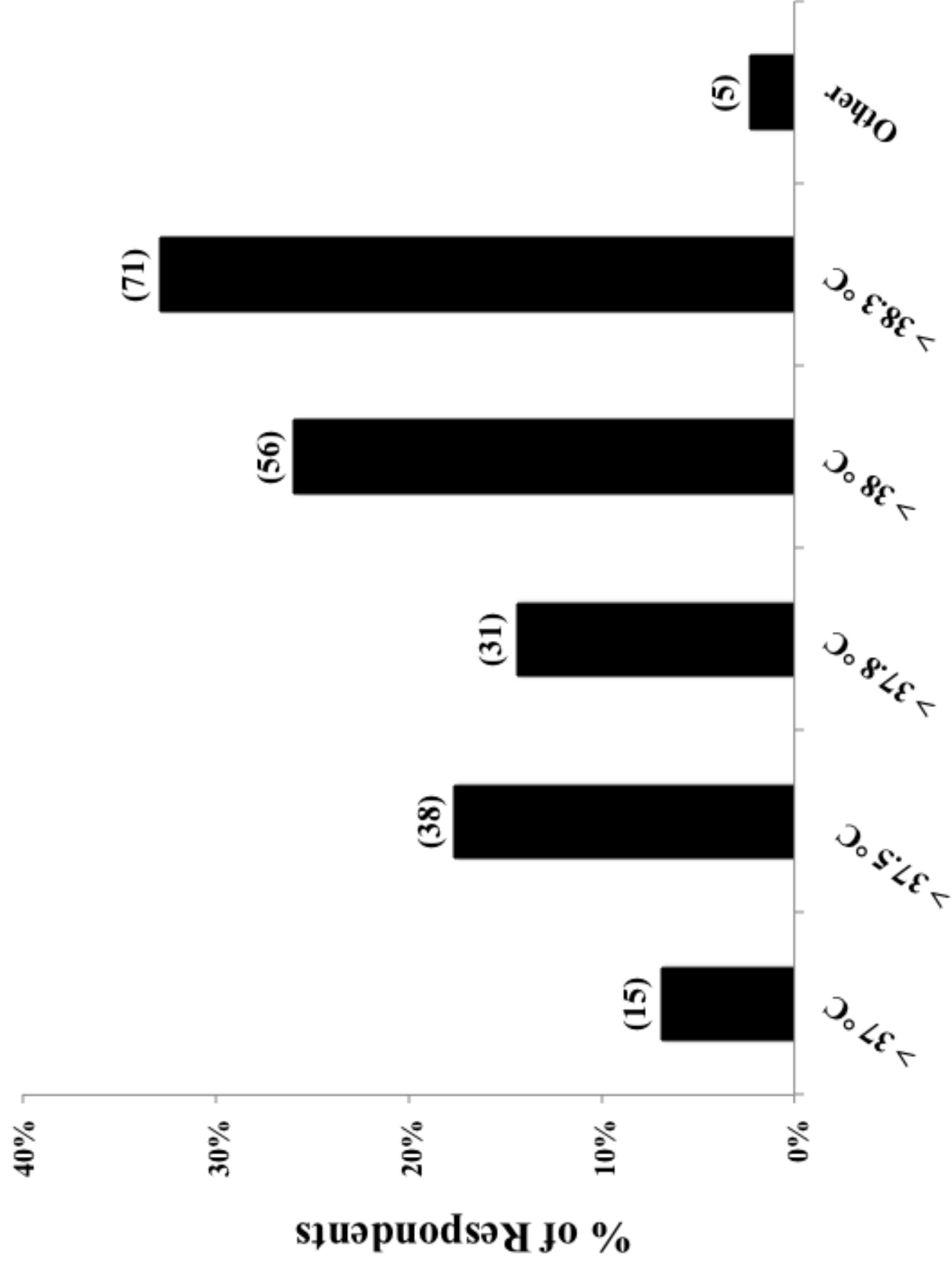


Figure 2

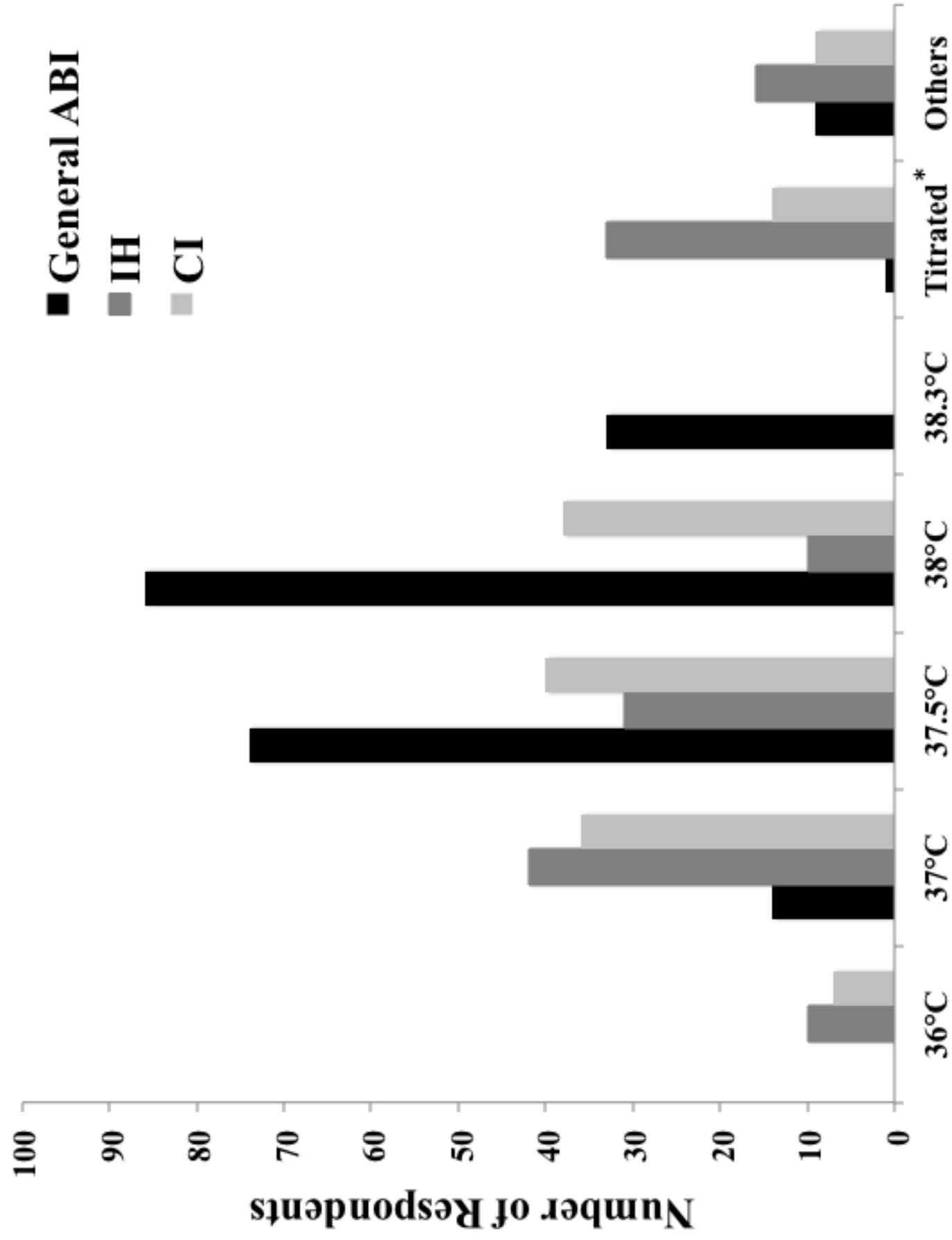


Figure 3

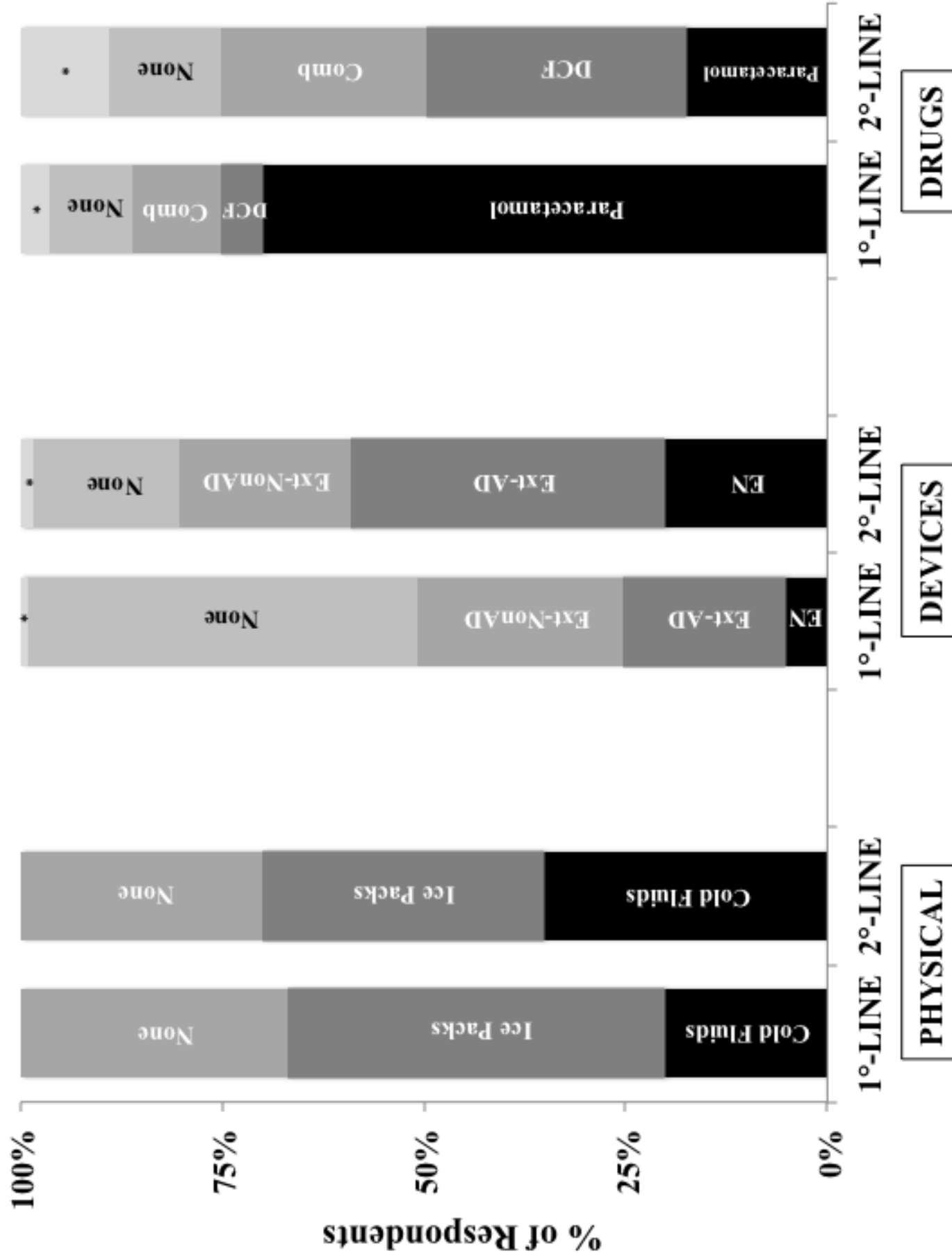


Figure 4

Table 1. Baseline characteristics of the population.

Respondents (n=231)	
Specialty	
<i>Intensive care medicine</i>	124 (54%)
<i>Anesthesiology</i>	67 (29%)
<i>Neurology</i>	26 (11%)
<i>Surgery (including neurosurgery)</i>	8 (4%)
<i>Internal medicine</i>	5 (2%)
Years of practice in critical care	
< 5	43 (19%)
6 - 10	51 (22%)
11 - 15	48 (21%)
16 - 20	28 (12%)
21 - 25	32 (14%)
> 25	29 (12%)
Type of ICU	
<i>General medical-surgical</i>	120 (52%)
<i>Neuro-ICU</i>	76 (34%)
<i>Surgical ICU</i>	19 (8%)
<i>Medical ICU</i>	5 (2%)
<i>Others</i>	10 (4%)
Responsible for ABI care in ICU	
<i>Intensivist</i>	181 (78%)
<i>Anesthesiologist</i>	30 (13%)
<i>Neurosurgeon</i>	11 (5%)
<i>Neurologist</i>	7 (3%)
<i>Others</i>	2 (1%)
ICU beds	
< 10	34 (15%)
10 – 20	92 (40%)
20 – 30	27 (12%)
30 – 40	22 (10%)
40 – 50	12 (5%)
50 – 60	14 (6%)
60 – 70	6 (3%)
70 – 80	7 (3%)
80 – 90	3 (1%)
90 – 100	3 (1%)
> 100	11 (4%)
Hospital beds	
<i>University</i>	109 (47%)
<i>University affiliate</i>	68 (30%)
<i>Non-university</i>	54 (23%)
ABIs usually treated	
<i>TBI</i>	193 (89%)
<i>SAH</i>	184 (85%)
<i>ICH</i>	195 (90%)
<i>AIS</i>	142 (66%)
<i>Status Epilepticus</i>	164 (76%)
<i>Meningitis</i>	143 (66%)

Table 2. Duration of fever management (numbers of respondents = 193).

DURATION OF THERAPY	
Entire ICU stay	64 (33%)
Until IH and/or CI resolution	61 (32%)
First week after ABI	41 (21%)
First two weeks after ABI	25 (13%)
First three weeks after ABI	2 (1%)

Abbreviations: ICU = intensive care unit, IH = intracranial hypertension, CI = cerebral ischemia, ABI = acute brain injury.

Appendix - 1. Survey questionnaire.

1) In which country do you practice?

2) Your primary specialty is:

- intensive care medicine
- anesthesiology
- internal medicine
- neurology
- surgery (including neurosurgery)
- other (please specify)

3) Numbers of years of practice in critical care:

- < 5
- 6 - 10
- 11 - 15
- 16 - 20
- 21 - 25
- > 25

4) The intensive care unit (ICU) where you work is a:

- specialized Neuro-ICU
- medical ICU
- surgical ICU
- cardiac ICU
- general medical-surgical ICU
- other (please specify)

5) Who is responsible for the care of patients with acute brain injury in your ICU?

- intensivist
- anesthesiologist
- neurosurgeon
- neurologist
- other (please specify)

6) What is the total number of ICU beds in your center?

7) Hospital size (number of beds):

- < 500
- 500 - 750
- 750 - 1000
- > 1000

8) Type of institution:

- university

- university affiliate
- non-university

9) What are the acute brain injuries usually treated at your ICU (allowed more than one answer)?

- traumatic brain injury (TBI)
- subarachnoid hemorrhage (SAH)
- intracerebral hemorrhage (ICH)
- acute ischemic stroke (AIS)
- status epilepticus

10) Where do you usually measure body temperature in acute brain injury patients?

- bladder
- rectum
- esophagus
- pulmonary artery
- skin
- tympanum
- other (please specify)

11) Do you measure patients' temperature in multiple sites?

- yes
- no

12) Do you measure brain temperature?

- yes
- no

13) Usually you measure body temperature:

- continuously
- intermittently

14) What's your definition of fever (in °C)?

- > 37
- > 37.5
- > 37.8
- > 38
- > 38.3
- other (please specify)

15) In general, in acute brain injury patients, what is the body temperature threshold (in °C) at which you start antipyretic therapy?

- > 37
- > 37.5
- > 37.8

- > 38
- > 38.3
- other (please specify)

16) Does your threshold differ in patients with elevated ICP?

- yes
- no

17) If the answer to the previous question was yes, what is your threshold (in °C) if ICP is elevated?

- 36
- 37
- 37.5
- < 38
- titrated to ICP control
- other (please specify)

18) Does your threshold differ in patients with cerebral ischemia? If the answer to the previous question was yes, what is your threshold (in °C) if cerebral ischemia is present?

- 36
- 37
- 37.5
- < 38
- titrated to resolution of cerebral ischemia
- other (please specify)

19) Do you consider treatment of fever in all NICU patients or only if Glasgow Coma Scale (GCS) < 9?

- all
- only if GCS < 9

20) What is your first-line method to treat fever (combination allowed)?

- physical: a) none
 - b) cold fluids
 - c) ice packs
- devices: a) none
 - b) external non-automated devices
 - c) external computerized automated devices
 - d) endovascular computerized automated devices
 - e) other
- drugs: a) none
 - b) paracetamol
 - c) diclofenac sodium
 - d) other
 - e) a combination

21) What do you use in case of persistent fever refractory to first-line methods (combination allowed)?

- physical: a) none
b) cold fluids
c) ice packs
- devices: a) none
b) external non-automated devices
c) external computerized automated devices
d) endovascular computerized automated devices
e) other
- drugs: a) none
b) paracetamol
c) diclofenac sodium
d) other
e) a combination

22) How long do you aggressively treat fever?

- first week after acute brain injury
- first two week after acute brain injury
- first three week after acute brain injury
- during ICU stay
- until intracranial hypertension and/or cerebral ischemia are resolved

23) How do you manage shivering? (more than one answer allowed)

- magnesium
- meperidine
- nefopam
- propofol
- benzodiazepines
- opiates
- muscle paralyzers
- other (please specify)

24) Do you have a written protocol for the management of fever at your ICU?

- yes
- no

25) Do you have a written protocol for the management of shivering at your ICU?

- yes
- no

26) What is your practice for patients' rewarming?

- active rewarming (> 0.5 °C/h) to predefined temperature target
- controlled rewarming (0.1 - 0.4 °C/h) to predefined temperature target
- controlled rewarming (0.1 - 0.4 °C/h) titrated to ICP
- no specific recommendations

Figure - S1. Numbers of respondents in relation to completed items.

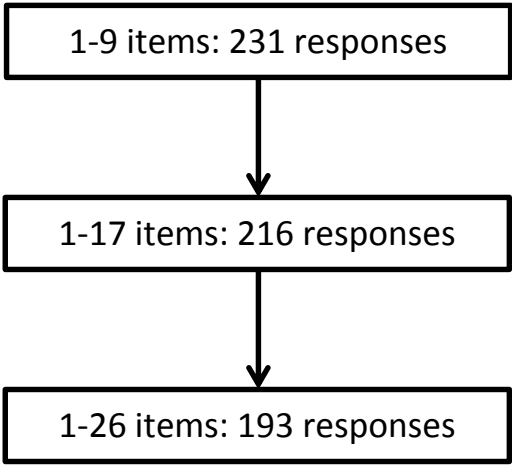
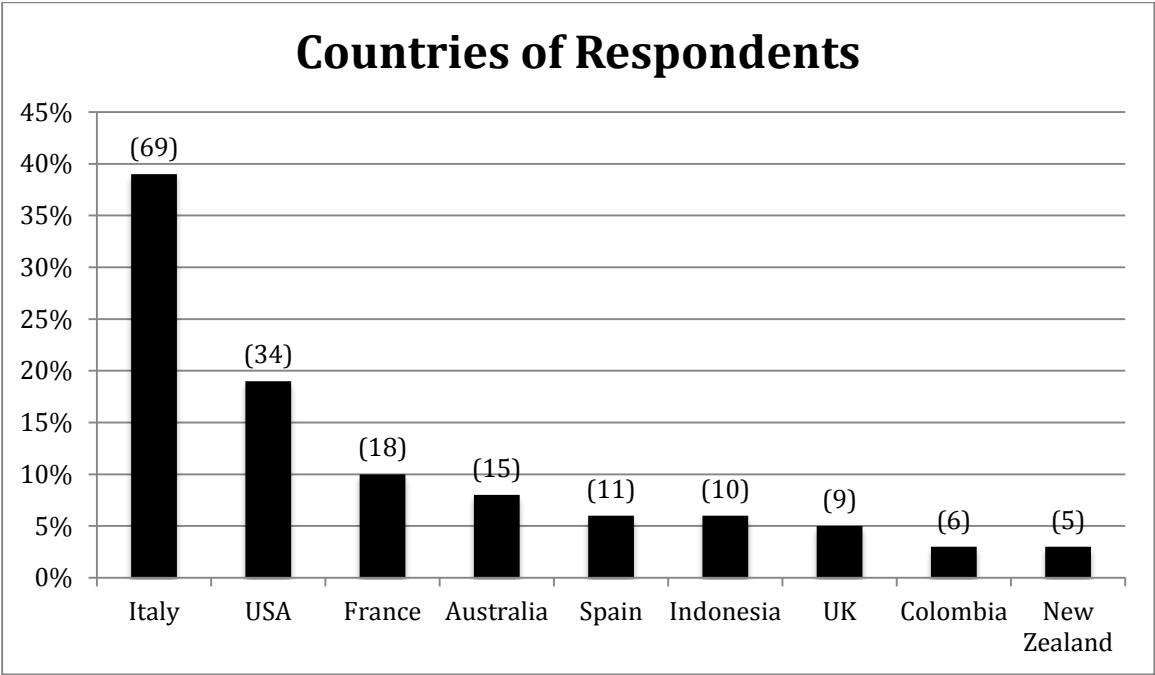


Figure - S2. Number of respondents per country. Only countries with a number of responses > 4 have been included.



Abbreviations: USA = United States of America, UK = United Kingdom.
The number of respondents is shown in brackets.

Table - S1. Drugs for shivering management.

DRUGs	<i>n</i> (%)
- Opiates	115 (60%)
- Propofol	104 (54%)
- BDZs	99 (51%)
- NMBA _s	96 (50%)
- Magnesium	50 (26%)
- Meperidine	50 (26%)
- Nefopam	9 (5%)
- Others*	14 (7%)

Abbreviations: *n* = number, BDZ = benzodiazepine, NMBA = neuromuscular blocking agent.

* Alpha-2- agonists: 11 (6%) respondents.

Table - S2. Practices for patients’ rewarming.

TYPE of REWARMING	<i>n</i> (%)
- Controlled (0,1-0,4 °C/h) to predefined temperature target	75 (39%)
- Active (> 0.5 °C/h) to predefined temperature target	11 (6%)
- Controlled (0,1-0,4 °C/h) titrated to ICP	55 (28%)
- No specific recommendations	52 (27%)

Abbreviations: *n* = number, h = hour, ICP = intracranial pressure.

Table S-3: Comparisons between European (EU) vs. non-European (Non-EU) centers and between specialized neuro-intensive care unit (NICU) vs. non-specialized NICUs (“Others”).

	Non-Eu	Eu	P	Other ICUs	NICU	P
Definition of fever						
>37.0	4(5)	11(9)	0.06	11(8)	4(6)	0.02
>37.5	18(21)	20(16)		28(19)	10(14)	
>37,8	10(11)	21(16)		27(19)	4(6)	
>38.0	21(24)	35(27)		37(25.7)	19(26)	
>38.3	30(34)	41(32)		38(26.4)	33(46)	
Other	5(6)	0(0)		3(2.1)	2(3)	
Threshold for therapy						
37.0	3(3)	11(9)	0.36	11(8)	3(4)	0.07
37.5	30(34)	45(35)		57(40)	18(25)	
38.0	40(46)	46(36)		49(34)	37(51)	
38.3	12(14)	23(18)		22(15)	13(18)	
Other	3(3)	3(2)		5(4)	1(1)	
Adjusted threshold for ICP						
No	38(43)	36(28)	0.02	52(36)	22(31)	0.42
Yes	50(57)	92(712)		92(64)	50(69)	
New threshold for ICP						
36.0	4(9)	7(8)	0.09	7(9)	4(8)	0.87
37.0	11(24)	33(39)		30(37)	14(29)	
37.5	15(33)	16(19)		19(23)	12(25)	
<38.0	6(13)	4(5)		5(6)	5(10)	
To control ICP	9(20)	25(29)		21(26)	13(27)	
Adjusted threshold for ischemia						
No	24(32)	34(29)	0.71	33(26)	25(37)	0.11
Yes	52(68)	83(71)		93(74)	42(63)	
New treshold for ischemia						
36.0	2(4)	5(6)	0.18	5(5)	2(5)	0.72
37.0	9(17)	27(33)		26(28)	10(24)	
37.5	20(39)	20(24)		28(30)	12(29)	
<38.0	14(27)	24(29)		23(25)	15(36)	
To control Isch	7(14)	7(8)		11(12)	3(7)	

		Non-Eu	Eu	P	Others ICU	NICU	P
First-line method to treat fever							
Physical	Fluid	10(13)	29(25)	0.12	29(23)	10(15)	0.01
	Ice	40(53)	50(43)		67(53)	23(34)	
	None	26(34)	38(33)		30(23)	34(51)	
Device	EV	2(3)	8(7)	0.16	8(7)	2(3)	0.24
	EA	19(26)	20(17)		28(23)	11(16)	
	EnA	22(30)	27(23)		34(27)	15(22)	
	None	31(42)	62(53)		54(44)	39(58)	
Drugs	DCF	1(1)	9(8)	0.03	8(6)	2(3)	0.04
	PCM	52(68)	83(71)		84(67)	51(76)	
	Combination	9(12)	12(10)		18(14)	3(5)	
	None	8(11)	12(10)		14(11)	6(9)	
	Other	6(8)	1(1)		2(2)	5(8)	
Second-line method to treat fever							
Physical	Fluid	28(37)	40(34)	0.93	48(38)	20(30)	0.02
	Ice	26(34)	41(35)		49(39)	18(27)	
	None	22(29)	36(31)		29(23)	29(43)	
Device	EV	12(16)	27(23)	0.06	23(19)	16(24)	0.75
	EA	35(48)	40(34)		49(40)	26(39)	
	EnA	18(25)	23(20)		29(23)	12(18)	
	None	8(11)	27(23)		23(19)	12(18)	
Drugs	DCF	8(11)	54(46)	<0.01	45(36)	17(26)	0.58
	PCM	22(29)	12(10)		21(17)	13(19)	
	Combination	24(32)	25(21)		32(26)	17(25)	
	None	12(16)	15(13)		15(12)	12(18)	
	Other	10(13)	11(9)		13(10)	8(12)	
How do you aggressively treat fever							
	1 week	19(25)	22(19)	0.18	22(18)	19(28)	0.22
	2 weeks	10(13)	15(13)		19(15)	6(9)	
	3 weeks	0(0)	2(2)		2(2)	0(0)	
	ICP recovery	18(24)	43(37)		42(33)	19(28)	
	ICU stay	29(38)	35(30)		41(33)	23(34)	

Legend – number (percentage); EU = european country; Non-Eu = non-european country; ICU = intensive care unit; NICU = neuroICU; ICP = intracranial pressure; EV = endovascular computerized automated devices; EA = external computerized automated devices; EnA = external non-automated devices; DCF = Diclofenac; PCM = Paracetamol.