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Interchangeability and Diagnostic Accuracy of Digital and Infrared Thermometers in Paediatric Settings: An Alternative to the Mercury-in-Glass Thermometer

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To my Family

Gazi, Rois & Deon

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Summary

Body temperature (BT) measurement is considered part of the initial health assessment in children in hospitals, since it can lead to a correct diagnosis and an appropriate therapeutic approach. Therefore, it is crucial that the device used to measure BT should be valid and reliable. Although the glass mercury thermometer (GMT) has historically been considered the 'gold standard', a current global trend to replace it with modern alternative devices can be observed, due to the alarm raised by the Minamata Convention (MC) on mercury hazards. Considering that, in Albania, the axillary glass mercury (AXL_{MER}) thermometer is still available, we compared it to the alternative thermometers. This allowed us to significantly contribute to the international debate on the validity and reliability of the modern clinical devices and fill the gaps in evidence-based practice. The availability of high-quality research to confirm the validity and reliability of alternative devices is needed to reduce the risk of misdiagnosis, unnecessary treatments and omission of nursing care in the paediatric population. In fact, alternative devices have been introduced in clinical practice due to their convenience and acceptability to patients, especially in the paediatric setting.

This study aimed at documenting the interchangeability and accuracy of modern alternative devices such as the digital axillary (AXL_{DGT}), infrared tympanic (TYM_{IR}), and non-contact infrared forehead (FHD_{IR}) thermometers compared to the AXL_{MER}. A comparative observational study was conducted in a fifty-bed paediatric ward of a general hospital in Albania from September 2018 to January 2019. The study included all the 356 hospitalized children aged up to 14 years. Twice a day, morning and afternoon, the body temperature of each child was measured, making a total of 711 measurements. We hypothesized that all alternative devices were

interchangeable with the AXL_{MER} thermometer and diagnostically accurate in detecting fever in the paediatric setting.

BT values detected with alternative devices showed a significant moderate ($p<0.001$) to strong bivariate correlation ($p<0.01$) with the 'gold standard' (AXL_{MER}). Our results showed that the AXL_{DGT} thermometer is the best alternative to the AXL_{MER} in paediatric clinical settings. AXL_{DGT} also showed a better performance in detecting fever than the 'gold standard'. In accordance with the not significant clinical differences, TYM_{IR} and FHD_{IR} should be used taking in consideration the clinical picture of the paediatric patient. Our hypothesis is fully confirmed in relation to the AXL_{DGT}.

Abbreviations

BT	Body Temperature
CBT	Core Body Temperature
SBT	Skin Body Temperature
HCW	Healthcare Worker
GMT	Glass Mercury Thermometer
AXL_{MER}	Axillary Glass Mercury Thermometer
AXL_{DGT}	Axillary Digital Thermometer
TYM_{IR}	Infrared Tympanic Thermometer
FHD_{IR}	Forehead Non-Contact Infrared Thermometer
°F	Degree Fahrenheit
°C	Degree Celsius
FT	Forehead Temperature
TT	Tympanic Temperature
AT	Axillary Temperature
RT	Rectal Temperature
FUO	Fever with Unknown Origin
SBI	Serious Bacterial Infection
NICE	National Institute of Health and Care Excellence
UK	United Kingdom
MC	Minamata Convention
WHO	World Health Organization
UNEP	United Nations Environment Programme

Introduction and Background

Body temperature (BT) measurement is one of the most common procedures performed in the paediatric clinical routine. Although normal BT varies in individuals due to some variables, normothermia is established to be equal to 36.8 °C (Geneva, Cuzzo, Fazili, & Javaid, 2019). In case of influence from external (Adams, Fox, Fry, & MacDonald, 1975) and/or biological factors (circadian rhythm, metabolism, hormones) (Hall, 2015), the human body is capable of maintaining constant BT through thermoregulation.

NICE recommends BT measurement as part of initial assessments in adults and children (Davis, 2013). Usually, BT values are important for clinical decisions, especially as regards orienting the physicians towards specific diagnoses (Call, Vollenweider, Hornung, Simel, & McKinney, 2005; Coburn, Morris, Tomlinson, & Detsky, 2012; Eskin & Levy, 2007; Shaw & Gorelick, 2000; Taniguchi, Tsuha, Takayama, & Shiiki, 2013) contributing to a set, making differential diagnosis, determining the prognosis (DePorre, Aronson, & McCulloh, 2017; El-Radhi, Carroll, & Klein, 2009; Mohamed & Ali, 2012), which is the determining factor for treatment (Bartlett, 1996; McCallum & Higgins, 2012), or even detecting whether a person is healthy or not (Kluger, Kozak, Conn, Leon, & Soszynski, 1998; Sessler, 2008; Sund-Levander & Grodzinsky, 2013). However, for the HCW, it is important to pay attention to the full clinical picture, taking numerous factors into consideration, and not just focus on BT level. An inaccurate measurement or misinterpretation of BT values could lead to a wrong diagnosis and, therefore, to a wrong treatment (Hernandez & Upadhye, 2016) exposing patients to a real risk of damage.

Also, clinical decisions and prognoses seem to be affected by a misunderstanding of the definition and threshold of fever (fever phobia) among parents/caregivers and HCW (Anochie, 2013; Figueroa, Forero, León, Londoño, & Echandía, 2012), which may lead to erroneous management and inappropriate use of antipyretics; or the use of an unreliable device, which could lead to erroneous diagnoses and inappropriate treatments.

Historically, GMT has been considered the 'gold standard' for BT measurement (Chiappini et al., 2011). However, considering the alarm raised by the Minamata Convention on mercury hazards (Kessler, 2013), it is currently being replaced by alternative modern devices. Actually, the accuracy of the alternative devices is a matter of the biggest concern to many researchers and HCW, considering the transition period in which health facilities face this issue. Although infrared and electronic thermometers are the most commonly used alternative devices in clinical practice, some doubts regarding their reliability still remain (Dodd, Lancaster, Craig, Smyth, & Williamson, 2006; Niven et al., 2015; Park, Park & Kang, 2013). As BT value represents the primary indicator of diagnosis, treatment, and sometimes prognosis, its measurement should be accurate. Therefore, the thermometer should reflect the core temperature and be reliable, easy to use, safe, hygienic, and noninvasive.

CHAPTER 1

GENERAL ASPECTS OF BODY TEMPERATURE

1.1 What Is Body Temperature? Definition, Clinical Significance, Normal and Abnormal Values

Body temperature is the balance between the heat production and the energy consumption (Hall, 2015) of an organism, determined by physio-pathological processes occurring in the organism. In most cases, a rise in BT is as a result of pyrogenic effect and comes in form of a possible infection (van Laar & Cohen, 2003). Core BT (brain and thorax) is usually 2 to 4 °Celsius (°C) higher than peripheral BT (skin and subcutaneous temperature) (Bindu, Bindra, & Rath, 2017). Usually, in a healthy person, internal BT is constant during the day with only slight changes related to the circadian rhythm and to some internal and external factors (Kelly, 2006). Even though a normal BT does not indicate a 'fully health person', it is obvious that its increase or decrease indicates a disorder in the thermoregulatory system. Measuring and evaluating BT values are clinically significant, especially in cases of absence of infectious etiology or drugs causes, because BT changes may be the consequence of a damage of the thermoregulatory center (Hocker et al., 2013; Young et al., 1988; Zawadzka, Szmuda, & Mazurkiewicz-Beldzinska, 2017).

In cases of suspicion of inaccurate measurement, especially when the measurement does not match the clinical symptoms, repeating it should be considered (Childs, 2018). The invariability of BT values in healthy people and their variations in cases of disease were the main factors that, in the last two decades, have led scientists to conduct deeper studies to understand the clinical significance of the variability of BT values in humans.

Historically, the importance of BT as a sign of acute disease was recognized by Hippocrates (Pappas, Kiriaze, & Falagas, 2008). Antoine Cesar Becquerel and Gilbert Breschet in 1835 for the first time established that the mean BT value of a healthy adult was 37.0 °C/98.6 °F. More than one century later, Das Verholten der Eigemvarme enhanced the special clinical significance of BT in medicine (Haller, 1985). Even though the 'set point' of core BT was defined as 37.0 °C/98.6 °F, normal BT should be considered in the context of a 'scale' and not a 'constant degree'. The 'set point' temperature is the estimated reference temperature, which cannot be measured directly but only deduced with respect to the BT, according to the presence and direction of thermoregulatory responses (Briese, 1998).

In 1868, Carl Reinhold August Wunderlich, using a large sample, conducted the first study on BT and thermoregulation. He established a range of normal BT from 97.2 °F/36.2 °C to 99.5 °F/37.5 °C (Table 1), measured with an axillary mercury thermometer, and 100.4 °F/38.0 °C as the upper limit of the normal range (Mackowiak, Wasserman, & Levine, 1992). Even though his research was developed nearly two centuries ago, it remains a reference point for many authors. However, recently, this range has encountered some contradictions, perhaps because studies on BT have been conducted using modern clinical thermometers. In this regard, some authors do not agree with this range because they conclude that BT values vary based on the measurement site (Geneva et al., 2019) (Table 2), the type of thermometer used (Blatteis, 2012; Childs, 2018; Lu & Dai, 2009; Sund-Levander, Forsberg, & Wahren, 2002), the gender, the race, and the age (Geneva et al., 2019; Hancock & Hancock, 2014; Keil, Cummings, & de Magalhães, 2015).

Table 1. The normal and abnormal ranges of BT (Mackowiak et al., 1992)

Term		Range of BT in °C=°F
Collapse BT	Moderate collapse	35.0 °C- 36.0 °C = 95.0 °F-96.8 °F
	Deep, fatal algid collapse BT	33.5 °C = 92.1 °F
	Algid collapse with great danger	33.5 °C-35.0 °C = 92.3 °F-95.0 °F
Normal BT	Subnormal BT	36.0°C- 36.5°C = 96.8° F-97.7° F
	Really Normal	36.6 °C-37.4 °C = 97.0 °F- 99.1 °F
	The Norm	37.0 °C = 98.6 °F
	Sub-febrile temperatures	37.5 °C-38.0 °C = 99.5 °C-100.4 °F
Febrile BT	Slight febrile action	38.0 °C- 38.4 °C = 100.4 °F-101.1 °F
	Moderate fever	38.5 °C-39.5 °C = 101.3 °F-103.1 °F
	Considerable fever	39.5 °C-40.0 °C = 103.1 °F-104.0 °F
	High fever	39.5 °C-40.5 °C = 103.1 °F-104.9 °F
	Hyperpyretic temperatures	42.0 °C = 107.6 °F

Factors such as circadian rhythm, exercise, food intake, infection, thyroid dysfunction, menstrual cycle, and anesthetics drugs are known to alter temperature thresholds (Childs, 2018; Kelly, 2006; Sessler, 1997; Sund-Levander & Grodzinsky, 2009). Sund-Levander and her colleague showed that BT should be evaluated according to the individual variability, and that the best approach is to use the same site without adjustment to other sites. In order to avoid misinterpretations, it is important that the normal BT definition should be the same both at home and hospital (Davis, 2013).

Among HCW, nurses should have a basic understanding of the BT mechanisms and its effects on human body, because the measurement and evaluation of vital signs like BT are key to providing structured and adequate nursing care. In this regard, nurses should use their professional skills based on scientific knowledge and evidence-based experience in assessment, diagnosis, planning, implementation of actions of interventions, and evaluating outcomes (Hogston, 2011; Mohamed & Ali, 2012).

Recent evidence show that BT also has some impact on ageing and longevity, especially in healthy older men and women, perhaps as a consequence of neuroendocrine mechanisms in response to low temperature, particularly when challenged by environmental thermal extremes (Blatteis, 2012; Keil et al., 2015).

Table 2. Normal BT ranges according to Canadian Paediatric Society (Leduc & Woods, 2017)

Site	Normal temperature range
Ear	35.5 °C to 37.5 °C (95.9 °F to 99.5 °F)
Oral	35.5 °C to 37.5 °C (95.9 °F to 99.5 °F)
Axillary	34.7 °C to 37.3 °C (94.5 °F to 99.1 °F)
Rectal	36.6 °C to 38.0 °C (97.9 °F to 100.4 °F)

1.2 Thermoregulation

As a homeotherm, the ability of the human organism (warm-blooded body) to maintain a constant core BT (Szelényi & Komoly, 2019) is called 'homeostatic regulation'. The word, 'homeostasis', originates from the Greek words, 'homoios' (meaning 'same' or 'like') and 'stasis '(meaning 'to stand'), and in a general sense refers to stability, balance or equilibrium. Homeostasis is defined as the process by which an organism is able to maintain an unchanged immune-independent physiological environment, regardless of the external environment (Davies, 2016; Osilla & Sharma, 2019). Ivanov (2006) described a range of 36.0 to 42.0 ^{o}C BTs in homeotherms.

The capability of maintaining a constant BT is called thermoregulation, which is a physiologically complex, integrative, and ultimately autonomic phenomenon

(Charkoudian & Stachenfeld, 2016). Normally, BT fluctuates throughout the 24 hours of a day, lower in the early morning (04:00 and 06:00) and higher in the afternoon (16:00 and 18:00) (Krauchi, 2002). Temperature regulating centers are located in the hypothalamic preoptic area, which is the main body regulatory thermostat. This area responds to temperature changes by nervous feedback mechanisms, using the heat-sensitive neurons and cold-sensitive neurons; it stimulates the nervous system, the circulatory system, the skin, the sweat glands, and induces shivering mechanisms to maintain homeostasis. BT disruptive mechanisms, which can lead to excessive production or loss of heat, trigger the nervous system to balance these interchanges (Fig. 1). A signal is given, through the detectors which recognize the deviation, to the integrative center that gives an order to stimulate or inhibit an activity in order to establish the normal state (Hall, 2015). The skin, the respiratory system, the digestive and excretory system, the nervous system, and the skeletal muscles are put in motion to maintain the BT within its normal limits. The thermoregulatory mechanisms are under the influence of many factors such as metabolism, hormones, physical activity, 24-hour rhythm, and environmental conditions. These factors operate in dynamic equilibrium, which means that the core temperature does not change when the output energy remains constant. When the environmental conditions (air temperature, humidity, air motion, solar radiant heat energy) change significantly, the balance between production and loss of heat breaks and BT begins to change. All homeotherms manifest different forms of biological rhythm in 24 hours; this is called circadian rhythm (Te Lindert & Van Someren, 2018). During the light hours, the intraperitoneal temperature is from 35.6 to 36.0 °C and during the dark hours from 37.8 to 38.0 °C, with a difference of about 2 °C (Briese, 1998). Circadian temperature rhythm creates a preliminary response to environmental changes that occur due to the darkness cycle which pervades the calmness-activity state. Alteration in lifestyle such as changes in diet, sleep habits,

light exposure, and environmental factors can change rhythmic aspects of BT. According to Tansey & Johnson (2015), a person in a state of calmness, wearing a suitable outfit inside a room with a temperature of 20 °C temperature and normal moisture, has an internal temperature of approximately 37.0 °C, with variations of ± 0.8 °C during the day. Increasing temperature over the norm would cause unrecoverable disorders in the central nervous system (Zawadzka et al., 2017), and also in the denaturing of proteins (Morrison, 2016), so the thermoregulatory center in the hypothalamus promotes the very accurate mechanisms that regulate BT. If the nervous system is damaged, the BT will rise or fall depending on the affected area and the amount of blood in the vessels that feed it. Production and loss of heat are constantly reversed by metabolic changes. Under calm conditions, the metabolism of a healthy person can be measured simply by measuring the amount of heat produced by the body. Increasing the rate of metabolism will result in an increase in the internal temperature, and for every 1 °C temperature increase, the metabolic rate increases by ∼13% (Schieber & Ayres, 2016), hence any factor that increases the rate of metabolism will increase temperature and vice versa. For instance, after consumption of food, mainly carbohydrates, fats or proteins, metabolism levels increase as a result of the increased rate of chemical reactions to the distribution of the nutrients, resulting in increased heat production and consequently in BT rise. Indeed, obese subjects who exercise in a hot environment show a greater increase of the rectal temperature and heart rate rather than do lean subjects (Bar-Or, Lundegren, & Buskirk, 1969).

During an increased physical activity, the maximum muscle contraction will increase the heat production to about 50 times more than in an inactive state. Therefore, in cold conditions the body reacts with shivering (Van Someren, Raymann, Scherder, Daanen, & Swaab, 2002), increasing the amount of heat

produced to cope with exposure to this cold temperature of the environment. The contrary occurs in cases of exposure to high environmental temperatures, where the body responds with a decrease in skeletal muscular excitement and sweating (Cheuvront et al., 2009), but the amount of heat lost in this case is negligible. Thyroid and sexual hormones, leptin, epinephrine, norepinephrine, and cytokines are hormones which contribute to regulating the BT.

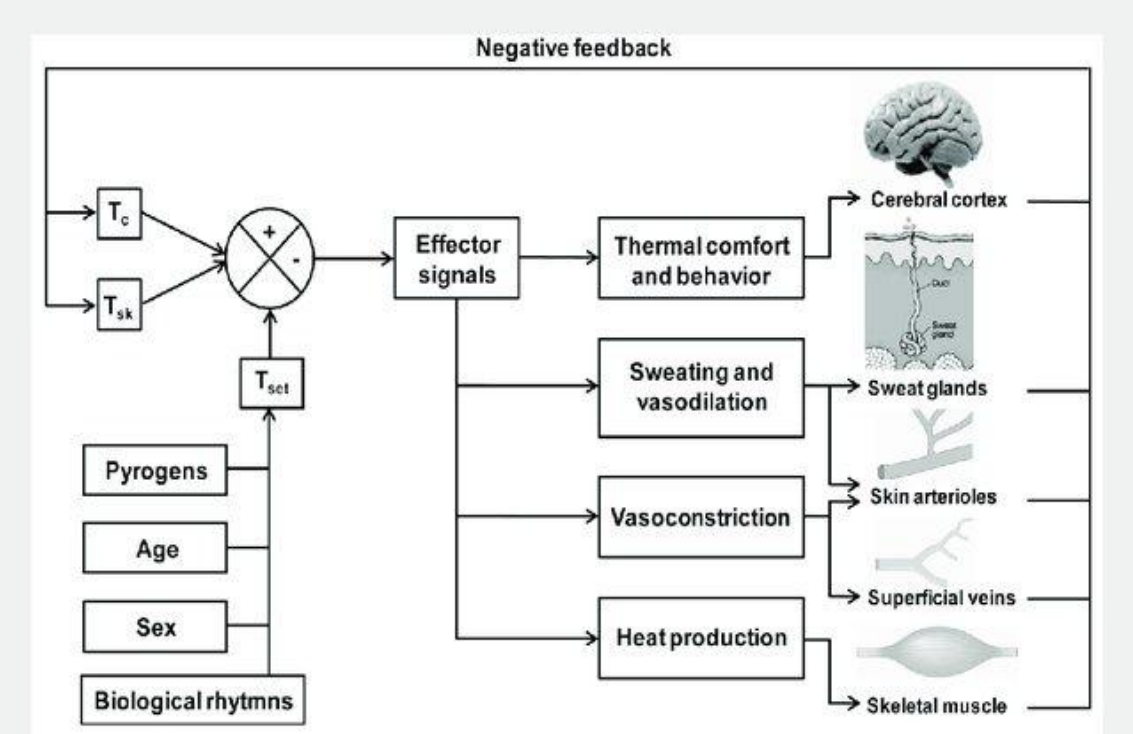

Fig.1 Negative feedback in Thermoregulation (Eijsvogels, 2019)

1.2.1 Temperature-increasing mechanisms when the body is too cold

The body loses heat through radiation, conduction, convection and evaporation (respiration and sweating) (Kuht & Farmery, 2018). Vasoconstriction of skin blood vessels occurs due to the stimulation of the posterior hypothalamic sympathetic centre's which strongly inhibit vasodilation. These fluctuations are captured by the skin thermoreceptors that transmit information to the hypothalamus which controls the production and loss of heat through effectors. The thermoreceptors are able to catch the signals that change the peripheral BT and the central ones which can be found in the hypothalamus, the spinal cord, and the internal abdominal and thoracic organs. If heat loss continues, the only process that helps to compensate this loss is chemical reaction that responds to muscular contraction. Under cold conditions, the body responds with a gradual increase in muscular contraction until the point of shivering, whereas the hypothalamus sends impulses to motoneurons in the nervous skeletal muscle. When shivering is most intense, body heat production can rise by 4-5 times, normally increasing the tone of the skeletal muscles throughout the body by facilitating the activity of the anterior motor neurons. Another mechanism that can produce heat in response to cold stress is non-shivering thermogenesis. This type of thermogenesis is stimulated by the activation of the sympathetic nervous system, which releases norepinephrine and epinephrine that can increase the metabolic activity and heat generation (Hall, 2015).

Physiological mechanisms that can help regulate temperature in case of heat loss through radiation and conduction are covering of exposed body parts in appropriate clothing and being in a clement environment. Skin loses heat directly when exposed to an outside environment, therefore covering the body reduces the surface exposed to the environment. Clothing provides insulation and protection for the body surface from very high or low temperatures, for example white outfits are more appropriate

in hot conditions because they reflect radiant energy. In situations where the organism cannot respond to changes in ambient temperature, it tries to adapt through acclimatization, which is a reversible process whereby the organism returns to the normal state as soon as the ambient temperature is normalized. Personal behavioral mechanisms include curling up, rubbing hands and body, finding shelter and putting on more clothes, all of which represent important ways of adapting to changes in BT.

1.2.2 Temperature-decreasing mechanisms when the body is too hot

When the thermoregulation centre in the hypothalamus detects a rise in BT, it starts to stimulate all physiological mechanisms to bring back the system towards the 'set point' (~37.0 °C) determined by the hypothalamus through neural feedback mechanism. For example, the organism feels convulsions, in response to a temperature which is above 40.0 °C. When BT increases, vasodilation of skin blood vessels occurs because of the restraining of the sympathetic center in the posterior hypothalamus which stimulates vasoconstriction. Full vasodilation can increase the rate of heat transferred to the skin approximately eightfold (Rowell, 1983; Tansey & Johnson, 2015).

Evaporation is a physiological mechanism through which the body loses heat. Sweating represents a form of evaporation through which the person loses up to 10 times of the extra °C gained (Cheuvront & Kenefick, 2017). Indeed, sweating can dissipate about 600 kcal per hour (Bouchama & Knochel, 2002). When it's hot outside, the human mucus feels dry; they blush all over the face and there is an increase in their respiratory and pulse rate. Behavioral mechanisms are also important when it comes to regulating BT. Consuming cold liquids, having a bath

with tepid or cold water (swimming in pools or in the sea), looking for fresh shelter are usually the most useful behavioral personal mechanisms against heat.

1.3 Abnormal Body Temperature

1.3.1 Hyperthermia

There is need to distinguish between fever and hyperthermia, two conditions that cause BT increase. They often get confused but in fact they change secondary to the systemic inflammatory response because their biological response and mechanisms are different (Briese, 1998; Cheshire, 2016; Doyle & Schortgen, 2016; Santelli, Sullivan, Czarnik, & Bedolla, 2014). In contrast to fever, the core BT in hyperthermia can exceed 40.0 °C (104.0 °F) as a result of malfunction in the mechanisms modulating peripheral heat production and loss (Beard & Day, 2008; Bouchama & Knochel, 2002; Kuht & Farmery, 2018). Clinically, these thresholds are important, even if they seem similar as 'elevated BT', because they come in different forms, i.e. pyrogenic (fever) and non-pyrogenic (hyperthermia). Due to these differences, the two conditions will be discussed separately in this thesis.

Hyperthermia, unlike fever, is not a response to the invasion of the organism by a pyrogen but is an uncontrolled increase in peripheral heat production which the body is unable to lose it despite haemodynamic and adaptive behavioural responses when the hypothalamus set point 'remains normal' (Wasserman & Healy, 2018). It is a state of thermoregulatory failure resulting from the inability to dissipate heat at a sufficient rate, or excessive heat production with a normal rate of heat loss, not mediated by a pyrogen or Interleukin-1 (Walter & Carraretto, 2016). Hyperthermia appears as a physiological response to specific causes which may be environmental

(heatstroke) (Jones et al., 1982) or pharmacological (malignant hyperthermia) (Schneiderbanger, Johannsen, Roewer, & Schuster, 2014).

Long-term exposure to high environmental temperatures and the production of large amounts of heat lead to an increase in the internal BT which can be dangerous. In fact, more than 371 deaths from 1979 to 1997 in the USA were attributable to 'excessive heat exposure' (Jones et al., 1982). Also, simple dehydration, intoxication (Simon, 1993), drug abuse (El-Radhi, 2009), and alcohol abuse (Epstein, Moran, Shapiro, Sohar, & Shemer, 1999; Mozzini, Xotta, Garbin, Pasini, & Cominacini, 2017) appear to be some of the common causes of hyperthermia. Old age, chronic illness, poor mental health, alcohol intake, previous history of hyperthermia (Wasserman & Healy, 2018), poor acclimatization, poor cardiovascular conditioning, wearing heavy clothing, and excessive exertion (Simon, 1993) are some risk factors of hyperthermia. In order to give the correct diagnosis, HCWs are usually guided by previous clinical history (O'Connor, 2017), by central nervous system dysfunction (altered mental state, disorientation, stupor, seizures, or coma) and by the body's response to antipyretic treatment (Simon, 1993) since hyperthermia does not respond to antipyretics.

The accompanying symptoms of hyperthermia are orthostatic hypotension, hyperventilation, tachycardia, diaphoresis, fatigue, dizziness, headache, and paresthesia, and then weakness, muscle cramps, oliguria, nausea, agitation, syncope, confusion, delirium, seizures, and coma (Cheshire, 2016; Simon, 1993; Wasserman & Healy, 2018).

Patients also show symptoms of neurological dysfunction, including cognitive dysfunction, agitation, seizures, unsteadiness, or disturbance of consciousness from lethargy to coma (Walter & Carraretto, 2016). The longer the hyperthermia, the higher the risk of being deadly, particularly in those with malignant hyperthermia

(Britt & Kalow, 1970). Often, it may be deadly even if there is timely intervention, perhaps due to irreparable neurologic damage which is associated with high mortality (20 % of the patients) (Dematte et al., 1998). The death from heatstroke happens at 42 °C (107.6 °F), which indicates a 'fatal termination' (Kuht & Farmery, 2018; Mackowiak et al., 1992). It is not clear which is the major risk factor to which this 'fatal termination' is attributed, but it is evident how early it is suspected and the appropriate treatment is initiated, the better the prognosis will be (Schneiderbanger et al., 2014). Patients affected by hyperthermia should also be monitored for signs of encephalopathy, rhabdomyolysis, acute renal failure, acute respiratory distress syndrome, myocardial injury, hepatocellular injury, intestinal ischemia or infarction, and/or pancreatic injury, especially hemorrhagic complications, because these kinds of patients may be at risk of being affected by disseminated intravascular coagulation (Kenny, Yardley, Brown, Sigal, & Jay) as the most serious complications of hyperthermia (al-Mashhadani et al., 1994; Bouchama & P Knochel, 2002).

In addition to having these harmful effects in the organism, hyperthermia has been shown to be beneficial, but as 'induced' hyperthermia. It has found extensive use as a technique in the treatment of tumours in chemotherapy and radiotherapy, whereby the patient is exposed to very high temperatures in order to enhance immunogenicity against tumour cells and reduce malignant cellular function for better clinical outcome for a certain time (Chang et al., 2018; S. Lee et al., 2018).

1.3.2 Hypothermia

As heat loss occurs more rapidly than the amount of heat produced, the BT decreases below the normal level. Hypothermia is defined as a core temperature < 35°C (Brown, Brugger, Boyd, & Paal, 2012; Faulds & Meekings, 2013; Mehrotra & Misir, 2018). Until the 1980s, the 'lethal triad' hypothermia, acidosis and coagulopathy, was considered the main cause of mortality in critical trauma patients (Avellanas et al., 2012). Also, in the United States, there are on average more than 1300 deaths per year from hypothermia, which is approximately twice the number of deaths annually from exposure to heat (Meiman, Anderson, Tomasallo, 2015). The body begins to respond to hypothermia with shivering, which at a later and more severe stage of the hypothermia becomes uncontrollable. The patient may present respiratory depression, cardiac dysrhythmias, impaired mental function, mydriasis, hypotension, and muscle dysfunction, which can progress to cardiac arrest or coma (Cheshire, 2016). Classical hypothermia is classified into mild (35.0 °C–32.0 °C), moderate (32.0 °C–28.0 °C), and severe or deep hypothermia (< 28.0 °C) (Table 3) (Brown et al., 2012; Cheshire, 2016). Etiologically, it can be classified into acute, subacute and subchronic hypothermia (Avellanas et al., 2012). If the core BT is difficult to measure, hypothermia can be classified according to the clinical Swiss staging system which distinguishes the different stages clinically on the basis of vital signs. The five stages of hypothermia according to this system are: stage I – clear consciousness and shivering; stage II – impaired consciousness without shivering; stage III – unconsciousness; stage IV – apparent death; and stage V – death due to irreversible hypothermia (Deslarzes, Rousson, Yersin, Durrer, & Pasquier, 2016). This guide helps HCW in the early detection of hypothermia symptoms. In mild hypothermia, the patient presents symptoms like vigorous shivering, lethargy, apathy, impairment of motor skills, extreme cold, polyuria, pallor, tachypnea, and

tachycardia, while in moderate stage the patient suffers from respiratory and pulse depression, slurred speech, further impairment of mental function, paradoxical undressing, gross impairment of motor control, cessation of shivering, cyanosis, muscle rigidity, mydriasis, atrial or ventricular cardiac dysrhythmias, bradycardia, decreased blood pressure, hypoventilation, hyporeflexia, and loss of consciousness (Brown, Brugger, Boyd, & Paal, 2012; Kuht & Farmery, 2018). In severe hypothermia vital signs are absent; hypotension, pulmonary congestion and edema, muscle rigidity, areflexia, oliguria, spontaneous ventricular fibrillation, cardiac arrest, and coma are manifested (Durrer, Brugger & Syme, 2003). Death comes from ventricular tachycardia at 28.0 °C (Kuht & Farmery, 2018). It is also found that Cold Injury Syndrome (CIS) is most common in newborn babies, which results in multi-organ dysfunction, including decreased tissue oxygenation, circulatory collapse, hepatic and renal failure, dehydration, and DIC (Mehrotra & Misir, 2018). Alcohol, drug ingestion, extremes of age or co-morbid illness, and multiple traumas or central nervous system trauma are the likely risk factors of hypothermia (Brown et al., 2012; Daulatzai, 2010; Ruhland, Ameli, & Binder, 2016). Hypothermia can be caused by exposure to cold environment and the inability of the body to initiate behavioral responses, but also by pharmacological stimuli (Díaz & Becker, 2010). People ill with a wide variety of medical conditions – like neurologic disorders and endocrine disorders such as hypothyroidism, hypoglycemia, and adrenal insufficiency, all of which impair metabolic thermogenesis (Brown et al., 2012; Cheshire, 2016) – are at high risk of suffering from hypothermia. Major consequences of inadvertent hypothermia include morbid myocardial events, reduced resistance to surgical wound infection, impaired coagulation, delayed recovery, and postoperative shivering (Díaz & Becker, 2010). A variety of endocrinological conditions may also cause decreased heat production, for example hypopituitarism, hypoadrenalism, and hypothyroidism (Faulds & Meekings, 2013).

Table 3. Classification of Hypothermia (Cheshire, 2016)

Term	Range of hyperthermia °C
Mild Hypothermia	35.0 °C–32.0 °C
Moderate Hypothermia	32.0 °C–28.0 °C
Deep Hypothermia	< 28.0 °C

Hypothermia show similar trends in both children and adults. Newborn babies, children, elderly patients and patients recovering from anesthesia are at high risk of being affected by hypothermia from physiological and cognitive factors (Childs, 2018; Shah & Madhok, 2019). For several reasons, children are more prone to hypothermia than adults. Their thermoregulatory mechanisms are still not fully developed, notably their behavioral mechanisms, despite having large amounts of brown adipose tissue compared to adults. They also have the ability to generate more metabolic heat than adults, so they tend to be more affected by hypothermia than adults (Falk, 1998). Elderly people also are at increased risk due to their decreased physiological reserve, higher vulnerability to chronic disease and higher chances of having taken medications that may impair compensatory responses (Paal et al., 2016).

In addition, despite these harmful effects on the body, the literature clearly shows that ‘induced’ hypothermia has been found to be neuroprotective, with a significant impact on mortality and long-term functional outcome in cardiac arrest, stroke, traumatic brain or spinal cord injury, and neonatal hypoxic-ischemic encephalopathy (Holzer & Sterz, 2002; Smith & Bleck, 2002).

In fact, the benefit of hypothermia in central nervous system injuries has been reported a long time ago, since Hippocrates recommended using ice as treatment for fever in suspected cerebral haemorrhages (Song & Lyden, 2012).

1.4 Fever

Fever, also known as pyrexia, has been a concern to HCW for decades. 'Fever' comes from the Latin words 'febris' and 'pyrexia' and from the Greek word 'pyr' which means 'fire'. It has been considered an illness for a long time, until the Wunderlich's study (1868), in which a new definition of fever was established as 'a sign of a disease'. Surely, it is supposed that this new understanding of fever will help in the diagnosis, in describing proper treatments, but also lead to better prognoses, especially of many infectious diseases, such as upper respiratory tract infection, pneumonia, otitis, meningitis, malaria, dysentery and even diarrhea, in which fever can be indicative of ongoing clinical decisions, especially in paediatric settings (El-Radhi & Barry, 2006).

In 1961, Petersdorf and Beeson recognized a new type of fever of unknown origin (FUO), present for one week or more in the patient as 'a state of febrile illnesses'. In 1992, Mackowiak and colleagues defined fever as 'a complex physiological response' to the consequence of the process of inflammation, characterized by a cytokine-mediated rise in temperature, as well as by the generation of acute-phase reactants and the activation of a panoply of physiological, endocrinologic, and immunologic systems emphasizing its beneficial effects. In fact, fever is more than an elevated BT (Thompson, 2005). However, despite a large number of studies on the topic, there are some contrary takes on whether fever is beneficial or not (Harden, Kent, Pittman, & Roth, 2015).

Fever is caused by exogenous and endogenous pyrogens. Exogenous pyrogens (protozoans, bacteria and their endotoxins, viruses, yeasts, spirochetes, immune reactions, several hormones, medications, and synthetic polynucleotides), as fever-producing microbial products, act directly on the hypothalamic thermoregulatory center. Endogenous pyrogens, also called cytokines – which are identified as interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor (TNF-α), and interferons produced when the organism is invaded by a virus or bacterium – begin to respond against the inflammatory process, stimulating the proliferation of the immunocompetent cells, such as the T and B lymphocytes. This is the 'acute phase', which results in fever, is essential for tissue remodeling and repairing, and, finally, for the release of prostaglandin E2 (PGE2) at the blood-brain interface in the hypothalamic region of the brain (Anochie, 2013; Hall, 2015).

About the threshold of fever, a systematic review conducted by Egi & Morita (2012) showed that it varies widely from at least 37.5 °C to greater than 39.0 °C and that the high fever (39.3 °C-39.5 °C) was significantly associated with mortality. The Society of Critical Care Medicine and the Infectious Disease Society of America (2008) recommended a threshold of 38.3 °C of core temperature (intravascular, esophageal, or bladder thermistor, followed by rectal, oral, and tympanic membrane measurements) or higher as fever, for adults admitted in Intensive Care Unit. However, some other authors defined the threshold as a core temperature of 38.0 °C (100.4 °F) (Table 2) (Borio et al., 2002; Mackowiak, Wasserman, & Levine, 1992), considering that it depends on the cause. Hence, there is no universal threshold for fever, considering that BT varies in individuals depending on several factors.

Fever can either be caused by infection or not. For fever caused by infection (about 74% of all cases) (Kaul, Flanders, Beck, & Saint, 2006), the distinction between community-acquired and nosocomial infection should be considered, which

manifests 48 hours or more after admission to hospital (Garner, Jarvis, Emori, Horan, & Hughes, 1988). It is important to detect these causes to avoid inappropriate treatment. Bacterial infection consists 30% of all infection causes (Bor et al., 1988). Serious bacterial infection (SBI) is represented mainly by urinary tract infection and, less commonly, by pneumonia, sepsis, meningitis or bacteremia (Manzano et al., 2011), and the fever notably exceeds 39 °C in children aged from 0 to 5 years (De et al., 2015). Fever is less common in adults with confirmed viral respiratory infections, including influenza (Chughtai, Wang, Dung, & Macintyre, 2017; Harper et al., 2009; Peltola, Ziegler, & Ruuskanen, 2003), with a lower febrile response to bacterial infections (for adults more than 75 years) (Bor et al., 1988) than described in children. Respiratory (Chughtai et al., 2017) and urinary tract infections, neoplasm, myocardial infarction, and drug reaction are the most common causes of fever in adults (Walter, Hanna-Jumma, Carraretto, & Forni, 2016). In cases where adults do not present fever, and this does not coincide with their clinical picture, symptoms like hypotension, tachycardia, tachypnea, confusion, rigors, skin lesions, respiratory manifestations, oliguria, lactic acidosis, leukocytosis, leukopenia, immature neutrophils or thrombocytopenia should be taken into consideration as indicators of a severe infection (O'Grady et al., 2008).

Central nervous system lesions, neoplasms, endocrine abnormalities, and connective tissue diseases appear to be some of the most common symptoms of non-infectious causes (Walter et al., 2016), although cases of fever not caused by infection are rare. High fevers (≥ 39.5 °C) not caused by infection are accompanied by a greater risk of death (Lee et al., 2012). There are some nonspecific accompanying symptoms such as depression, anorexia, hyperalgesia, fatigue, myalgias, back pain, headache, diaphoresis, hypotension, tachycardia, confusion, rigors, skin lesions, respiratory manifestations, which should be considered, even when fever is not present (O'Grady et al., 2008), to avoid erroneous diagnosis and inappropriate treatment.

Sweating, chills, sensation of cold, and other subjective sensations are common in patients with fever.

Fever was also found in 15–50% of patients after surgery. In some of them, the fever indicated the development of infection, whereas in some others it was only an indicator of the postoperative inflammatory response (Barone, 2009). Fever is also common in ward patients and patients in Intensive Care Unit (Ferguson, 2007).

1.4.1 The course of fever

As documented by Pontieri (2012), fever progresses in three phases: prodromal, fastigium, and defervescence, each of which has different characteristics.

The prodromal phase is characterized by the subjective sensation of cold, shivering and skin pallor which is a consequence of vasoconstriction. It corresponds to the moment when the action of PGE2 begins. The body temperature increases progressively, sometimes rapidly and sometimes slowly. During this phase, the level of the thermoregulatory centers is higher than that of the physiological one. The cold feeling is replaced by the hot. This stage is maintained throughout the period in which excessive endogenous pyrogens and PGE2 production lasts.

Fastigium is characterized by cutaneous vasodilation, which leads to the skin becoming warm and flushed. In this phase, the patient is too hot.

The last phase (defervescence) is characterized subjectively by the feeling of warmth and objectively by the lowering of body temperature. Because of the reduced production of PGE2 and pyrogenic cytokines, which can be gradual or rapid, the thermoregulatory centers report their sensitivity threshold to the thermal stimuli. Frequent sweating often encourages the elimination of heat. The decrease of BT can happen gradually or quickly.

1.4.2 Types of fever

The level of BT (°C/°F), its characteristics and accompanying symptoms vary in accordance with the type of fever. Based on its causal factors, fever is classified into:

1. Continued fever. The patient's temperature remains above the normal value (37.0 °C) with minimal variations, usually less than 1 °C. Drugs, endocarditis, tuberculosis, fungal disease, bacterial pneumonia, as well as *Salmonella typhi* may cause this type of fever (Dall & Stanford, 1990; Parry, Hien, Dougan, White, & Farrar, 2002).

2. Remittent fever. The patient's BT does not return to normal, although it varies a few degrees in either direction. Remittent fever is associated with viral upper respiratory tract, legionella, and mycoplasma infections. It is common in septicemia (L. S. Young, 1988).

3. Continuous-remitting fever. During fastigium, BT oscillations may be higher or lower than one degree Celsius, without ever reaching defervescence (G.M., 2012).

4. Intermittent fever. Fever periods alternate with apyrexia periods in a regular or non-regular way. This type of fever is associated with gram-negative or gram-positive sepsis (Schortgen, 2012), abscesses (Baiu & Melendez, 2018), and infective endocarditis (Douglas, Moore-Gillon, & Eykyn, 1986).

5. Recurrent fever. The fever persists for some days, followed by some days of apyrexia (John & Gilsdorf, 2002). Recurrent fever in young children is mostly caused by respiratory infections. This type of fever is typical of brucellosis (Roushan, Ebrahimpour, & Moulana, 2016).

1.4.3 Body systems altered during fever

The cardiovascular system is notably influenced by fever. In such a case, the heart rate increases with increase in BT. Generally, a 1 °C increase in BT produces an 8 beat/minute increase in heart rate (Hall, 2015) due to increased metabolism. However, considering that increased heart rate may also be due to hyperthyroidism (Patanè & Marte, 2010), a differential diagnosis should be made if the heart rate doesn't coincide with the BT level. Therefore, HCWs must consider this fact during assessment of vital signs in a patient with fever.

Respiratory rate is also affected by fever mechanism. In fact, an increase by 5 to 7 breath/minutes for each °C rise has been documented (Gadomski, Permutt, & Stanton, 1994).

Nausea and vomiting demonstrate the influence of fever on the digestive tract (Hall & Driscoll, 2005). The central nervous system may also be influenced, in which the most common manifestation is delirium (Kashiwagi, Tanabe, Shichiri, & Tamai, 2003).

1.5 Fever in Children

Fever represents the most common symptom faced by HCWs every day (about 30% of all symptoms) (Barbi, Marzuillo, Neri, Naviglio, & Krauss, 2017; Crocetti, Moghbeli, & Serwint, 2001; Nelson, Walsh, & Fleisher, 1992) in Paediatric Emergency Departments (Keil et al.). Feverish illness is very common in young children, with between 20 and 40% of parents reporting such an illness in their children each year (Davis, 2013). Usually, parents are alarmed by untreated fever due to its adverse effects like brain damage, seizures and death, even if some studies

do not support this evidence (Poirier, Collins, & McGuire, 2010; Richardson & Purssell, 2015).

Since non-infectious conditions account for 50% of all causes of fever (Launey et al., 2011), it follows that infection accounts the other 50% (Soman, 1982; Soon & Laxer, 2017). Generally, non-infectious causes include immune-mediated, inflammatory, or neoplastic conditions (Barbi et al., 2017). In these cases, the causes of the chronic fever cannot be identified by past history and physical examination. The risk of a high rate of SBI seems to negatively correlate with age; that is, it increases with decreasing age (© Department of Health, Government of South Australia, 2016, De et al., 2015, Greenhow, Hung, Herz, Losada, & Pantell, 2014). Meningococcal disease, bacterial meningitis, herpes simplex encephalitis, pneumonia, urinary tract infection (in children younger than 3 months), septic arthritis/osteomyelitis, and Kawasaki disease are the most common illnesses that cause fever in children. Pallor, mottled appearance, ashen or blue skin color, reduced tachypnea and tachycardia, capillary refill time > 3 s, and reduced urine output are symptoms that indicate high vulnerability to SBI (Tessa Davis, 2013).

Color (of skin, lips or tongue), activity, respiratory rate, circulation rate and hydration level are crucial in classifying the level of risk of serious illness in children with fever into low, intermediate and high (Traffic light system) (Tessa Davis, 2013). This stratification is essential in the investigation and initial management of this condition by HCW, considering that fever in infants and young children (< 6 years) can be associated with febrile seizures in up to 4-5 % of all cases (Harden et al., 2015). Febrile convulsions in children are common for temperatures greater than 41.0 °C. High fevers can be dangerous to the central nervous system, particularly in children. A sustained temperature greater than 42.0 °C may lead to permanent brain damage.

1.5.1 Treatment of fever in children

In order to provide appropriate fever treatment, it is advisable to know the causes of the fever and to proceed with a careful physical examination. If these conditions are met, it is likely that the best treatment for the specific clinical situation will be chosen. In particular, for the physical interventions, the HCW should consider placing ice bags over the major arteries of the groin and axilla or undressing the child during fastigium, even if these interventions may cause shiver and discomfort (Davis, 2013; Purssell, 2000). The UK National Institute for Health and Care Excellence (2007) recommend administering intravenous fluid (0.9% sodium chloride) to treat possible dehydration.

Regarding the administration of antipyretics, it is recommended in cases of discomfort and apparent distress (Chiappini et al., 2017; Davis, 2013), and not only to reduce the BT. Mayoral and colleagues (2000) reported that most caregivers (89% of the population sample) admitted that they would administer antipyretics to a comfortable-looking child with fever, and that parents believe the most important use of antipyretics is to treat fever, not to ease pain or irritability. Until 1980, aspirin (acetylsalicylic acid) was widely used to treat fever (Desborough & Keeling, 2017). Considering the harmful effects of aspirin as a gastric irritant and its role as a causal agent of Reye's syndrome (Kauffman, 1998), for a long time now, acetaminophen (paracetamol) and ibuprofen have been the standard agents for the treatment of fever in children because of their effectiveness, low cost, and minimal side effects (Mayoral et al., 2000; Sullivan & Farrar, 2011). Their dosage should be prescribed according to the child's age, weight and other characteristics (Chiappini et al., 2017). Comparing the effects of ibuprofen to those of acetaminophen, a meta-analysis (Pierce & Voss, 2010) showed that ibuprofen is a more effective antipyretic than acetaminophen (10-15 mg/kg) at 2, 4, and 6 hours post-treatment.

While the two antipyretics are used together as combined therapy for fever, the main purpose being to reduce the BT in the febrile state, there are contrary views as to the effectiveness. Although there are some systematic reviews, meta-analyses and guidelines that support the combined therapy for fever if the distress persists or the febrile episodes recur after the administration of one antipyretic (Davis, 2013; Noori, Miri-Aliabad, Boryri, Teimouri, & Soleimani, 2016; Wong et al., 2014), there is not enough evidence to say that alternating antipyretic therapy is more effective than monotherapy (Chiappini et al., 2017; Pereira, Dagostini, & Pizzol Tda, 2012). In addition, some authors and guidelines do not support the use of acetaminophen and ibuprofen as combined therapy (2013), considering the increased risk of overdose and toxicity (Hay et al., 2008), as well as the lack of evidence for their role in preventing seizures in susceptible children (Offringa & Newton, 2013).

If the child is shocked, unrousable or show signs of meningococcal disease, the HCW should immediately administer parenteral antibiotics (a third-generation cephalosporin), until culture results are available. The HCW should also administer oxygen to correct the oxygen saturation of less than 92% when breathing in air (Richardson & Lakhanpaul, 2007), even if reducing temperature in case of infection may be harmful (Harden et al., 2015) since fever could inhibit the growth of the causal agents (Mackowiak et al., 1992). It is very crucial for HCWs to have appropriate knowledge of fever, thermoregulation, and pathophysiology, and the skills to manage them. In addition, they should know the pharmacological content, dosages, effects, side effects and contra-indications of the administered medication (Jellinek et al., 2010). Only with these skills and knowledge will they be able to treat fever properly.

CHAPTER 2

MEASUREMENT AND THERMOMETERS

2.1 The Historical Development of Thermometry

Historically, Hippocrates emphasized the importance of physicians having appropriate knowledge of fever and its treatment. Since the 19th century, changes in BT have been considered signs of specific diseases. For this reason, it is necessary to use a valid and reliable instrument to detect these changes. Before Galileo invented the first water thermometer (thermoscope) (Fig. 1) in 1593, physicians used three principal methods to detect BT: the patient's appearance, the patient's own perception of body heat, and the use of the 'educated hand' to determine the BT level (Haller, 1985).

The mercury thermometer was invented in 1714 by Gabriel Fahrenheit, and it has been considered the 'gold standard' for a long time due to its ability to give valid and reliable results (Wright, 2016). Ten years later (1724), Fahrenheit introduced the 'Fahrenheit scale' (°F) as the measurement unit for mercury thermometer, followed by the 'Centigrade scale' (°C) which was introduced by the Swedish astronomer, Anders Celsius, and later the Kelvin scale (K) by William Thompson Kelvin in 1848. Hermann Boerhaave and van Swieten, professors of medicine at the University of Vienna, emphasized the importance of using mercury thermometer in routine clinical practice, placing it in the axilla or mouth, in order to replace the historical methods, especially the 'educated hand' method. The use of thermometers facilitated the clinical recognition of diseases, their diagnosis and their appropriate treatments. Nowadays, these historical thermometers are being replaced by modern clinical thermometers that will be explained in the following sections.

Fig.1 Galileo's thermoscope. This figure was uploaded by Meaad Kadhum Hassan (El-Radhi et al., 2009)

2.2 Core and Peripheral Body Temperature Measurement Methods

BT temperature measured at deep tissue level is known as core body temperature (CBT) (Hall, 2015). The most commonly used sites for the detection of CBT are the rectum, the esophagus, the digestive tract, the nasopharynx, the bladder, the uterus, and the aortic arch, though the pulmonary artery is considered the 'gold standard' site (Peron, 2010). Measurement of CBT involves the invasion of any of these sites by a thermometer. Among these sites, the rectum seems to be the most recommended since it reflects the CBT without the instrument being too invasive or inconvenient for the subject (Fulbrook, 1993; Shin, Kim, Song, & Kwak, 2013).

CBT measurement is indispensable in the examination of critical patients where the maximum reliability of devices is required to provide effective care. It is crucial to consider some special requirements during CBT measurement such as sterilization,

maximum safety and minimum disturbance to the organs, tissues, and good physiological conditions and comfort, good repeatability and high reliability, high biological affinity and low toxicity, and accuracy (Chen, 2019).

The peripheral temperature refers to the temperature of the skin and the subcutaneous tissues. The most common anatomical sites used to estimate skin body temperature (SBT) are the sublingual, the axilla, the groin, the neck, the ear (tympanum and ear canal) and the forehead.

The SBT is easy and convenient to measure but, considering that it is more susceptible to environmental temperature, humidity and rate of air motion, it is supposed to be less accurate and can be considered only a proxy of CBT (Hernandez & Upadhye, 2016; McCallum & Higgins, 2012). Currently, there are various approaches and techniques for peripheral BT measurement. However, their common goal is to obtain an estimate of a patient's CBT. For this reason, it is fundamental for these methods to be accurate, reliable and valid if they will contribute to correct diagnoses and appropriate treatments. Since 2002, when the Global Mercury Assessment developed by UNEP alerted the world of mercury pollution, there has been a tendency to replace mercury thermometers, historically used to detect peripheral BT, with other devices like infrared and electronic thermometers (Kessler, 2013). In recent years, some studies have undertaken to compare these new devices with the mercury thermometer, although there is no high quality scientific evidence yet to prove their validity and reliability (Çultu et al., 2008; Gerensea & Murugan, 2016; Jensen, Jensen, Madsen, & Lossl, 2000; Kongpanichkul & Bunjongpak, 2000; Moran & Mendal, 2002; Niven et al., 2015; Sermet-Gaudelus, Chadelat, & Lenoir, 2005; Zhen, Xia, Long, & Pu, 2014).

BT measurement methods can be classified according to some aspects such as invasiveness (noninvasive, semi-invasive, and invasive measurements), thermal transfer mechanisms (contact and non-contact measurements), signal source (direct

and indirect measurements), usability (daily healthcare and medical checkup oriented measurements), and data presentation in temporal and spatial domains (infrared thermography, microwave, ultrasound, and electrical impedance for noninvasive thermographic imaging) (Chen, 2019). Oral, rectal, axillary and tympanic measurements are the most commonly used in paediatric daily clinical practice (El-Radhi & Barry, 2006). It is important to take into consideration the site, the time of day, patient's age and gender when measuring the BT (Sund-Levander & Grodzinsky, 2013). Inaccurate BT measurement can lead to false-positive fever detection and consume significant resources in unnecessary diagnostic workups and medical treatments, or to false-negative detections which can delay diagnosis and treatment of serious illnesses (McCallum & Higgins, 2012; Zhen et al., 2014). In repeated measurements, it is important to use the same thermometer, the same site and the same side.

In the coming subsections, rectal BT measurement (as the 'gold standard' measurement) will be discussed, followed by some CBT and peripheral BT measurement methods.

2.2.1 Rectal Temperature

Rectal temperature (RT) measurement method has traditionally been considered the 'gold standard' among invasive methods in children under 2 years (McCarthy, 1998), since RT correlates most closely with CBT (Schmitz, Bair, Falk, & Levine, 1995). Despite this advantage, it is physically uncomfortable (compared to peripheral sites), psychologically harmful or even abusive, and it is not preferred by parents or caregivers for routine use (Bernardo, Henker, & O'Connor, 1999). In addition, since the probe of a rectal thermometer should be placed into the rectum, and some evidence highlighted bowel perforations, it is not recommended in children younger than 5 years, especially for routine use (Fulbrook, 1993). Also, the

hygienic aspect should be considered to avoid contamination among children, since transmissions of the Clostridium difficile was reported (Brooks et al., 1992). Depth measurements, the presence of fecal material, the condition of the blood vessels, and surgical intervention in the rectum could affect RT measurement (Sund-Levander & Grodzinsky, 2013).

2.2.2 Axillary Temperature

The axilla is one of the traditional peripheral sites used to measure the BT due to its convenience and ease of access.

Axillary temperature (AT) could be affected by some factors such as the environmental temperature (Schmitz et al., 1995), inappropriate placing of the probe, sweat or closure of the axillary cavity, and local blood flow (Sund-Levander & Grodzinsky, 2013). In addition, there are evidence (Quintana, 2004) showing that the difference between axillary and oral/rectal temperature (‘gold standard’ measurement) increases when BT increases, making it difficult to consider axillary BT fully reliable. Nevertheless, axillary measurement seems to be preferred to rectal and oral measurements, due to its associated comfort.

The axillary thermometer should be placed deeply in the center of the dry and uncovered armpit for 1-5 min, depending on the technology (digital or mercury). It is important to keep the child's arm unwashed before thermometry. If there is hyperemia due to inflammation in the armpit, it is preferable to select an alternative anatomical site for BT measurement.

2.2.3 Tympanic Temperature

Tympanic temperature (TT) measurements seems to be close to CBT (Barnett et al., 2011; Dzarr, Kamal, & Baba, 2009) because the tympanic membrane receives blood directly from the carotid artery and, thus, its temperature reflects the temperature of blood flowing into the hypothalamus. Therefore, the tympanic temperature is recognized for precision and accuracy since it is close to the BT measured by the standard nasopharyngeal method (Asadian, Khatony, Moradi, Abdi, & Rezaei, 2016). Being less invasive, quick, easy to use, time efficient, hygienic, and comfortable, the TT method is one of the most preferred for measuring BT in hospitals and homes (El-Radhi & Barry, 2006). The American Society of PeriAnesthesia Nurses recommend the use of TT method in perioperative period, considering it the most accurate alternative measurement method to both invasive and noninvasive methods in critical care units (Hooper & Andrews, 2006). Tympanic membrane temperatures are accurate so long as the probe of the thermometer is properly positioned, the ear canal is occluded, and the face is protected from direct thermal manipulation (Lenhardt & Sessler, 2006).

2.2.4 Forehead Temperature

The temperature of the temporal artery, measured by a forehead infrared non-contact device, can give the BT. It is essential to put the infrared thermometer on a clean and dry skin, achieved after the subjected has waited at least 30 minutes after a possible bath. Forehead temperature (FT) method is a non-traumatic, easy and very fast method, requiring no more than 5 seconds to detect the fever. However, there are some factors that could affect BT measurements by this method such as environmental temperature (radiant warmer), sweaty forehead and inability of the child to remain still (Teller, Ragazzi, Simonetti, & Lava, 2014). Also, there is no

consensus yet on its accuracy, and it is not recommended by current guidelines (© Department of Health, Government of South Australia, 2016, © World Health Organization, 2013, © NICE, 2013, © Canadian Guidelines, 2013).

2.3 Thermometers

A thermometer is an instrument used to measure BT. Nowadays, several different types of thermometers are used, such as liquid-filled (mercury or galistan), digital **(**thermistors or thermocouples), and infrared (non-contact) thermometers.

Measuring BT is one of the most common procedures in nursing practice, especially in paediatric settings. According to protocols and guidelines, the HCW should choose the most appropriate device to measure BT. During BT measurement, the patient must feel comfortable and safe. Thermometers should be accurate, reliable, noninvasive, non-traumatic, hygienic, time efficient, cost effective, safe, environment-friendly and easy to use (Asadian et al., 2016; Işler, Aydin, Tutar Güven, & Günay, 2014; Kanegaye et al., 2016). The modern noninvasive thermometers, such as digital and infrared thermometers, are replacing the glass mercury thermometer, which historically has been considered the 'gold standard', around the world. Their greatest advantages consist of speed and convenience. However, their validity and reliability remain a controversial issue. A large amount of research comparing thermometers (Batra & Goyal, 2013; Dzarr et al., 2009; Işler et al., 2014; Kanegaye et al., 2016; Schmitz et al., 1995) is available, though studies conducted in paediatric settings have not solved the issue of the validity and reliability of alternative devices commonly used in paediatric clinical settings. In some countries such as Albania, the glass mercury thermometer is still used in clinical settings, as in some other developing countries (Benkovich, Farrell, Nimunkar, Baran, & Webster, 2009). However, according to the Minamata Convention, the GMT will no longer be in use after the year 2020.

2.4 An Overview of the Minamata Convention on Mercury Pollution

Mercury is a heavy metal ranked among the top ten environmental chemicals of major public health concern by WHO. Mercury is generally used in the artisanal sector and gold mines, resulting in the pollution of air, water and food. Thus, it is hazardous for humans. It has been highlighted that humans are mostly exposed to mercury through the use of dental amalgams during manipulations in clinical dental practice (Fisher, 2003). Also, batteries, lamps, and thermometers contain mercury as an elemental component, mainly in the form of liquid at normal temperature.

The oceans are the most important natural and re-emission sources, contributing 36% of the natural and re-emitted emissions of mercury (Sundseth, Pacyna, Pacyna, Pirrone, & Thorne, 2017). Therefore, consuming sea food from contaminated waters is considered a threat for humans.

In fact, mercury has been known for its hazardous properties and adverse health effects. For years, when mercury compounds were used to treat syphilis in the mid-20th century, before penicillin was discovered, humanity suffered dramatic tragedies leading to fatalities (Frith, 2012).

Frequent exposure to mercury leads the inhalation, expressed by symptoms such as cough, dyspnea, chest pain, rash, tremor, weight loss, and abdominal pain (Caravati et al., 2008). There are also the gastro-intestinal and subcutaneous symptoms. Grandjean P. and colleagues (1997) highlighted impaired brain function, especially neuropsychological dysfunctions caused by increased exposure to methylmercury from maternal consumption. Pulmonary irritation, renal toxicity and cumulative neurotoxin may also be consequences of mercury inhalation. Mercury does not poison just a person, but all the community. Consequently, considering mercury pollution a global concern needing mandatory preventive measures was required.

The Minamata Convention (Kessler, 2013) is an international treaty between more than 100 countries from all over the world, which came into force in 2017, with the objective to protect humans and the environment from exposure to mercury and its compounds (e.g. methylmercury), considering the analytical data of the first Global Mercury Assessment in 2002 by UNEP. It was named 'Minamata' in memory of the Minamata Bay disaster in Japan in the late 1950's that resulted from environmental pollution from methylmercury. It took so many years to realize that mercury was particularly poisonous to humans and fauna, as it is easily absorbed by the body and can accumulate in certain human organs, including the brain.

The signatories to the Minamata Convention resolved to phase out the use of mercury by banning its production by factories, by prohibiting its use and that of its compounds, and by barring the import or export of non-essential mercury products. The eradication program consists in establishing a mercury monitoring process (to control the harmful effects of mercury pollution), supporting signatory countries, and conducting surveys particularly in the developing countries, with the main objective of achieving the goals of the convention.

In the aspect of health, the convention was focused in two directions: prevention and treatment. It encourages the parties to promote, implement and evaluate science-based educational programs and appropriate health-care services for prevention. For the population already exposed to mercury and its compounds, it encourages the strengthening of professional health capacities for diagnosis, treatment and care. With regards to the risk associated with the use of dental amalgam, the MC drafted strategies on the harmonization of the codes of use of dental amalgam, with the aim of tracing the role of mercury in its worldwide. MC recommends using alternative materials without mercury, thus preventing the use of its commonest source of exposure to humans.

Each party to the treaty must promote and facilitate education, public awareness and training, in relation to the effects of exposure to mercury.

The Illinois Department of Public Health found that the concentration of elemental mercury, from broken thermometers and thermostats, in air was a negligible 0.001 mg/m^3. However, to prevent its vaporization, proper cleaning is recommended, even if mercury diffusion in the air from broken GMT is insignificant. A recent study showed that evaluating the effectiveness of the Minamata Convention will require biomonitoring of multiple species that represent different trophic and ecological niches in multiple regions of the world (Wang et al., 2019). Therefore, many developed and developing countries find it difficult achieving the goals of the convention, which are politically and economically motivated (Kessler, 2013). As a consequence of the hazardous effects of mercury on vulnerable human population, especially children (Aprahamian et al., 2009; Geier, King, Sykes, & Geier, 2008), mandatory measures were put in place at the convention to ban the use of many mercury-containing products and processes, including medical devices such as thermometers and manometers, as well as mercury in soaps and cosmetics, in 2020 (Kessler, 2013).

2.4.1 The Glass Mercury Thermometer

Historically, the glass mercury thermometer has been considered the 'gold standard' for BT measurement (Chiappini et al., 2011; Uslu et al., 2011). A glass mercury thermometer (GMT) consists largely of a vacuum glass tube, inside of which is placed another tube containing approximately 0.5–3 grams of methylmercury (fig. 2) (Periasami, Naaraayan, & vishwanathan, 2017). The outer tube is sealed at its two ends, one of which is a silver slightly narrower bulb, so that there is no mercury flow when removing the device from the measurement site. The silvery line of mercury

fluid inside the inner glass tube determines the temperature, rising and falling with temperature. The common temperature scales are the Fahrenheit scale (°F) and the Celsius scale (°C). Fahrenheit scale is widely used in the USA and Great Britain, while Celsius scale is used in the rest of Europe. GMT is scaled from a minimum (34 °C) to a maximum (42 °C). Before proceeding with measurement, it is essential to shake the thermometer until the mercury line is at the lowest possible level, since mercury does not return to its original position after it has been displaced. The narrow bulb should be placed in the depth of the armpit, taking care that it does not touch the clothes, and the arm should be kept fixed. The GMT is calibrated by the manufacturer and their accuracy is preliminarily verified.

Being made of glass and containing mercury, GMT is easily broken and considered dangerous and harmful if the mercury evaporates into the surrounding air or contaminates the environment (Aprahamian et al., 2009; Caravati et al., 2008). Owing to this, it has been replaced in many countries by digital and infrared thermometers.

There are some disagreement as to how long the thermometer should be placed on the measurement site to achieve accuracy in BT measurement. Some authors (Hadgu et al., 2017) showed that 5-10 minutes is an adequate time for reliable BT detection, but some other authors (Perera, Fernando, Mettananda, & Samaranayake, 2014) concluded that the placement time for a given individual cannot be predicted because it varies according to age. In this regard, the use of GMT is time-consuming and keeping children still for at least 5 minutes could pose a challenge.

After BT measurement, it is necessary to disinfect the device before placing it in the holder to avoid spreading infections (Rosenthal & Leslie, 2006).

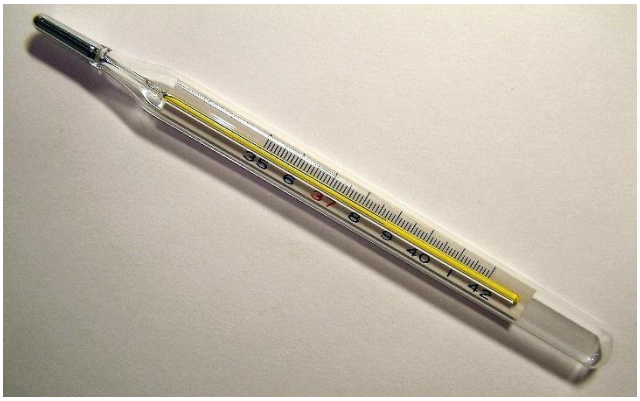

Fig.2 Glass Mercury Thermometer (Product code 10901902464, GEA®, Indonesia).

2.4.2 Axillary Digital Thermometer

Digital thermometers are widely used as alternative devices to GMT. Axillary digital thermometer (AXL_{DGT}) is not an in-glass device; rather, it is equipped with a digital display that shows BT values. At one end, it has the sensor which produces electronic signals, reflecting the temperature as a number in the numerical digital screen. The thermistor, contained within a metal probe, should be placed deeply in the armpit for less than two minutes. It must be removed from there once the digital thermometer beeps. After concluding the procedure, it should be disinfected and placed in its holder. AXL_{DGT} seems to provide a fast, easy and accurate BT measurement compared to GMT (Gasim, Musa, Abdien, & Adam, 2013; Marui, Misawa, Tanaka, & Nagashima, 2017). However, this is still a controversial issue since some evidence showed only partial interchangeability between digital axillary device and AXL_{MER} (Jensen et al., 2000; Kongpanichkul & Bunjongpak, 2000; Zengeya & Blumenthal, 1996).

Fig. 3 Digital axillary thermometer (Product code 00006929000000, Chicco®, Italy)

2.4.3 Non-Contact Infrared Forehead Thermometer

Non-contact infrared forehead thermometer (FHD_{IR}) is a non-contact and easily accessible device for detecting BT. It estimates temperature as a measure of the infrared emission from the temporal artery, which is supplied by blood directly from the carotid artery (Crawford et al., 2006). The heat generated by an infrared sensor probe is converted to an equivalent temperature value which is showed on the wide LCD display. To detect the BT, the thermometer probe should be placed on the right or left forehead. BT detection can be obtained within five seconds. For this reason, FHD_{IR} is reported to be an easy, quick and noninvasive device (Chiappini et al., 2011; Kelechi, Michel, & Wiseman, 2006) that could be used even when the child is sleeping, without causing distress.

Not needing a prober cover and being a non-contact thermometer, the risk of spreading infections due to public use is negligible (Sound Levander, 2014).

However, FHD_{IR} also has some disadvantages, since temperature of the surrounding environment, sweaty forehead, hair on the skin, and having a possible bath before measurement could affect BT measurement (Crawford, Hicks, & Thompson, 2006; Teller et al., 2014).

Fig. 4 Non-contact Infrared Forehead Thermometer (Product code 00004757100000, Chicco®, Italy)

2.4.4 Infrared Tympanic Thermometer

Infrared tympanic thermometer (TYM_{IR}) is designed to sense the infrared heat waves emanating from the tympanic membrane through an infrared sensor housed in the probe. The probe contains optical sensors which are capable of converting thermal energy into electricity. These infrared heat waves are converted to a temperature value. As the probe contacts the auditory canal, the cover probe is necessary to avoid possible cross-infection. BT measurement using this device could be affected by ear wax (Hasel & Erickson, 1995), so a tolerance to account for changes due to the wax should be considered before proceeding with the tympanic measurement. Being non-invasive, non-traumatic, very quick, culturally acceptable, user-friendly, hygienic, comfortable for the subject, easy to use and to read, it is useful and practical at home and in healthcare settings for children (Çultu et al., 2008).

Fig. 5 Infrared Tympanic Thermometer (Product code 00000656000000, Chicco®, Italy)

2.4.5 Other Available Types of Thermometers

Nowadays, there are some other thermometers which are widely used in nursing practice instead of the GMT. The Galinstan-in-glass and the chemical dot thermometers are two such devices.

Galinstan-in-glass thermometer is an eco-friendly device; Galinstan is an alloy mainly consisting of gallium, indium, and tin, and is the equivalent of mercury in GMT. Like the GMT, the Galinstan-in-glass thermometer requires careful handling during use due to the risk of accidental injury from breakage. Some authors support it as the best alternative to GMT for fever measurement in adults and children (Schreiber et al., 2013; Smith, 2003).

The Tempa Dot thermometer is a device usually used to detect BT from oral and axillary sites. It is a single-use device and quick to use. It should not be used orally in newborn babies, the mentally ill, patients for oral surgery, and unconscious patients. It appears to be a reliable alternative to the mercury thermometer (Bruel, Aertgeerts, Boeck, & Buntinx, 2005).

2.5 Available Guidelines on Fever and Thermometry

Several guidelines on clinical practice are made available by national health agencies and scientific societies to assist HCWs and parents/caregivers in assessing and managing fever in children (© Department of Health, Government of South Australia, 2016, © World Health Organization 2013, © NICE, 2013, © Canadian Guidelines, 2013, © American Academy of Pediatrics, 2011). However, some divergences have been found between the clinical practice of HCWs and the recommendations of these guidelines (Chiappini et al., 2012; Chiappini et al., 2017). Clinical decisions about fever management depend on the full clinical picture of the child and accurate measurement of its temperature. Accordingly, the child should be assessed considering the color of the skin, tongue or lips, the level of activity, the respiratory system, circulation and hydration.

Sometimes physicians, HCWs or parents/caregivers administer antipyretics due to the fear of possible complications, which is known in the literature as 'fever phobia' (Gunduz, Usak, Koksal, & Canbal, 2016). Fearing that fever may lead to brain damage or SBI, together with other misconceptions they have about fever, most parents and caregivers administer antipyretics once they detect that the child's BT is high (El-Radhi, 2012). It is important to emphasize that none of the guidelines recommends this. What the guidelines recommend is prescribing pharmacological treatment only when the child with fever appears distressed, and not definitely with the purpose of reducing the BT.

Acetaminophen and ibuprofen are the most recommended antipyretics, which should be dosed according to the age and weight of the child. Aspirin is contraindicated because of the risk of Reye's syndrome (McGovern, Glasgow, & Stewart, 2001).

Children under 3 months of age who present life-threatening symptoms, including elevated BT, should be immediately assessed by HCWs (Davis, 2013).

The thermometer for detecting BT should provide reliable results. Although historically considered the 'gold standard', mercury thermometer is no longer recommended due to mercury hazards (Kessler, 2013). Indeed, GMT is not recommended by any guidelines (table 4).

Considering that rectal temperature measurement is the established 'gold standard' measurement (McCarthy, 1998), electronic rectal thermometer is the most recommended for definitive clinical decisions (table 4), excepting the NICE which recommend AXL_{DGT}. AXL_{DGT} appears to be the most recommended for screening purposes, followed by TYM_{IR}.

Table 4. Outcome of the comparison of guidelines on recommended thermometers

Guidelines	Under 4 weeks	4 weeks-2 years	4 weeks-5 years	Note
Nice 2019	Electronic axilla thermometer	Electronic and chemical dot axilla thermometer, and infra-red tympanic thermometer	Electronic and chemical dot thermometer in the axilla; Infra-red tympanic thermometer	Forehead thermometers are not recommended
Chiappini 2017	-	-	-	Don't describes thermometer's type
Canadian guidelines 2013	Electronic rectal thermometer	Electronic axillary and rectal thermometer	Electronic axillary, rectal, orally and infra-red tympanic thermometer	Forehead thermometers are not recommended
South Australia 2016	Electronic axillary and infra-red tympanic thermometer	Electronic axillary and rectal thermometer	Electronic axillary and infra-red tympanic thermometer	Forehead thermometers are not recommended
American Academy of Pediatrics	Electronic axillary thermometer	Digital rectal thermometer, tympanic and forehead thermometer	Digital oral thermometer, tympanic and forehead thermometer	Mercury thermometers not recommended
Who 2013	Electronic axillary thermometer	-	-	To detect hypothermia, it is recommended to use a low-reading thermometer.

CHAPTER 3

COMPARISON OF PERIPHERAL MODERN THERMOMETERS AND AXILLARY MERCURY THERMOMETER

3.1 Introduction

Recently, some advanced digital and infrared devices have been introduced in clinical settings, despite the lack of high-quality evidence on their validity and reliability, especially in paediatric settings. This is due to global trends to replace GMT, considering the toxic effects of mercury and its compounds to public health, as highlighted by the Minamata Convention (Mackey, Contreras, & Liang, 2014). Therefore, improving thermometry is considered one of the contemporary challenges, considering that thermometers with low validity and reliability increase healthcare costs and the risk of morbidity and mortality (Pompei, 1999). BT values seem to be influenced by measurement sites (Geneva et al., 2019) and individual factors such as age, circadian rhythm, metabolism, and ovulatory cycles, all of which should be considered when assessing BT (Obermeyer, Samra, & Mullainathan, 2017; Sund-Levander & Grodzinsky, 2013). Precise estimates of BT are critical to establishing correct diagnoses, initiating proper treatments and, as a consequence, having better prognoses. To achieve this, it is essential to choose an appropriate device that will provide the most reliable and valid measurements.

Historically, GMT has been used to measure BT. It has been considered the ‘gold standard’ for centuries and, as a consequence, has been used as a reference tool in many studies whose goals were to test the interchangeability, reliability and validity of the alternative devices (Chiappini et al., 2011; Gasim et al., 2013; Işler et al., 2014; Kocoglu, Goksu, Isik, Akturk, & Bayazit, 2002; J. Smith, 1998; Uslu et al.,

2011; Vertedor-Hurtado, Padin-Lopez, Carreira-Pastor, & Lopez-Martinez, 2009). Alternative devices seem to be easier and faster to use and more comfortable for subjects when compared to GMT (Chiappini et al., 2011; Çultu et al., 2008; Tessa Davis, 2013; I. Franconi, La Cerra, Marucci, Petrucci, & Lancia, 2018). However, evidence in the literature proving the safe interchangeability of digital and infrared thermometers with GMT, is still questioned. In fact, accuracy is not yet fully proved due to conflicting findings. For instance, several authors showed that TYM_{IR} provides reliable and accurate readings when compared to GMT (Gasim et al., 2013; Kocoglu et al., 2002; Shinozaki, Deane, & Perkins, 1988); whereas other authors showed that the use of TYM_{IR} in clinical routine is less reliable and less accurate than GMT (Dodd et al., 2006; Paes, Vermeulen, Brohet, van der Ploeg, & de Winter, 2010), probably due to the HCW's poor performance, incorrect probe positioning, presence of earwax or possible tympanic inflammation.

Some studies support the reliability and accuracy of FHD_{IR}, showing that it is very useful in screening for fever in paediatric population (Chiappini et al., 2011; Sollai et al., 2016; Teran et al., 2011). However, majority of the findings do not confirm its accuracy and reliability (Fortuna et al., 2010; Sethi, Patel, Nimbalkar, Phatak, & Nimbalkar, 2013; Vernon, 2014).

Axillary digital thermometer readings seem to be the closest to AXL_{MER} results, and are consequently the most recommended (Childs, 2018; Gerensea & Murugan, 2016; Periasami et al., 2017; Richardson & Lakhanpaul, 2007). However, according to the results of a systematic review (Craig, Lancaster, Williamson, & Smyth, 2000), axilla does not reflect CBT, and this may have implications for clinical situations. In addition, a meta-analysis conducted by Ryan-Wenger and colleagues (2018) highlighted that none of TYM_{IR}, FH_{DIR} and AXL_{DGT} should be used to measure the BT of individuals for screening, monitoring, diagnostic and treatment purposes.

Regardless of these results, while TYM_{IR} and AXL_{DGT} are recommended by several guidelines (Leduc & Woods, 2017, © Department of Health, Government of South Australia, 2016, © World Health Organization, 2013) as the best alternative to GMT for BT measurement, none of them recommend FHD_{IR} (Davis, 2013).

In any case, to obtain a correct diagnosis and an adequate treatment, as well as prevent potential complications, reliable, comfortable, noninvasive, safe, easy and inexpensive thermometers are required.

3.2 Purpose

The aims of this study were to detect any differences in measurement values between the old 'gold-standard' mercury axillary thermometer and the new digital and infrared thermometers in a paediatric setting, and to explore the accuracies of the thermometers in detecting fever.

The study hypothesis was that no clinically significant differences exist between the old mercury thermometer and the modern devices with regards to paediatric patients, even in terms of sensitivity and specificity for fever detection.

3.3 Materials and Methods

3.3.1 Study design, setting, and participants

A comparative observational study was conducted from September 2018 to January 2019 in a fifty-bed paediatric ward of a general hospital in Albania. Approximately one thousand children are admitted yearly to this ward because of the broad range of medical health issues. The main admission diagnoses are related to respiratory diseases, such as bronchopneumonia or pharyngotonsillitis, and other infective conditions like enteritis. Using consecutive sampling, the study population included all children, who are aged up to 14 years and needed BT measurement, hospitalized in the paediatric ward of the 'Xhaferr Kongoli' Hospital Center of Elbasan

(Albania). The children were enrolled after their parents gave their written informed consent; those unable to tolerate multiple BT measurements (e.g. because they are irritable) or hospitalized in critical conditions were excluded.

The minimum sample size (n = 326) was estimated with G* Power 3.1.9.2 software to provide a minimum detectable BT difference of 0.2 with a 95% power (1-β) and a 5% α error.

3.3.2 Variables

In order to perform a secondary analysis of subgroups potentially affecting differences in BT detection between the different thermometers, data about demographic and clinical variables, such as age, gender, site of BT measurements, admission diagnosis, antipyretic drugs assumption, were also collected.

In this study, AXL_{MER} was considered the 'gold standard' while AXL_{DGT}, $FHD_{IR,}$ and TYM_{IR} were considered the alternatives.

3.3.3 Instruments and procedure

The axillary temperature was measured using the Easy Touch Digital thermometer (product code 00006929000000, Chicco®, Italy) and the GEA Medical Mercury thermometer (product code 10901902464, GEA®, Indonesia). Both the digital and mercury devices were placed deeply in each child's left or right armpit, taking 1 and 5 minutes (Hadgu et al., 2017) respectively to measure BT by heat conduction. The AXL_{MER} was used after shaking and lowering the mercury to the minimum level (35.0 °C). Recordings were timed with a stop clock for the AXL_{MER} and a beeper for the AXL_{DGT}. The narrow bulb was placed in the depth of the armpit, taking care not to touch the clothes, while the arm was held steady.

The tympanic temperature was detected using the InfraRed Comfort Quick device (product code 00000656000000, Chicco®, Italy) by a one-second scan of the infrared radiation from the tympanic membrane. It was ensured that the ear was not in contact with a pillow. To obtain accurate measurements, the following steps were taken:

1) The ear was gently pulled backward in children up to two years old, while in all others it was pulled upward and backward for direct visualization of the ear canal;
2) For each measurement, the probe of the tympanic thermometer was replaced;
3) If the child had been lying with their ear on a pillow, they were allowed 20 minutes so their temperature could normalize;
4) Lastly, the reading shown on the digital screen just after the beep was recorded as the ear temperature.

The forehead temperature was measured using the Infrared Easy Touch thermometer (product code 00004757100000, Chicco®, Italy) by scanning the infrared radiation from the temporal artery for 5-8 seconds on average (30 seconds maximum). Measurements did not begin until at least 30 minutes after bath, to make sure that the skin was clean and dry. Following the instructions in the device's manual and in the literature, measurements were taken from the same side in the morning and afternoon, because the BT can change according to the depth of blood vessels.

Five well-trained nurses, who had attended a theory-practice learning session to ensure the accuracy of measurements, performed all BT detections and recorded all data in a collection form.

For each child, all the measurements were performed simultaneously twice daily (morning and afternoon). Regarding the measurements with the alternative devices, it was a time difference between successive measurements about two minutes.

Following the manufacturers' instructions, all the modern thermometers were already in the temperature room at least five minutes before taking measurements. All the measurements were performed simultaneously during 5 min of AXL_{MER} and also, they were all collected as degree Celsius. All thermometers were calibrated according to the manufacturers' standards before being used.

3.3.4 Data analysis

Data were synthesized by calculating frequencies (n), percentages (%), central tendency indexes (mean, median), and dispersion measures [standard deviation (John & Gilsdorf), range]. The normality of the distribution of numerical variables was explored using the Kolmogorov-Smirnov test. To document the interchangeability of the alternative devices, Pearson *r* correlation coefficients and mean differences were computed. Student's two-tailed paired t-test was used to explore the differences between the average BTs obtained with the alternative devices and the 'gold standard'. Furthermore, the degree of agreement of each alternative device with the 'gold standard' was shown using the Bland–Altman plots (Bland & Altman, 1986). Moreover, the 95% Limits of Agreement (LoA), defining the range within which most differences between measurements by the two methods will lie, were computed with the formula $X \pm 1.96 \times$ *standard deviation* (John & Gilsdorf) of the measurement differences (Bland & Altman, 1999; Giavarina, 2015). According to available guidelines (Bland & Altman, 1986; Leick-Rude & Bloom, 1998), the expected maximum acceptable LoA values were $X \pm 0.5$ °C. In regard to the secondary aim, which was to document the diagnostic accuracy of the alternative devices to detect fever, sensitivity ['true positives' / ('true positives' + 'false negatives')], specificity ['true negatives' / ('true negatives' + 'false positives')], positive predictive value (PPV) ['true positives' / ('true positives' + 'false

positives')] and negative predictive value (NPV) ['true negatives' / ('true negatives' + 'false negatives')] were calculated (Stojanovic et al., 2014).

Since normal BT values may be related to the site of measurement with no international agreement on one single definitive value for fever (Crawford et al., 2006; Oguz et al., 2018; Sund-Levander et al., 2002), this study adopted the value, ≥37.0 °C using the 'gold standard' device, to define fever in paediatric patients 0 to 14 years of age..

Significance level for all tests was $p \leq 0.05$. All data were analyzed using IBM SPSS version 19.0 (IBM Corp., Armonk, New York, USA).

3.3.5 Ethics

This study was made possible, thanks to the cooperation between the University of Elbasan, 'Aleksander Xhuvani' and the University of L'Aquila, Italy (letter of agreement #1883/2018), and was conducted in accordance with the Declaration of Helsinki. It was approved by the board of the 'Xhaferr Kongoli' Hospital Center, Elbasan, Albania, according to Albanian Law (letter of approval #1693/2018). According to national laws, the confidentiality of the data concerning participants has been guaranteed. Following the approval by the board of the hospital, the Head of Paediatrics Ward was informed with an official letter of cooperation and also verbally. Before data collection, the aim of the study was explained at least to one of the two parents from whom the written informed consent on their child was obtained and who was present during the data collection. Data was treated confidentially, and subjects were identified by number only. Despite the parental consent, all children had the opportunity to refuse the multiple BT measurements. No child was forced to participate where there was verbal or non-verbal refusal.

3.4 Results

3.4.1 Participants

A total of 356 children were enrolled (Table 1). Two hundred and eleven (59.3%) were males and the average age was 3.0 ± 3.0 years (median 2.0; IQR 3.1; range 0.1-14).

The main reasons for hospitalization were respiratory (209, 59.3%) and gastrointestinal diseases (73, 20.6%). Forty patients (11.2%) received one antipyretic drug administration before BT measurements.

Table 1. Participants' characteristics (n = 356)

***Missing data n = 3**

		N	%	Mean	SD
Gender					
	Male	211	59.3		
	Female	145	40.7		
Age (years)				3.0	±3.0
Admission diagnoses (grouped by system) *					
	Respiratory	209	59.0		
	Gastrointestinal	73	20.6		
	Neurologic and sensorial	29	8.2		
	Urinary	9	2.5		
	Locomotor and articular	3	0.8		
	Other	31	8.8		
Received antipyretic drugs before BT measurements	Yes	40	11.2		
	No	316	88.8		

3.4.2 Agreement among thermometers

A total of 711 paired measurements were carried out. Descriptive analysis showed that the mean of BT values by AXL_{MER} (36.61°C) was higher than that of the FHD_{IR} (36.58°C), AXL_{DGT} (36.57°C) and TYM_{IR} (36.49°C) (Figure 1).

At the bivariate level, comparing forehead BT values with AXL_{MER} (Figure 1), no significant mean difference was detected (Δ = -0.03, SD = ± 0.46, p = -0.141).

Conversely, comparing AXL_{DGT} and TYM_{IR} mean BT values with AXL_{MER}, significant mean differences were detected (Δ = -0.04, SD = ± 0.29, p <0.01; Δ = -0.12, SD = ± 0.47, p <0.001, respectively).

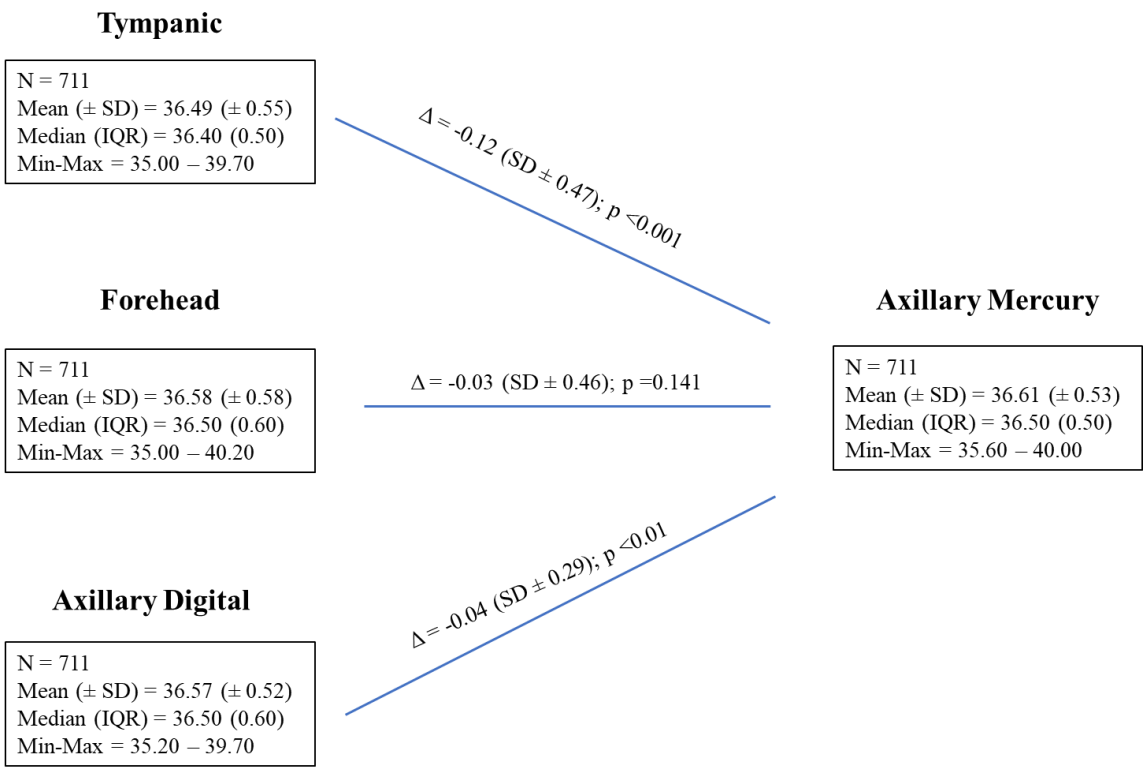

Fig. 1 Comparison of BT values of each alternative device with those of the axillary mercury

Furthermore, a moderate correlation (p<0.001) was detected between $TYM_{IR,}$ FHD_{IR}, and AXL_{MER} measurements (*r* 0.623 and *r* 0.665, respectively). A strong correlation (p<0.01) emerged from the comparison between digital and AXL_{MER} measurements (*r* 0.844).

3.4.3 Agreement between each peripheral devices and axillary mercury thermometer BT measurements

The Bland-Altman scatterplots (Figures 2a, 2b, 2c) highlight the level of agreement of BT measurements by each peripheral device with those by the mercury thermometer. AXL_{DGT} showed narrower 95% LoA (-0.62 °C to +0.53 °C) compared to FHD_{IR} and TYM_{IR} (-0.92 °C to +0.87 °C and -1.04 °C to + 0.81 °C respectively). In addition, FHD_{IR} and TYM_{IR} showed a greater number of outliers above and below the 95% LoA values when compared to AXL_{DGT}.

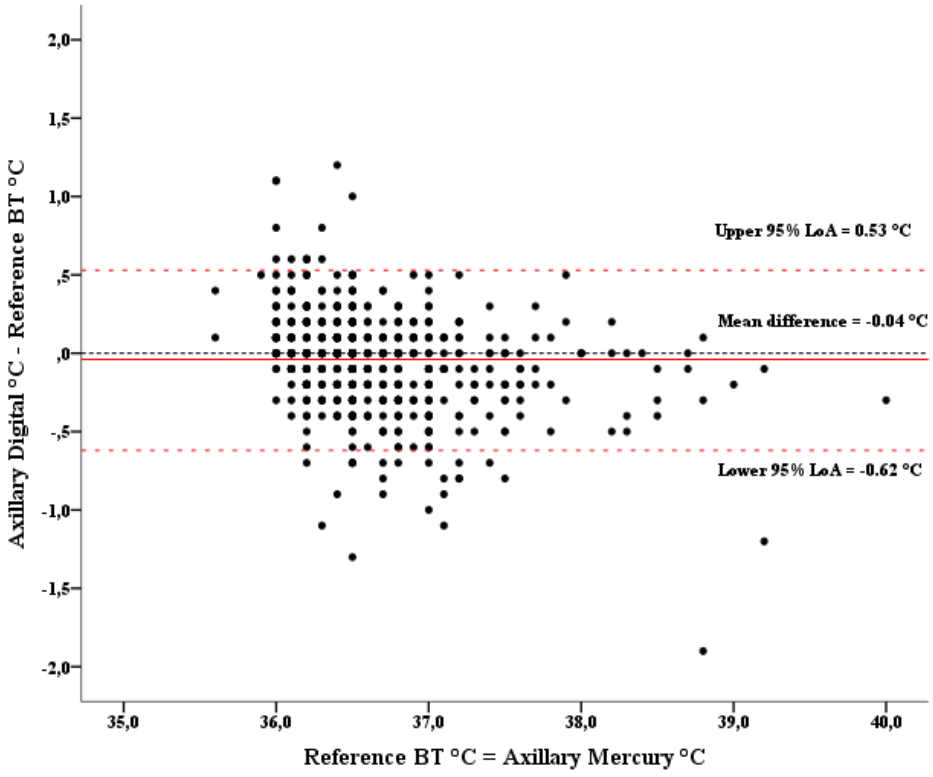

Fig. 2a Bland-Altman plot of differences between AXL_{DGT} and the 'gold standard'

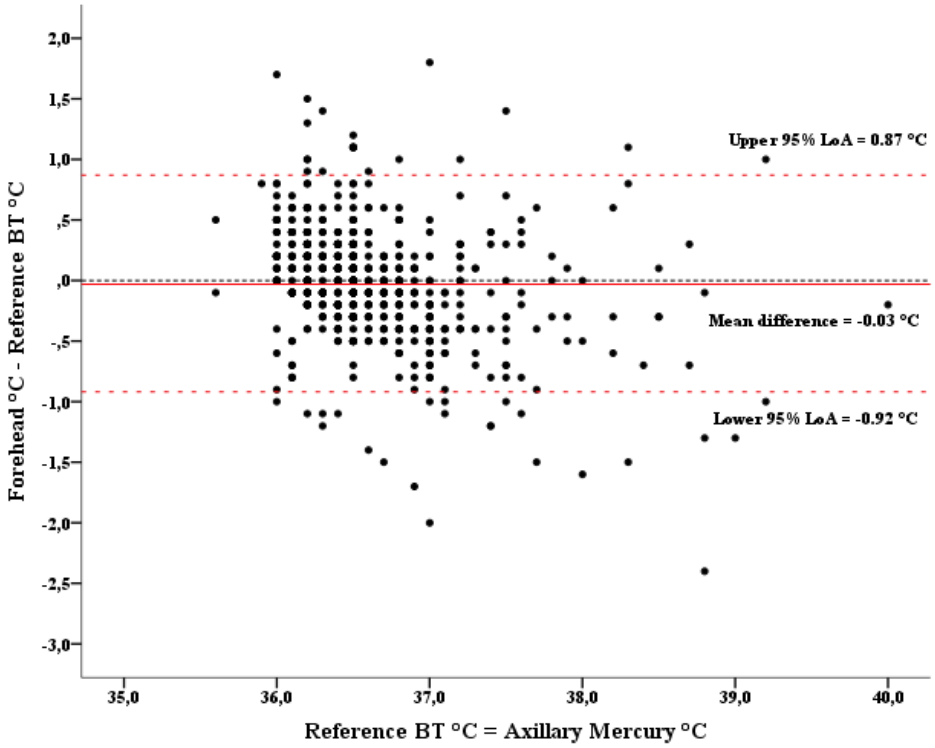

Fig. 2b Bland-Altman plot of differences between FHD_{IR} and 'gold standard'

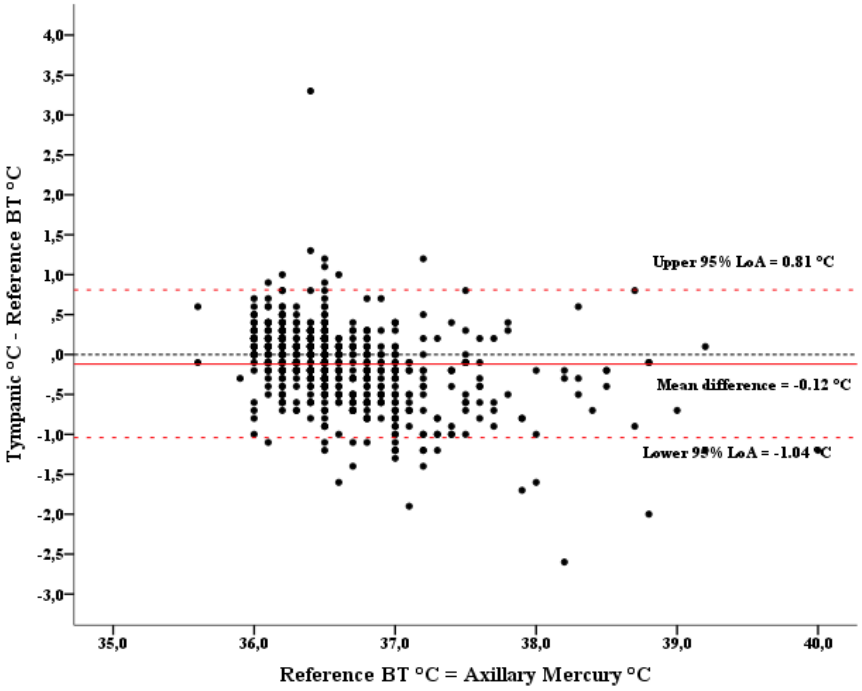

Fig. 2c Bland-Altman plot of differences between TYM_{IR} and 'gold standard'

For each instrument, Considering the pre-established range of acceptability ±0.5 °C of the differences between each measurement and the AXL_{MER} value, the 91.80%, 80.50%, and 77.60% of AXL_{DGT}, FHD_{IR}, and TYM_{IR} measurements and -0.5 °C, 8.20%, 19.50%, 22.40%, respectively, were included in such range (Figure 3).

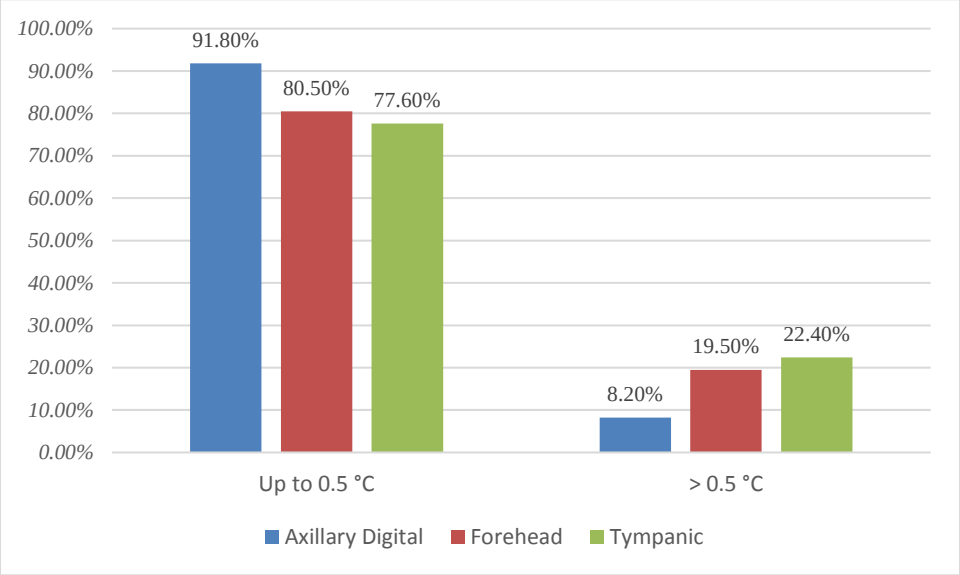

Fig.3 Percentage of mean differences that fell within the maximum acceptable LoA (*X* ±0.5 °C)

Among the alternative devices, AXL_{DGT} thermometer showed the highest level of sensitivity and specificity to detect fever in paediatric patients (table 2).

Table 2. Diagnostic accuracy of alternative devices to detect fever compared to the 'gold standard' (BT ≥ 37.0 °C)

Indexes	AXL_{DGT}	FHD_{IR}	TYM_{IR}
Total sample (n = 711)			
Sensitivity	67.4	50.4	47.4
Specificity	95.3	91.7	94.8
PPV	77.1	58.6	68.1
NPV	92.6	88.7	88.5

3.5 Discussion

In accordance with the Minamata treaty (Kessler, 2013), a large number of hospitals worldwide are undergoing a change from the use of mercury thermometers to the use of alternative devices. Considering that in Albania this process of change is not yet complete, and mercury thermometers are still in use in some hospitals, we had the opportunity to compare them and the alternative thermometers. This allowed us to significantly contribute to international debate on the validity and reliability of the clinical modern devices (Chiappini et al., 2011; Uslu et al., 2011). In fact, the alternative devices have been introduced in clinical practice due to their convenience and acceptability to patients, especially in paediatric settings. They are safe, easy and fast to use, and provides little or no discomfort to the subjects. However, no strong evidence on their safe interchangeability with mercury devices is available. In this regard, this study aimed at documenting the degree of interchangeability of alternative devices (AXL_{DGT}, $FHD_{IR,}$ and TYM_{IR}) with AXL_{MER} in paediatric settings, and at exploring their diagnostic accuracy in detecting fever.

Participants were all hospitalized children aged 0 to 14, like in some other studies (Franconi, La Cerra, Marucci, Petrucci, & Lancia, 2016; Isler, Aydin, Tutar Guven, & Gunay, 2014; Vertedor-Hurtado et al., 2009). The descriptive analysis highlighted that average BT values given by AXL_{MER} (36.61 °C) were significantly higher than those detected with AXL_{DGT} ($p<0.01$) and TYM_{IR} ($p<0.001$).

These results were similar to those reported by some authors (Olasinde, Ernest, Popoola, & Ernest, 2018; Smith, 1998), but in contrast to some others (Duran, Vatansever, Acunas, & Sut, 2009; Gasim et al., 2013).

If we consider the clinically insignificant differences between the mean BT values given by AXL_{MER} and each of FHD_{IR}, AXL_{DGT}, and TYM_{IR} (-0.03 °C, -0.04°C and -

0.12 °C, respectively), and the strong and direct correlation between AXL_{DGT} and AXL_{MER}, it seems that the alternative devices, especially AXL_{DGT}, and the mercury thermometer could be used interchangeably. This result is in line with the recommendations of the Italian Pediatric Society, which considered AXL_{DGT} as the best alternative device in measuring BT in children (Chiappini et al., 2009).

Even if the results of other studies do not seem to agree that AXL_{DGT} is the best alternative to mercury thermometer for BT measurement in sick children (El-Radhi & Barry, 2006; Kitsommart & Phatthanasiriwetin, 2005; Sganga, Wallace, Kiehl, Irving, & Witter, 2000), analysis of the 95% LoA estimated for this study, comparing AXL_{MER} and AXL_{DGT} (-0.62°C to +0.53°C), we concluded that the two methods, i.e. showed that AXL_{MER} and AXL_{DGT} are more or less equivalents and can be used interchangeably in clinical practice.

Some authors highlighted the poor accuracy of TYM_{IR} and do not recommend it for fever diagnosis in children, but only for screening purposes (Childs, Harrison, & Hodkinson, 1999; Devrim et al., 2007; Vertedor-Hurtado et al., 2009; Yetman, Coody, West, Montgomery, & Brown, 1993; Zhen et al., 2014).

Conversely, Gallimore (2004), though, pointed out that there is sufficient evidence on the speed and convenience of TYM_{IR} to continue its use. Based on the results of our own study, we can consider tympanic thermometer safe and useful in clinical practice only if the use is subjected to clinical observation (Davis, 2013).

We detected no significant difference between the mean values of FHD_{IR} and AXL_{MER}, considering that some authors (Ataş Berksoy, Bağ, Yazici, & Çelik, 2018; Teller et al., 2014), in accordance with recent guidelines, do not recommend FHD_{IR} (© Department of Health, Government of South Australia, 2016, © World Health Organization 2013), though several others consider it a reliable tool (Chiappini et al., 2011; De Curtis, Calzolari, Marciano, Cardilli, & Barba, 2008; Sollai et al.,

2016). Like for the tympanic devices, the results of our own study suggest using forehead thermometer for BT measurement preferably under clinical observation.
It is important to highlight that, in accordance with available guidelines (Davis, 2013), our study suggests AXL_{DGT} as the best alternative to AXL_{MER}. However, TYM_{IR} and FHD_{IR} seem to be useful alternatives if used with caution, considering the child's clinical picture.

3.6 Study Strengths and Limitations

Considering that studies comparing alternative devices with the historical glass mercury thermometer in paediatric settings are limited, this comparison in itself is the greatest strength of this research. The study limitations arise from the monocentric approach of the research and the environmental temperature that was not considered. However, this condition is similar to the clinical reality in which possible variations in environmental temperature can occur and are not considered.

3.7 Conclusions

The results of this study confirmed that the AXL_{DGT} is the best alternative to the AXL_{MER} in paediatric clinical settings. AXL_{DGT} showed also the best performance in detecting fever of all the alternative devices compared to the 'gold standard'. In view of the insignificant clinical differences between their performance and that of AXL_{MER}, TYM_{IR} and FHD_{IR} should be used but only after serious consideration of the clinical picture of the paediatric patient.

Our hypothesis that these alternative devices are interchangeable with AXL_{MER} in paediatric settings and diagnostically accurate in detecting fever was fully confirmed in relation to the AXL_{DGT} device.

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