

# Whole-Body Hyperthermia Guideline

Version 1.0 | October 2018

# Content

Introduction

Objective

Purpose

Whole-body hyperthermia / General definition

## 1. Mild and fever-range whole-body hyperthermia

1.1. Definition

1.2. Technical specification

1.2.1. Hyperthermia technology

1.2.2. Temperature control / monitoring

1.3. Staff specifications

1.3.1. Nursing staff

1.3.2. Medical staff

1.3.3. Technical staff

1.3.4. Laboratory

1.4. Indications

1.5. Contraindications

1.6. Performance of mild /fever-range whole-body hyperthermia

1.6.1. Preparation

1.6.2. Temperature control

1.6.3. Sedation

1.6.4. Chemotherapy

1.6.5. Supportive therapy

1.6.6. Follow-up / monitoring

## 2. Extreme whole-body hyperthermia

2.1. Definition

2.2. Technical specification

2.2.1. Hyperthermia technology

2.2.2. Temperature control / monitoring

2.3. Staff specifications

2.3.1. Nursing staff

2.3.2. Medical staff

2.3.3. Technical staff

2.3.4. Laboratory

2.4. Patient selection and confirming the indication

2.5. Contraindications

2.6. Performance of extreme whole-body hyperthermia

2.6.1. Preparation

2.6.2. Temperature control

2.6.3. Anesthesia

- 2.6.4. Chemotherapy
- 2.6.5. Supportive therapy
- 2.6.6. Hyperthermia procedure
- 2.6.7. Follow-up / monitoring

### 3. Documentation and quality assurance for whole-body hyperthermia

- 3.1. Recording therapy and temperature data
- 3.2. Recording and managing side effects
- 3.3. Follow-up examinations
- 3.4. Documentation of treatment results

### 4. Outlook

### 5. Annexes

### 6. Literature

## List of figures and annexes

#### Figure 1

Three stages of whole-body hyperthermia (WBH) according to “heckel medizintechnik” and “Von Ardenne Institute for Applied Medical Research” updated 01/2018 [4]

#### Figure 2

Evidence levels modified according to Agency for Healthcare Research and Quality (AHRQ) [3]

#### Annex 1

Publication-based treatment regimens for whole-body hyperthermia (WBH) for select non-oncological indications

#### Annex 2

Temperature and parameter monitoring as well as their automatic documentation IRAsoft® in conjunction with IRAcom® Von Ardenne Institute for Applied Medical Research [9]

#### Annex 3

Temperature and parameter monitoring with automatic documentation.

FebroData®, heckel medizintechnik [8]

#### Annex 4

Sample follow-up and monitoring protocol according to WHO classification. gisunt® Klinik Wilhelmshaven [80]

## Abbreviations

Fig.	Figure
Par.	Paragraph
CT	Controlled trial
DGHT	German Society for Hyperthermia
ECG	Electrocardiogram
EORTC	European Organization for Research and Treatment of Cancer
FACT	Functional Assessment of Cancer Therapy
WBH	Whole-Body Hyperthermia
h	Hour
HR	Heart rate
HT	Hyperthermia
IV	Intravenous
LDH	Lactate dehydrogenase
mmHg	Millimeters of mercury or Torr
min	Minutes
NIBP	Non-invasive blood pressure
NYHA	New York Heart Association
Pt.	Point
paO <sub>2</sub>	Partial arterial pressure of oxygen
pCO <sub>2</sub>	Partial pressure of carbon dioxide
pO <sub>2</sub>	Partial pressure of oxygen
PPT	Partial thromboplastin time
PTZ	Plasma thrombin time
RESP	Respiratory rate
RCT	Randomized controlled trial
sCMT	Systematic cancer multi-step therapy
SpO <sub>2</sub>	Oxygen saturation
T	Temperature
Th.	Thousand
WBH	Whole-body hyperthermia
WHO	World Health Organization
S.p.	Status post
μl	Microliters
5-FU	5-fluorouracil

# Whole-Body Hyperthermia Guideline

## **Authors**

### **For the Scientific Advisory Board and the DGHT Board of Directors:**

Dr. med. Dipl.-Med. Holger Wehner, Professor, Institute for Integrative Medicine, Medical Academy Moscow (RUS)  
Chief physician, gisunt® clinic, Wilhelmshaven

Dr. med. Stephan Wey, specialist for internal medicine, naturopathy, emergency medicine, palliative care  
Advanced training: Nutritional medicine, expert in biological medicine (University of Milan)

Dr. med. Arno Meyer, specialist for anesthesiology

### **With appreciation for contributions by:**

Dr. rer. nat. Alexander von Ardenne, CEO, Von Ardenne Institut für Angewandte Medizinische Forschung GmbH (Institute for Applied Medical Research)

Stefan Heckel-Reusser, CEO, heckel medizintechnik GmbH

Dr. med. Hüseyin Sahinbas, specialist for radiation therapy and radiology, palliative care

Dr. med. Wulf-Peter Brockmann, specialist for radiology and radiation therapy

Christian Wehner, assistant for science and economics, gisunt® clinic

### **Correspondence address:**

Deutsche Gesellschaft für Hyperthermie e.V.

Scientific Advisory Board

Infanterieweg 30 b

D- 26129 Oldenburg, Germany

Phone: 0441-93654586

E-Mail: [info@dght-ev.de](mailto:info@dght-ev.de)

## Introduction

Whole-body hyperthermia (WBH) or “systemic hyperthermia” – defined as the controlled increase of the core body temperature for therapeutic purposes – is one of medical history's oldest therapy forms, with traditions in most cultures and a very broad spectrum of indications [1]. A frequently quoted saying, ascribed to Hippocrates, states that “*Fever is a healing effort of the organism against disease; it cleanses the body like a fire.*”

WBH, among other factors, is based on appreciating infectious fever as a natural mechanism occurring in all warm-blooded creatures, in which an increase in the core body temperature serves as an essential trigger for initiating and controlling an extraordinary immune response. Numerous preclinical studies have confirmed the therapeutic potential of controlled increases in core body temperature and have gradually examined the underlying biological mechanisms [2].

For some non-oncological and oncological indications, the effectiveness of WBH has already been documented with clinical studies at various levels of evidence. Mechanisms of action include increased perfusion and metabolic activity associated with the increase in core body temperature as well as effects on the hormonal and immune system. The range of WBH extends from mild thermal applications that can be performed at home to actual “fever temperatures” and extreme WBH administered in intensive care settings. This spectrum requires clear definitions and differentiations.

## Objective

In full recognition of its long tradition and within the framework of quality assurance required in modern medicine, modern WBH is subject to the following dual requirements:

- 1) Definition and establishment of standards for staff qualification as well as for patient care and monitoring, which
  - guarantee a high level of safety for patients and users and
  - serve as the basis for health insurance reimbursement.
- 2) Examination and optimization of the therapeutic potential of WBH in individual indications based on scientific studies. Both the comparability of prospective studies and the combination of data from routine applications in registry studies require standardization, particularly in terms of terminology and capturing vital parameters.

Guidelines always walk a fine line. They must balance the above-described need for standardization with the recognition of the traditional methodological pluralism that can promote the scientific discussion to optimize therapeutic concepts and take individual patient needs into account.

This Guideline is open to new scientific findings and was ultimately written as a point of reference for critical debate and discussions to be continuously reviewed, updated and further improved.

## Purpose

This Guideline by the German Society for Hyperthermia primarily concerns the methodology of performing WBH. It is based both on published scientific data and on extensive bodies of experience, specifically those of the Society's members that are communicated and discussed at its regular conventions.

This is the first guideline to include the entire temperature range of WBH. Previously published guidelines on partial aspects of WBH were taken into account. This Guideline does not include “fever therapy,” also referred to as “active hyperthermia,” which relies on pyrogenic substances to increase the body temperature.

Furthermore, this Guideline does not refer to the application of mild, short-term whole-body thermal applications, in which increasing the core body temperature is not defined and measured as the objective of the application, such as, for instance, sauna, infrared applications and packs (see Fig. 1, first column). This is in no way intended to deny the medical benefit of such applications, but makes reference to the extensive body of existing research and professional literature, especially with regard to saunas.

Figure 1 provides a summary of WBH with its various levels of intensity and requirements. In spite of their fluid transitions, the three levels, “mild,” “fever-range” and “extreme” represent clear reference points with fundamentally different characteristics. While mild and fever-range WBH, both of which have reference points to traditional naturopathy, comprise temperatures in the sub-febrile and regular fever range, extreme WBH represents a modern intensive care measure.

The level of evidence for the medical indications of WBH listed in this Guideline was determined based on a slightly modified recommendation of the Agency for Healthcare Research and Quality [3], which only distinguishes three main groups due to the current data situation on WBH (see Fig. 2):

- A** High evidence (Level 1 + 2),
- B** Medium to low evidence (Level 3 + 4) and
- C** Low evidence (Level 5).

In the main group “Low evidence,” the Guideline also touches on traditional indications and indication areas of traditional healing, in which WBH frequently plays an important role as part of multi-modal, individualized therapy concepts, even though scientific proof of efficacy is not (yet) available at a higher level of evidence.

It should be emphasized that users of WBH, in the context of therapeutic freedom, remain fully responsible for the indication and performance of therapy. In individual cases they can, and may have to, deviate from this Guideline as required by the patient’s individual situation.

The recommendations of this Guideline, particularly with regard to sedation (see Sections 1.6.3 and 2.6.3), are subject to medical discretion and under no circumstances confer liability.

Indication-specific guidelines by other medical professional associations have not been taken into account for this Guideline.

	Mild WBH		Fever-range WBH		Extreme WBH
Target temperature Body core, T(rectal)	< 38.5 °C x)		38.5 °C – 40.5 °C x)		> 40.5 °C x)
Application time in the specified temperature range	≤ 30 min	> 30 min	≤ 180 min	> 180 min	generally ≥ 60 min
Patient stress	Perspiration, no thermo-regulatory stress	Perspiration, no thermo-regulatory stress	Thermo-regulatory stress, non-sedated / lightly sedated	Thermo-regulatory stress, lightly / heavily sedated	Thermo-regulatory stress, deep intravenous anesthesia or general anesthesia
Patient monitoring	Without nursing care	Nursing care  T(axillary) or T(rectal) or T(sublingual) or T(tympanic)	Nursing care under medical supervision <sup>xx)</sup>  continuous T(rectal) <sup>+) ± T(axill / tymp) + HR / SpO2 ± ECG periodic ± NIBP ("±" means optional)</sup>	Nursing care under medical supervision  continuous T(rectal) <sup>+) ± T(axill) + HR / SpO2 ± ECG / RESP periodic + NIBP</sup>	Medically supervised treatment  Intensive care monitoring
Indication area (Selection)	Relaxation, Wellness	Rehabilitation, Physical therapy, Rheumatology, Orthopedics	Rheumatology, Dermatology, Oncology, Psychiatry Immunology, Environmental medicine	Oncology, Chronic infection	Oncology, Chronic infection
Obligations of device manufacturer	CE marking as a medical device with participation of a "Notified body" and official monitoring				
<p>x) Temperature limits between WBH levels are given for orientation only since they are subject to individual variations</p> <p>xx) in Germany also under the supervision of "Heilpraktiker"</p> <p>+) if rectal temperature measurement is not an option, vesical or vaginal body temperature measurements may be used as well</p>					

Figure 1: Three stages of whole-body hyperthermia (WBH) according to "heckel medizintechnik" and "Institute Von Ardenne for Applied Medical Research" updated 01/2018. [4]



<b>Level of evidence</b>	
<b>1a</b>	<b>at least one meta-analysis based on randomized controlled trials (RCT) with high quality methodology</b>
<b>1b</b>	<b>at least one sufficiently large RCT</b>
<b>2a</b>	<b>at least one CT without randomization</b>
<b>2b</b>	<b>at least one study of a different type, quasi-experimental</b>
<b>3</b>	<b>more than one non-experimental study such as comparative studies, correlation studies, case control studies or clinical pilot studies</b>
<b>4</b>	<b>expert committee opinions; descriptive studies</b>
<b>5</b>	<b>case series or one or more expert opinions</b>

Figure 2: Levels of evidence modified according to Agency for Healthcare Research and Quality (AHRQ) [3].

## Whole-body hyperthermia – general definition

WBH is the controlled increase of core body temperature based on an external energy supply in accordance with the currently preferred categorization shown in Figure 1. It is also referred to as “passive hyperthermia”.

### 1. Mild and fever-range whole-body hyperthermia

#### 1.1. Definition

Mild WBH involves increasing the core body temperature to target temperatures up to 38.5°C. The application time is divided into two temporal levels of intensity, a short duration under 30 minutes and a longer duration over 30 minutes (see Figure 1).

Fever-range WBH involves increasing the core body temperature to target temperatures from 38.5°C to 40.5°C. The application time of the respective target temperature again is divided into two temporal levels of intensity, a short duration under 180 minutes and a long-duration over 180 minutes (see Figure 1).

#### 1.2. Technical specification

##### 1.2.1. Hyperthermia technology

WBH in the mild and fever-range temperature ranges comprises contact heat, e.g. in water baths, and heat from infrared radiation. The use of water-filtered infrared A, which is particularly well tolerated from a physical and physiological perspective, is especially popular. A significant portion of the infrared radiation is absorbed at the depths in which the circulating blood transports the absorbed heat energy to all regions of the body with the blood flow [5, 6, 7]. In Germany, the most widely used hyperthermia techniques include the method according to Heckel (using infrared A+B radiation in older systems or a regional application of water-filtered infrared A along with infrared C radiation in current systems) [8] and the IRATHERM® technology according to von Ardenne (exclusively based on water-filtered infrared A radiation) [9].

An overview of WBH including the applied technology can be found in [10].

##### 1.2.2. Temperature control / monitoring

In the case of mild WBH, temperature control is mandatory from an application time exceeding 30 minutes. This can involve axillary, rectal, sublingual or tympanic temperature measurements taken at selected times. Measured values have to be documented together with the applied measuring technology. However, measuring systems with continuous temperature acquisition documented on a PC (e.g. IRacom® with IRAsoft® [9], FebroData® [8], see annexes 2 and 3) are preferable.

From the temperature level of fever-range WBH, the increasing temperature creates thermoregulatory stress for patients, which requires nursing care under medical supervision as noted in Figure 1. Starting from temperatures of 38.5°C, continuous rectal temperature measurement as well as heart rate and SpO2 monitoring are minimum requirements. There is broad consensus that the rectal temperature reflects the core body temperature. Should the application time extend beyond 180 minutes at a

temperature over 38.5°C, periodic blood pressure measurements are required, while ECG/RESP measurement and a second continuous temperature measurement can be added. If rectal temperature measurement is not an option (e.g. in the case of an artificial anus), vesical or vaginal temperature recording can be taken into consideration. It is important to note that the axillary and to an even larger degree, the tympanic temperature can differ by about 0.5 to 1°C from the rectally measured temperature in the late warm-up phase.

### **1.3. Staff specifications**

#### **1.3.1. Nursing staff**

Nursing supervision is required for mild WBH with an application time exceeding 30 minutes. Medical technicians, medical assistants, physical therapists and nurses are qualified for this task.

For fever-range WBH without or under light sedation with an application time of 180 minutes or more, nursing care under medical supervision is required according to Figure 1. At a minimum, nursing care means permanent on-call availability with a patient call option and guaranteed uninterrupted attention to warning or alarm signals in a reliable patient monitoring system. Medical supervision refers to the presence and availability of a physician in the medical practice or clinic where the WBH is being performed.

Fever-range WBH under sedation with an application time exceeding 180 minutes requires the constant presence of a person with special training in intensive care in the treatment room as well as periodic check-ups by the supervising physician.

The nursing staff must have received training by the manufacturer, the manufacturer's representative or in a clinic / hospital that uses the same technology and has been certified by DGHT as a training center. The training must include at least one, preferably 2 to 3, guided performances of WBH treatments under real-life conditions. The training must be documented. The operator may designate members of the nursing staff who have received this training "commissioned persons" within the definition of the (German) Medical Devices Operator Ordinance (Medizinproduktebetriebsverordnung - MBetreibV) who can carry out training in their own clinic/hospital in the future, which must be documented as well. Training also includes detailed information about the risks and side effects listed in the Instructions for Use for the corresponding devices.

#### **1.3.2. Medical staff**

Fever-range WBH without sedation / under light sedation with an application time not exceeding 180 minutes may be supervised by physicians of any discipline. The performance of fever-range WBH under sedation with an application time over 180 minutes requires the corresponding qualification and experience with the performance of sedation.

In addition, physicians responsible for the administration of WBH must also have undergone training in the procedure described in Section 1.3.1 / last paragraph and can then function as "commissioned persons" within the meaning of the MBetreibV.

Mild and fever-range WBH under light sedation may also be performed or supervised by other persons authorized to independently practice medicine (in Germany: "Heilpraktiker"). It is presumed that such persons are qualified to perform relevant medical emergency measures as necessary. For simplification, this Guideline consistently uses the terms "physician" and "medical" with reference to all persons listed in Section 1.

#### **1.3.3. Technical staff**

No technical staff is required for the performance of mild and fever-range WBH. However, the assigned medical staff must have received training and instruction from qualified personnel or representatives of the manufacturer to reliably operate the equipment.

#### **1.3.4. Laboratory**

No special laboratory tests are needed for the ranges of mild and fever-range WBH. Laboratory tests prior to, during and after hyperthermia sessions are performed at medical discretion.

## 1.4. Indications

Due to its impact on the immune system, fever-range WBH in particular can be considered a non-specific therapeutic measure for the treatment of chronic illnesses, which are caused by a dysfunction of the immune system and/or restricted tissue perfusion. It is indicated for a range of conditions from chronic infection, inflammation and pain, autoimmune diseases and allergies to complementary cancer treatment. The long tradition of this treatment method and its low risks and side effects can justify the performance of WBH treatments in a wide range of diseases, provided the contraindications were carefully considered and the individual situation and therapeutic alternatives were weighed. The section below lists the indications and indication areas in three main groups:

Indication	Study	Literature
<b>A Indications based on at least CT or RCT (levels of evidence 1 + 2)<sup>1</sup></b>		
<ul style="list-style-type: none"> <li>• Fibromyalgia syndrome</li> <li>• Chronic back pain</li> <li>• Ankylosing spondylitis</li> <li>• Axial spondyloarthritis</li> <li>• Psoriatic arthritis</li> <li>• Arterial hypertension</li> <li>• Major depression</li> </ul>	RCT+CT+CT+ pilot study RCT+pilot study RCT+pilot study CT RCT RCT+pilot study RCT+RCT+pilot study	[11, 12, 13, 14] [15, 16] [17, 18, 19] [20] [21] [22, 23] [24, 25, 26]
<b>B Indications based on comparative studies, case control studies, clinical pilot studies (levels of evidence 3 + 4)</b>		
<ul style="list-style-type: none"> <li>• Immune activation</li> <li>• Cancer – reinforcement of standard therapies</li> <li>• Cancer in the palliative stage – relief of pain and the fatigue syndrome</li> <li>• Bronchial asthma</li> <li>• Osteoarthritis</li> <li>• Systemic scleroderma</li> <li>• Irritable bowel syndrome</li> </ul>	Pilot study Pilot study Pilot study Pilot study Pilot study Pilot study+pilot study RC pilot study	[27], [28, 29, 30, 31] [32] [32] [33] [34] [23, 35, 36] [37]
<b>C Indications and indication areas based on case series or expert opinions (level of evidence 5)</b>		
<ul style="list-style-type: none"> <li>• Maintenance therapy after curative cancer therapy</li> <li>• Allergic rhinitis</li> <li>• Chronic prostatitis</li> <li>• Arthritis</li> <li>• Ulcerative colitis and Crohn's disease</li> <li>• Lyme disease</li> <li>• Post-traumatic recovery</li> <li>• Detoxification</li> </ul>		[38, 39] [40] [40] [34] [41] [42] [40] [44]
<sup>1</sup> <b>Annex 1 specifies the corresponding treatment regimens of the WBH used in the publication with the highest level of evidence for the indications listed in the highest evidence group A.</b>		

In the area of sports medicine, regional hyperthermia applications have been shown to result in the accelerated regeneration of highly stressed muscles [45].

It should be pointed out in this place that this Guideline does not restrict the expansion of indications in any way. Indications that are not listed in this Guideline should not be considered excluded or unsuitable. On the contrary, traditional experiences with this therapy form should be critically reviewed to again take hyperthermia into consideration as a therapeutic option if necessary. An excellent historical overview of applied medical indications as well as a review of the professional literature published to date can be found in Section 2 of [1]. In addition, numerous indications allocated to various temperature levels are listed in [46].

## 1.5. Contraindications

Contraindications depend on the level of temperature increase and are primarily based on cardiovascular stress and the possibility of unwanted activation of inflammations and destabilization of unbalanced hormonal and metabolic constellations.

Hyperthermal increases of the core body temperature over 38°C are absolutely and relatively contraindicated for the diseases listed below. These contraindications were derived from publications and the experiences of therapists working with hyperthermia. The list may be both expanded and reduced in the future.

**Absolute contraindications:**

- arteriosclerotic-cerebral states of confusion
- severe cerebral perfusion defects; increased intracranial pressure from perifocal edema caused by brain tumors and brain metastases
- uncontrolled hyperthyroidism
- acute severe infections (e.g. lungs, liver, kidneys)
- manifest internal organ failure due to destructive inflammatory processes and/or obstructive or destructive neoplasia
- active cavernous pulmonary tuberculosis, late stages of liver cirrhosis and nephrosclerosis
- acute thermal skin damage (e.g. sunburn)
- pregnancy

**Relative contraindications:**

- cardiac arrhythmias and heart failure (ECG monitoring after cardiological assessment)
- acute infections
- reduced thermo-sensitivity of the skin and micro-circulation disorders (e.g. diabetic neuropathy, chemotherapy)
- increased skin sensitivity (e.g. application of photosensitizers)
- susceptibility to febrile seizures
- severely weakened or heavily impaired general physical condition

## 1.6. Performance of mild / fever-range whole-body hyperthermia

### 1.6.1. Preparation

It is presumed in daily practice that therapy sessions will be preceded by a conversation with the physician and that the patient will receive information about the current diagnostics and therapy options as well as the resulting indication. Such a preparatory conversation should also include information about side effects such as the commonly encountered sense of restlessness due to thermoregulatory stress, but also the risk of thermal lesions, which are very rare, but cannot completely be ruled out.

All practitioners must inform their patients about the cost of hyperthermia treatment. It is recommended to obtain the written consent of the patient, particularly in case of future legal disputes. The patient's preparation for starting the therapy (clothing, positioning, hygienic conditions) depends on the thermal dose to be applied (temperature and exposure time) as well as the involved technology.

### 1.6.2. Temperature control

Temperature control is mandatory for all whole-body hyperthermia treatments to achieve the indication-specific target temperature (see 1.2.2). The intensity as well as the type and scope of documentation depend on the WBH type and the temperature level and exposure time.

### 1.6.3. Sedation

The thermoregulatory stress experienced by patients varies considerably by individual. In the case of fever-range hyperthermia not exceeding 180 minutes (as shown in Fig. 1), generally no or just minor sedation is required, e.g. using plant-based or homeopathic sedatives. In rare cases, a gradual sedation by oral administration of lorazepam or as a supplement to an existing IV infusion with midazolam can be applied as needed.

In the case of fever-range hyperthermia exceeding 180 minutes (see Fig. 1), continuous sedation may be necessary, using midazolam, fentanyl and propofol. A sedation protocol mainly based on midazolam and fentanyl is described in [32, 47, 48, 49]

### 1.6.4. Chemotherapy

Any chemotherapy performed in addition to hyperthermia may only be applied under the supervision of an experienced physician, observing the precautionary measures and regulations for the application of cytostatic chemotherapy. The combination of WBH and chemotherapy is a complex process.

The intended mechanisms of action (increasing tumor tissue perfusion and drug accumulation, increasing the metabolism, immunological effects) must be defined with consideration for pharmacodynamic properties to determine the timing of both applications.

### 1.6.5. Supportive therapy

Dehydration must be actively counteracted prior to, during and after whole-body hyperthermia treatment. In the case of treatments without sedation, this can be achieved with drinking or infusion, while supportive therapy with electrolyte infusions is mandatory for treatment under sedation and for long-term treatments according to Fig. 1.

### 1.6.6. Aftercare / monitoring

The aftercare and monitoring of patients depends on the temperature level and duration of the therapy as well as on any side effects that may have occurred during the therapy, the cool-down or the aftercare phase. In case of fever-range hyperthermia treatments not exceeding 180 minutes and stable cardiovascular parameters, 30 minutes of rest can be considered a sufficient recovery time. For treatments over 180 minutes, longer rest and monitoring times are required until cardiovascular stability has been achieved.

## 2. Extreme whole-body hyperthermia

### 2.1. Definition

Extreme WBH involves increasing the core body temperature to target temperatures above 40.5°C. The application time in the range of the target temperatures is generally over 60 minutes (see Fig. 1).

The current specialist debate on the oncological use of extreme WBH is reaching the conclusion that cytoreductive effects require at least 41.5°C and can only be achieved under metabolically optimized conditions (glucose-induced lactic acidosis and hyperoxemia / see sCMT). In addition, metabolically optimized conditions are the prerequisite for realizing core body temperatures over 42°C.

In Germany, radiative systems currently use about three temperature-time regimens in practice: High-level temperatures above 41.5°C for 90 minutes or more, above 41.8°C for 60 to 90 minutes, or above 42.0°C for 30 to 60 minutes. The working group around von Ardenne for the first time introduced high-level temperatures of 42.3°C in the context of systemic multi-step cancer therapy / sCMT (extreme WBH + induced hyperglycemia + relative hyperoxemia) [50]. In practice, whole-body hyperthermia treatments now use this procedure to safely perform the therapy at a temperature level of 42.5°C. The conductive "Heatheal method" in a hot water bath can reach temperatures above 43°C for a few minutes [51].

With regard to extreme WBH from 41.5°C to 41.9°C, we refer to the data of Robins [52], Kerner [53], Wust [54], Hegewisch-Becker [55], Hildebrandt [56], Bakhshandeh-Bath [57], Atmaca [58], Deja [59], Ismail-Zade [60] Zhao [61] and Herzog [62, 63]. Reviews with practical information on performing extreme WBH in this temperature range and on hyperthermia technology were published by Hildebrandt [64] and Rowe-Horwege [10].

Documentation of extreme WBH above 42°C can be found in the working groups of Steinhausen [65], Krasny [66], Takeuchi [67], von Ardenne [68], Bremer / Meyer [69], Wehner [70], von Ardenne [71] and Suvernev [72].

### 2.2. Technical specification

#### 2.2.1 Hyperthermia technology

Systems such as IRATHERM®2000, Entermics, Aquatherm, heckel-HT3000, IRATHERM®1000 as well as Heatheal-WBH-TEC-LCC are used in extreme WBH.

### 2.2.2. Temperature control / monitoring

Continuous intensive care monitoring is required for extreme WBH that is performed under deep intravenous anesthesia or general anesthesia. Depending on the hyperthermia system, this involves up to four temperature sensors, which can be rectal or/and vesical, axillary and skin sensors. For local control of the skin temperature, a manual pyrometer with adjustable emission coefficients can be used. Temperatures, pulse oximetry and the radiation settings must be continuously recorded by a computer, and ECG / RESP systems must be available for monitoring. Blood pressure measurement is to be carried out periodically and must be documented.

In the case of extreme WBH administered with contact heat in a water bath, temperature measurement is also mandatory over multiple channels, i.e. water temperature as well rectal or vesical, esophageal or nasal measurements (see [54]).

The temperature measurements must be performed with appropriate equipment that is subject to the German Medical Device Act (Medizinproduktegesetz). The accuracy of the temperature measurement should be  $\pm 0.1$  °C.

Proven examples of monitoring and documentation systems include IRacom® with IRAsoft® [9] (s. Annex 2) and FebroData® [8] (s. Annex 3).

### 2.3. Staff specifications

Extreme WBH requires qualified staff.

#### 2.3.1. Nursing staff

It is recommended to have a nurse with experience in intensive care and/or training in extreme WBH accompany the treatment. Another staff member with the qualification of a registered nurse should be on call in case of an emergency, i.e. this person should be available for the nursing staff member supporting the therapy within less than one minute. When forming new teams, it is recommended to have two members of the nursing staff accompany the treatment.

In addition to a nurse with experience in intensive care medicine, a second nurse is required for additional measurements in the Heatheal® procedure. Another staff member (who can be a medical technician/medical assistant) is responsible for the continuous documentation of the high-speed therapy. Furthermore, another qualified staff member must control the water temperature at different points and mix the water mechanically or by hand to homogenize the water temperature. A qualified anesthesia nurse is essential to assist the physician inducing the anesthesia.

The nursing staff must have received training by the manufacturer, a representative of the manufacturer or in a medical clinic / hospital that uses the same technology and has been certified by DGHT as a training center. The training must include at least three, preferably more, supervised treatments under real-life conditions. The training must be documented. The operator may designate members of the nursing staff who have received this training "Commissioned persons" within the definition of the Medical Devices Operator Ordinance (MBetriebV) who can carry out training in their own clinic/hospital in the future, which must also be documented. Training includes detailed information about the risks and side effects listed in the instructions for use of the corresponding devices.

#### 2.3.2. Medical staff

In the case of extreme WBH, the physician performing the hyperthermia treatment not only is responsible for supervision, but actively carries out the therapy and monitors all processes. An anesthesiologist must be present in case of intubation anesthesia. If deep intravenous anesthesia is used (neuroleptanalgesia), the physician introducing the anesthesia (with the appropriate experience and/or training) may also be responsible for carrying out the hyperthermia treatment. A second physician must be on call in case of any complications, particularly if the physician introducing the anesthesia is also responsible for the hyperthermia treatment.

In the case of the Heatheal® procedure, the presence of two physicians to handle the hyperthermia treatment and anesthesia separately is mandatory. Another physician is required in addition to the physician performing the hyperthermia treatment and the anesthesiologist. Due to the special concerns of underwater treatment (ECG lead faults), this physician must monitor the cardiac action and pulse and continuously report to the physician performing the therapy. In the area of oncological indications, particularly with simultaneous application of chemotherapy, the physician carrying out the therapy must be familiar with the handling of cytostatic chemotherapy drugs or a corresponding physician must be present.

In addition, physicians responsible for the performance of WBH must also have undergone training in the procedure described in Section 2.3.1, last paragraph and can then function as "commissioned persons" within the meaning of the Medical Devices Operator Regulation (MBetriebV).

### 2.3.3. Technical staff

It is recommended to involve in-house technicians into the therapy briefing for extreme WBH and to have them available to quickly address technical problems with power, water or oxygen supply to avoid having to discontinue the therapy for a patient under anesthesia.

For the Heatheal® method, the presence of an in-house technician is absolutely required in case technical operations are required for a quick water exchange.

### 2.3.4. Laboratory

In-process laboratory controls are required for extreme WBH. This involves at least a standard blood count including hematocrit, creatinine, electrolytes, blood glucose levels and liver values in case of abnormalities at the start of the therapy and at the end of the high plateau to guarantee the safe performance of the therapy. The responsible physician must consult additional parameters, depending on co-morbidity, starting values and clinical situation.

If extreme WBH is performed as part of systemic multi-step cancer therapy, pH measurements are recommended in addition to frequent blood glucose and lactate controls (not mandatory but useful in terms of monitoring tumor acidification). In addition, blood gas analysis is advisable at the start, prior to and after the high temperature plateau to monitor oxygenation. The same applies to laboratory monitoring for the Heatheal® treatment.

## 2.4. Patient selection and confirmation of indication

Patient selection and confirmation of indication follow the previously published indications and contraindications for extreme WBH. The indications and contraindications described in the monograph "Systemic multi-step cancer therapy" [68] provide useful guidance. As a prerequisite for treatment with extreme WBH, patients should be in adequate general physical condition, Karnofsky index  $\geq 60\%$ , (differing from [68] based on increasing experience with large patient numbers), be between 3 and 78 years of age (differing from [68] as a result of increasing experience). The tumor stage should be confirmed and documented based on histology with evidence of current stage, and the patient must have given his or her written consent.

Oncological indications for extreme whole-body hyperthermia include therapy-resistant metastatic cancer, sarcoma, malignant melanoma, lymphoma and chronic lymphatic leukemia in need of therapy.

In the non-oncological area, there have been some reports on the effectiveness of extreme WBH for the treatment of chronic Lyme disease [43].

## 2.5. Contraindications

Contraindications for extreme WBH:

- primary brain tumors (astrocytoma / glioblastoma) and cerebral metastases close to vessels and/or ventricles; computed tomography/magnetic resonance imaging absolutely necessary prior to hyperthermia treatment
- psychoses, seizure disorders and encephalopathies with increasing intracranial pressure
- all forms of clinically manifest heart failure above NYHA stage II
- coronary heart disease, angina pectoris
- pathological exercise test ECG, complex cardiac arrhythmia
- cardiac valve prostheses, fixed-rate cardiac pacemakers
- S.p. apoplexy
- therapy-resistant respiratory failure ( $PO_2 \leq 64$  mmHg,  $PCO_2 \geq 48$  mmHg)
- select endocrinopathies
- history of or susceptibility to malignant hyperthermia
- pregnancy
- advanced or incorrigible impairments of the fluid or electrolyte balance
- advanced renal failure
- severe liver dysfunction
- therapy-resistant hypo- or dysproteinemia
- hematopoiesis impairments (hemoglobin reduction  $\geq 30\%$ ), leukocytopenia, thrombocytopenia  $\leq 80,000/\mu$ l
- advanced tumor cachexia without assured nutrition

- osteolysis in the axial skeleton at high risk of fracture

## 2.6. Performance of extreme whole-body hyperthermia

### 2.6.1. Preparation

Patients should have at least one day of acclimatization in the treatment facility, i.e. the first contact in the treatment facility should be 48 hours prior to the start of therapy. The laboratory parameters differential blood count, electrolytes, creatinine, urea, uric acid, cholinesterase, lipase, amylase, Quick value, PTT, PTZ, fibrinogen, LDH and liver values must be checked and treated if applicable. Patients should receive infusion therapy in the sense of a substitution and supportive therapy the day before the treatment. In addition to formal legal issues, patient information should also include comprehensive details about the course of the therapy. It must be ensured that ECG, lung function, chest x-ray and laboratory values are available as required for a surgical procedure. Information about the anesthesia to be performed also is part of the preparation. Premedication the evening before the session makes sense, and consideration for fasting times up to the time of the scheduled anesthesia is mandatory.

### 2.6.2. Temperature control

Temperature control is performed by recording the core body temperature (rectally and/or intravesically), the axillary temperature as well as up to two skin temperature values (ventral and dorsal). Furthermore, non-contact control of the skin temperature by way of a hand-held pyrometer is indispensable to check temperatures in areas at risk of overheating, e.g. reddened skin areas. Long-term thermal exposure of the skin at temperatures over 43.5°C should be avoided. Intra-luminal temperature measurements are an option, but not mandatory. Rectal and intravesical temperature measurements are methods recognized in the general professional discourse for recording the core body temperature. In the context of extreme WBH with contact heat in a water bath, temperature measurements should be taken as described in Section 2.2.2.

### 2.6.3. Anesthesia

Deep intravenous anesthesia in the form of neuroleptanalgesia while maintaining adequate spontaneous breathing is the preferred form of anesthesia for this special treatment process. It is imperative to have instruments for an immediate change to assisted or controlled ventilation with a laryngeal mask or an endotracheal tube available. This also applies to suction equipment. Premedication in the preparatory phase can consist of one tablet of Dormicum (midazolam 7.5 mg) immediately prior to positioning in the hyperthermia equipment, supplemented by diazepam via infusion (30 mg on average) during the positioning and wiring of the patient. Neuroleptanalgesia can be started when the core body temperature reaches 37.5°C to 38.0°C, e.g. with disoprivan by infusion or with an infusion pump (propofol, e.g. 1%) and administration of rapifen (alfentanil) via infusion pump. The anesthesia demand can be individually adjusted to the patient and therapy situation via IV syringe pumps. The involved drug combinations include propofol, midazolam and fentanyl as well as disoprivan and alfentanil [73, 74, 75, 76]. In case of certain constellations or necessities, the anesthesia can also be performed as intubation anesthesia.

In the context of extreme WBH administered in a water bath, especially with the objective of exceeding 42.5°C, intubation anesthesia, if applicable together with jet ventilation, is required [51].

### 2.6.4. Chemotherapy

Any chemotherapy must be administered by an experienced physician, observing the required precautions for the application of cytotoxic chemotherapy. According to current knowledge, the chemotherapy must be applied before a temperature of 41.0°C has been reached. It is important to bear in mind that most cytostatic chemotherapy drugs are significantly intensified under extreme WBH, which means that doses must be reduced accordingly.

Particular caution is advised for the use of nephrotoxic cytostatic drugs, especially cisplatin, since side effects, in contrast to almost all other cytostatic drugs, will also be significantly amplified in this case. This effect may be due to the stimulation of the antidiuretic hormone in high temperature ranges and would increase the activity of nephrotoxic substances in the phase of temperature-related reduced kidney output. In the worst case, this could lead to a dependency on dialysis. Accordingly, reducing the dose and strict indication review is required when using cisplatin in the context of extreme WBH.

### 2.6.5. Supportive therapy

Required supportive therapy in particular includes electrolyte solutions, glucose infusions, and inhaled oxygen application. Even if the extreme WBH is not to be performed as part of systemic multi-step cancer therapy [77], glucose infusions and oxygen inhalation are required to improve the tolerance for, or the therapeutic index of the treatment. It is best to choose a glucose concentration between 10 and 40% and to significantly increase the paO<sub>2</sub> level. The electrolyte substitution depends on the prior checkup at the responsibility of the physician and must particularly take magnesium, calcium, potassium and sodium levels into account.



### 2.6.6. Hyperthermia procedure

The process of hyperthermia must be consistently monitored with the help of suitable monitoring equipment. Body temperatures, pulse oximetry, ECG with multiple leads and respiration as well as data associated with the radiation intensity must be consistently acquired. In addition, the blood pressure must be measured periodically with a cuff and recorded digitally or manually.

All incidents and special measures occurring during extreme WBH must be recorded manually or with computer entries.

Extreme WBH can be divided into the following essential phases: Preparation, temperature increase, plateau phase, and cool-down phase (therapy length = temperature increase + plateau phase + cool-down phase). In the preparation phase, the leads of all monitoring equipment should be connected and an indwelling bladder catheter should be placed. When positioning the patient, particular attention must be paid to areas that are at risk of overheating and/or areas where pressure is exerted on the skin (heels, sacral bone, shoulder blades, elbows). The head should be slightly reclined in positioning and the patient should have the ability to turn his or her head. Arms should be positioned with elbow joints in a slightly angled position, while hand and finger joints should be in a gripping pose. Hips and knee joints should be brought to a slightly flexed position with a knee cushion. Carefully ensure that the knee cushion does not push against the fibular head from behind to avoid peroneus injury from extreme WBH and long-term positioning. Place a heel protector with a soft pad on the heels. At the same time, the nursing staff or physician has to introduce passive movement of the large joints once every 40 minutes.

It has been proven successful in practice, particularly in the case of overweight patients, to relieve the heels with a soft roll placed under the leg at a level above the ankle joint. Patients receiving treatment with 5-FU frequently experience deeper corneal damage, which may lead to injury during positioning and in case of overheating. If overheating is detected, e.g. by means of a non-contact hand-held pyrometer, it is recommended to temporarily apply local cooling (cold water spray).

There are no special positioning instructions for extreme WBH with contact heat in a water bath. In this method, the patient is lifted from the water bath when the target temperature has been reached and receives further ventilation during the cool-down phase. It must be taken into account that even after leaving the water bath, the achieved temperature may increase by a few tenths of a degree Celsius.

### 2.6.7. Aftercare / monitoring

Aftercare for extreme WBH involves bedside monitoring for several hours and depends on the individual course of the follow-up period. The patient's renal function requires particular attention (hourly measurement of urine flow). Aftercare measurements must include regular blood glucose level checks, repeated electrolyte controls (depending on the course) as well as lactate and, if necessary, blood count checks including hematocrit. A blood gas analysis for control purposes is also recommended in the aftercare period. If necessary, fluid regulation, substitution and supportive therapy, if applicable with intravenous buffering, may need to be performed. Intensive care monitoring may be required until the next day.

## 3. Documentation and quality assurance for whole-body hyperthermia

### 3.1. Acquisition of the therapy and temperature trend data

It is recommended to use special software programs to document hyperthermia treatments, which guarantee automatic capturing, clearly structured data presentation, and reliable storage of therapy-related parameters. The system should allow for entering medications, side effects and other special incidents during the treatment. After the completion of the treatment, a report including all saved information should be available with a print-out option.

For characterization and comparative analysis of mild or fever-range WBH, the "highest mean temperature of the hyperthermia session over 60 min", also known as T60 (or alternatively T30, T90 or T120) can be used.

For characterization and comparative analysis of extreme WBH, it is recommended to use the calculation of "thermal dose in equivalent minutes at 43 °C," or EM43 for short, in the scope of "quality assurance guidelines for ESHO protocols" [78].

Examples of the electronic recording of hyperthermia treatment in two different WBH systems can be found in Annex 2 and Annex 3.

### 3.2. Acquisition and management of side effects

All side effects occurring in the context of hyperthermia treatments (see table in Annex 4) must be documented in detail, either in writing or via computer data recording. This includes the manifestation, the treatment course over time and, if applicable, any necessary measures. Such side effect management makes it easier to identify the cause and to develop preventive strategies.

The log document for aftercare and monitoring included in Annex 4 can be used for patient monitoring, evaluation and comparison with other medical facilities and users. It is an example of a suitable tool for side effect management in a medical facility. Side effects must be entered prior to extreme WBH together with their maximum value after the performance of the hyperthermia

treatment, and 4 to 6 weeks after WBH.

Side effects that were caused by errors on the part of WBH systems must be immediately reported to the corresponding device manufacturer. The applicable reporting obligations vis-à-vis the authorities in accordance with the German Medical Device Safety Plan Ordinance (Medizinprodukte-Sicherheitsplanverordnung - MPSV) must be observed.

### **3.3. Follow-up examinations**

The therapeutic effects of WBH treatments frequently can occur with a time delay, which makes it necessary to perform coordinated follow-up examinations.

### **3.4. Documentation of treatment results**

To increase the level of evidence and the associated acceptance of WBH, it is essential to find a better way to document the results achieved in routine applications [79]. The resulting data can be published as case studies and retrospective evaluations or can be used in multi-institutional registry studies. In addition, such data can serve, among other applications, to develop study designs for controlled prospective studies. For cancer patients taking medications associated with multiple side effects (e.g. high risk of fatigue) as well as for patients in palliative therapy situations with significant symptoms (e.g. tumor pain) it is recommended to measure quality of life with validated instruments (e.g. EORTC, FACT, visual analogue scale for pain).

## **4. Outlook**

The long medical tradition of intentionally heating the body core to febrile temperatures (mild and fever-range WBH) for treating various, typically chronic diseases guarantees the safe application and broad therapeutic potential of this treatment method, which is based on recognizing the healing power of natural fever in the organism. Basic immunological research is making increasing progress in exploring the complex immunological mechanisms of action and provides a rationale for systemic hyperthermia of the human organism.

New drug therapies associated with rheumatology and oncology that aim to influence immunological processes at selected points, which in part achieve astonishing symptom relief and healing, are partly associated with significant risks and side effects. It is well worth looking (back) at a therapy that also has an extraordinary effect on the immune system, albeit with much lower risks and side effects. A suitable combination of both approaches should be the subject of future research.

Mild and fever-range WBH can be used as monotherapy or in combination with other treatment methods. Prospective studies have already yielded significant positive results for individual indications. The careful documentation of treatment results achieved in routine applications has the potential to initiate further controlled studies that will gradually increase the evidence level of mild and fever-range WBH in various indication areas.

In the routine application in a limited number of hospitals, extreme WBH has achieved a good safety standard. However, an unbiased review of systemic multi-step cancer therapy / sCMT and similar concepts with chemotherapy as well as the treatment results achieved to date is still lacking in oncological applications. There are publications with hopeful results for using extreme WBH for the treatment of chronic Lyme disease, which also need to be confirmed by unbiased review. Prospective studies to increase the level of evidence, i.e., the acceptability of methods in the area of extreme WBH, are urgently needed.

## 5. Annexes

Indication	Target temperature T(rectal)	Warm-up phase	Plateau phase; Heat storage	Restin g phase	Number of sessions	Moni- toring	Notes	Literature
	°C	min	min	min				
Arterial hypertension	38.3	30	0	30	8 (2 × / week) or 8 (every 2 days)	T(axill), pulse	↓ systolic by 22 mmHg, ↓ diastolic by 12 mmHg, 10% non-responders	[22, 23]
Chronic back pain	38.5	45	15	30	7 (1 × / week)	T(rect), T(axill), pulse	pre/post 1 year: analgesic drug consumption < 10%	[15, 16]
Fibromyalgia syndrome	38.1	40	15	30	6 (2 × / week) or 6 (every 2 days) or 6 consecutive days	T(axill), pulse	pre/post 6 mon 20% below initial pain acc to "Fibromyalgia Impact Questionnaire" / FIQ	[11, 12, 13, 14]
Psoriatic arthritis	38.5	45	15	30	6 (in 8 days) or 6 consecutive days	T(rect), T(axill), pulse	pre/post 6 mon pain relief, ↓ DAS28 to 3 mon (DAS28 = activity and function parameters)	[21]
Axial spondyloarthriti s	38	30	15	120 in bed	6 (2 × / week)	T(axill), pulse	pre/post 3 mon pain relief	[20]
Ankylosing spondylitis	38.5	45	15	30	6 (in 8 days) or 6 consecutive days	T(rect), T(axill), pulse	pre/post 3 mon pain relief, ↓ disease activity index (BASDAI) 3 mon ↓ blood sedimentation speed 3 mon ↑TLR-4, IL-10 (BASDAI = Bath AS Disease Activity Index)	[17, 18, 19]
Systemic scleroderma	38.5	30	0	30	15 (2 × / week) or 15 (every 2 days)	T(axill), pulse	Frequency and severity of Raynaud's attacks consistently and greatly reduced in approximately 50% of patients in two-year follow-up	[23, 35, 36]
Major depression	38.5	110	60	0	1	T(rect), T(axill), pulse	Even a single WBH session has a significant anti-depressive effect, which lasts up to six weeks after the treatment	[24, 25, 26]

Annex 1: Publication-based treatment regimens for whole-body hyperthermia for a few non-oncological indications.

Side effect		Severity according to WHO					before sCMT	max. after *) sCMT	max. 4 – 6 weeks after sCMT
		0	1	2	3	4			
<b>a)</b>	<b>Hematology</b>								
	Leukocytes	> = 4	3 ... 3.9	2 ... 2.9	1 ... 1.9	< 1			
	Platelets	> = 100	75 ... 99	50 ... 74	25 ... 49	< 25			
	Hb	> = 7	6 ... 6.9	5 ... 5.9	4 ... 4.9	< 4			
	Bleeding	none	petechiae	Low blood loss	Heavy blood loss: extended bruising	Bleeding affecting cardiovascular system			
<b>b)</b>	<b>Gastrointestinal</b>								
	Nausea, vomiting	no	Nausea	Occasional vomiting	Anti-emetic therapy	Life-threatening, need for infusion			
	Diarrhea	0	Up to 2 days	> 2 days	Therapy required	Hemorrhagia			
	Constipation	0	minor	Moderate	Subileus	Ileus			
	Stomatitis	0	Soreness, erythema	Ulcers, can eat solid food	Liquid food only	Infusion			
<b>c)</b>	<b>Renal</b>								
	Creatinine	< = 1.25N	< = 2.5N	< = 5N	< = 10N	> = 10N			
	Urine	Prot 0	< 3 g/l	< 10 g/l	> 10 g/l	neph. syndrome			
<b>d)</b>	<b>Laboratory</b>								
	Bilirubin	< = 1.25N	< = 2.5N	< = 5N	< = 10N	> 10N			
	Gamma GT	< = 1.25N	< = 2.5N	< = 5N	< = 10N	> 10N			
	AP	< = 1.25N	< = 2.5N	< = 5N	< = 10N	> 10N			
<b>e)</b>	<b>Neurological</b>								
	Peripheral n.	0	Paresthesia	Severe p., muscle weakness	Unbearable p., unsteady gait	paralysis			
	Other n.	0							
<b>f)</b>	<b>Skin injury</b>	0	Erythema 24 hours after sCMT	Blisters, painful induration	ulceration	Surgical therapy	IRA: pressure:		
<b>g)</b>	<b>Phlebitis</b>	0	local	extended	necroses				
<b>h)</b>	<b>Hair loss</b>	0	minimal	In patches	Completely reversible	irreversible			
<b>i)</b>	<b>Fever</b>	0	< 38.0 °C	38.0 ... 40.0 °C	> 40.0 °C	> 40.0 °C, with hypotension			
<b>j)</b>	<b>Infection</b>	0	low	moderate	severe	life-threatening:			
<b>k)</b>	<b>Pain</b>	0	low	Therapy required	Morphine required				

<b>l)</b>	<b>Pulmon. side effects</b>	<b>0</b>	<b>Minor symptoms</b>	<b>Stress dyspnea</b>	<b>dyspnea at rest</b>	<b>Complete bed rest required</b>			
<b>m)</b>	<b>Cardiac side effects</b>								
	<b>Heart rhythm</b>	<b>normal</b>	<b>Sinus tachycardia &lt; 110</b>	<b>Monotopic VPBs</b>	<b>Multifocal VPBs</b>	<b>Ventricular tachycardia</b>			
	<b>Cardiac function</b>	<b>normal</b>	<b>asymptomatic</b>	<b>Symptomatic, no therapy</b>	<b>Symptomatic, response to therapy</b>	<b>Therapy resistant</b>			
	<b>Arterial hypertension</b>	<b>none</b>	<b>No treatment required</b>	<b>Fluid intake or other therapy required</b>	<b>In-patient treatment required</b>				
<b>n)</b>	<b>Allergic reaction</b>	<b>none</b>	<b>Edema</b>	<b>bronchospasms, no treatment required</b>	<b>parenteral therapy required</b>	<b>anaphylactic shock</b>			
<b>o)</b>	<b>Joint pain</b>	<b>none</b>	<b>Minor pain, one-sided</b>	<b>Strong pain, two-sided</b>	<b>Restricted mobility</b>	<b>Swelling, effusion</b>			

## 6. Literature

- Schmidt KL. Hyperthermie und Fieber, Wirkungen bei Mensch und Tier. Stuttgart: Hippokrates Verlag 1987
- Evans SS, Repasky EA, Fisher DT. Fever and the thermal regulation of immunity: the immune system feels the heat. *Nat Rev Immunol* 2015; 6:335-49
- Agency for Healthcare Research and Quality (AHRQ) 2018. URL: <https://de.wikipedia.org/wiki/Evidenzgrad>
- Heckel-Reusser S, Ardenne A von. Die drei Stufen der Ganzkörperhyperthermie (GKHT) 2018. Heckel Medizintechnik und Von Ardenne Institut für Angewandte Medizinische Forschung
- Bachem A, Reed CI. The penetration of light through human skin. *Amer J Physiol* 1931; 97:86-91
- Witte E. Über die qualitativen und quantitativen Unterschiede in den Strahlungen von Natursonne und therapeutisch genutztem Kunstlicht sowie über eine neue Lampe zur künstlichen Herstellung praktisch sonnenähnlichen Lichtes. *Strahlentherapie* 1937; 58:113-24
- Vaupel P, Stofft E. Wassergefilterte Infrarot-A-Strahlung im Vergleich zu konventioneller Infrarotstrahlung oder Fango-Paraffin-Packungen: Temperaturprofile bei lokaler Wärmetherapie. In: Vaupel P, Krüger W, eds. *Wärmetherapie mit wassergefilterter Infrarot-A-Strahlung*. 2. Aufl. Stuttgart: Hippokrates Verlag 1995:135-147
- Heckel-Hyperthermiertechnik; heckel medizintechnik GmbH, Olgastrasse 25, D-73728 Esslingen; 2018. URL: <http://www.hyperthermie.de>
- Von Ardenne-Hyperthermiertechnik; Von Ardenne Institut für Angewandte Medizinische Forschung GmbH, Zeppelinstr. 7, 01324 Dresden; 2018. URL: <http://www.IRATHERM.de>
- Rowe-Horwege RW. Hyperthermia, Systemic. *Encyclopedia of Medical Devices and Instrumentation*, 2nd Ed., edited by John G. Webster, John Wiley & Sons 2006:42-62
- Brockow T, Wagner A, Franke A, Offenbächer M, Resch KL. A Randomized Controlled Trial on the Effectiveness of Mild Water-Filtered Near Infrared Whole-body Hyperthermia as an Adjunct to a Standard Multimodal Rehabilitation in the Treatment of Fibromyalgia. *Clin J Pain* 2007; 1:67-75
- Walz J, Hinzmann J, Haase I, Witte T. Ganzkörperhyperthermie in der Schmerztherapie - eine kontrollierte Studie an Patienten mit Fibromyalgiesyndrom. *Schmerz* 2013; 1:38-45
- Romeyke T, Stummer H. Multi-modal pain therapy of fibromyalgia syndrome with integration of systemic whole-body hyperthermia - effects on pain intensity and mental state: A non-randomised controlled study. *J Musculoskel Pain* 2014; 4:341-55
- Schleenbecker HG, Schmidt KL. Zur Wirkung einer iterativen milden Ganzkörperhyperthermie auf den Fibromyalgieschmerz. *Phys. Rehab. Kur Med* 1998; 8:113-117
- Ettrich U, Konrad B, Prate K, Seifert J, Krummenauer F. Milde Ganzkörperhyperthermie in Kombination mit stationärer multimodal orientierter Schmerztherapie - Evaluation bei Patienten mit chronischem unspezifischem lumbalem Rückenschmerz. *Orthopäde* 2014; 2:165-74
- Weller E, Ullrich D. Infrarot-A-Hyperthermie-Anwendung bei Patienten mit Analgetica-Abusus wegen chronischer Rückenschmerzen. Vortrag auf dem 95. Kongress der Gesellschaft für Phys Med und Rehab 5.10.1990
- Lange U, Müller-Ladner U, Dischereit G. Wirkung iterativer Ganzkörperhyperthermie mit wassergefilterter Infrarot-A-Strahlung bei ankylosierender Spondylitis - eine kontrollierte, randomisierte, prospektive Studie. *Akt Rheumatol* 2017; 2:122-28
- Zauner D, Quehenberger F, Hermann J, Dejaco C, Stradner MH, Stojakovic T, Angerer H, Rinner B, Graninger WB. Whole body hyperthermia treatment increases interleukin 10 and toll-like receptor 4 expression in patients with ankylosing spondylitis: A pilot study. *Int J Hyperthermia* 2014; 6:393-401
- Turner IH, Ladner UM, Uhlemann C, Lange U. The effect of mild whole-body hyperthermia on systemic levels of TNF-alpha, IL-1 beta and IL-6

in patients with ankylosing spondylitis. *Clin Rheumatol* 2009; 4:397-402

20 Stegemann I, Hinzmann J, Haase I, Witte T. Ganzkörperhyperthermie mit wassergefilterter Infrarot-A-Strahlung bei Patienten mit axialer Spondyloarthritis. *Orthopäd & Unfallchirurg Praxis* 2013; 10:458-63

21 Lange U, Schwab F, Müller-Ladner U, Dischereit G. Wirkung iterativer Ganzkörperhyperthermie mit wassergefilterter Infrarot-A-Strahlung bei Arthritis psoriatica – eine kontrollierte, randomisierte, prospektive Studie. *Akt Rheumatol* 2014; 5:310-16

22 Mischke M. Wirkungen einer einmaligen bzw. seriellen Infrarot-A-Hyperthermie bei Patienten mit arterieller Hypertonie der WHO-Stadien I und II. Diss. Humboldt-Universität Berlin 18.07.1991

23 Meffert H, Scherf HP, Meffert B. Milde Infrarot-A-Hyperthermie: Auswirkungen von Serienbestrahlungen mit wassergefilterter Infrarotstrahlung auf Gesunde und Kranke mit arterieller Hypertonie bzw. systemischer Sklerodermie. *Akt Dermatol* 1993; 19:142-48

24 Janssen CW, Lowry CA, Mehl MR, Allen JJB, Kelly KL, Gartner DE, Medrano A, Begay TK, Rentscher K, White JJ, Fridman A, Roberts LJ, Robbins ML, Hanusch KU, Cole SP, Raison CL. Whole-Body Hyperthermia for the Treatment of Major Depressive Disorder – A Randomized Clinical Trial. *JAMA Psychiatry* 2016; 8:789-95

25 Naumann J, Grebe J, Kaifel S, Weinert T, Sadaghiani C, Huber R. Effects of hyperthermic baths on depression, sleep and heart rate variability in patients with depressive disorder: a randomized clinical pilot trial *BMC Complement Altern Med* 2017; 17:172

26 Hanusch KU, Janssen CH, Billheimer D, Jenkins I, Spurgeon E, Lowry CA, Raison CL. Whole-Body Hyperthermia for the Treatment of Major Depression: Associations With Thermoregulatory Cooling. *Am J Psychiatry* 2013, 170:7

27 Kobayashi Y, Ito Y, Ostapenko VV, Sakai M, Matsushita N, Imai K, Shimizu K, Aruga A, Tanigawa K. Fever-range whole-body heat treatment stimulates antigen-specific T-cell responses in humans. *Immunology Letters* 2014; 162:256-61

28 Mace TA, Zhong L, Kokolus KM, Repasky EA. Effector CD8+T cell IFN- $\gamma$  production and cytotoxicity are enhanced by mild hyperthermia. *Int J of Hyperthermia* 2012; 1:9-18

29 Gaipf U. Immunologische Wirkungsmechanismen der Hyperthermie. 22. Jahrestag der Deutschen Gesellschaft für Radioonkologie 16.06.2016. Mannheim

30 Weigelin B. Activating serial killers of cancer cells with artificial fever: Hyperthermia as supporting strategy for immunotherapy of cancer. Symposium – Modern Hyperthermia 14.11.2015. Krakow

31 Skitzki JJ, Repasky EA, Evans SS. Hyperthermia as an immunotherapy strategy for cancer. *Curr Opin Investig Drugs* 2009; 6: 550-58

32 Bull JMC, Scott GL, Strebel FR, Nagle VL, Oliver D, Redwine M, Rowe RW, Ahn CW, Koch SM. Fever-range whole-body thermal therapy combined with cisplatin, gemcitabine and daily interferon- $\alpha$ : A description of a phase I-II protocol. *Int J Hyperthermia* 2008; 8:649-62

33 Zaltenbach G. Erfahrungen bei Asthma bronchiale und anderen Atemwegserkrankungen mit Sauerstoff-Mehrschritt-Therapie und Hyperthermie. *Erfahrungsheilkunde* 1988; 2:79-82

34 Brockow T, Beck I, Müller H, Resch KL. Applicability auf effectiveness of mild infrared whole body hyperthermia in symptomatic osteoarthritis – a pilot study. Abstract, 9th Annual Symposium on Complementary Health Care, 4th - 6th December 2002 Exeter, UK

35 Förster J, Fleischanderl S, Wittstock S, Storch A, Meffert H. Letter to the Editor: Infrared-Mediated Hyperthermia is Effective in the Treatment of Scleroderma-Associated Raynaud's Phenomenon. *J Invest Dermatol* 2005; 6:1313-16

36 Förster J, Storch A, Fleischanderl S, Wittstock S, Pfeiffer S, Riemekasten G, Worm M. Neutrophil respiratory burst is decreased in scleroderma and normalized by near-infrared mediated hyperthermia. *Clin Exp Dermatol* 2006; 6:799-806

37 Sachse C. Studie der Charité Berlin: Ganzkörperhyperthermie bei Reizdarmsyndrom. VII. Hyperthermie-Kongress der Deutschen Gesellschaft für Hyperthermie, Berlin Sept 2016:11

38 Wey S. Mammakarzinom – komplementäre Praxis. *EHK* 2017; 66:302-14

39 Wey S. 14 Jahre Fiebertherapie / Ganzkörperhyperthermie in der onkologischen Rezidivprophylaxe. Abstract VII. Hyperthermie-Kongress der Deutschen Gesellschaft für Hyperthermie, Berlin Sept 2016

40 Heckel M, Heckel I. Beobachtungen an 479 Infrarot-Hyperthermie-Behandlungen – Beitrag zur Methode der Ganzkörperüberwärmung. *Med Welt* 1979; 30:971-75

41 Lexer G. Hyperthermie bei entzündlichen Darmerkrankungen. Abstract „Hyperthermie einst und heute – Symposium aus Anlass des 80. Jahrestages der Verleihung des Nobelpreises für Medizin an Julius Wagner-Jauregg. GAMED Wien, 2007

42 Zais ODA. Hyperthermie und Borreliose – Verschiedene Therapiestrategien. Abstract VIII. Hyperthermie-Symposium der Deutschen Gesellschaft für Hyperthermie, Berlin Sept 2017:6

43 Douwes F. Komplextherapie der chronischen Borreliose (Lyme Disease) – Ein neuer Therapieansatz: die Antibiotika augmentierte Thermoeradikation (AAT). *OM & Ernährung* 2018 | Nr. 164, S. F10-F15

44 Kleef R. Hyperthermie und Entgiftung. *OM & Ernährung* 2011; 135:7

45 Hoffmann G. Prävention durch Bewegung und Sport. *Dt Ärzteblatt* 2002; 9:A577-80

46 Heckel M. Ganzkörper-Hyperthermie und Fiebertherapie, Grundlagen und Praxis. Stuttgart: Hippokrates Verlag, 1990

47 Dancsak T, Figueroa G, Ottosen M, Bull J, Koch S. Management of conscious sedation for patients undergoing fever-range whole body thermal therapy for advanced and metastatic malignancies. Poster Abstract ICHO 2008, 9.-12.04.2008

48 Scott GL, Bull GMC, Koch SM. Management of conscious sedation for the comfort and control of physiological/hemodynamic factors of patients with advanced/or metastatic malignancies undergoing fever-range whole-body hyperthermia (FR-WBH) thermo-chemo-bio-therapy. In: 9th Int Congr on Hyperthermic Oncology 2004 April 20. St. Louis Missouri, 2004:89

49 Kraybill WG, Olenki T, Evans SS, Ostberg JR, O'Lery KA, Gibbs JF, Repasky EA. A phase I study of fever-range whole-body hyperthermia (FR-WBH) in patients with advanced solid tumours: correlation with mouse models. *Int J Hyperthermia* 2002; 3: 253-66

50 Ardenne Mv. Systemische Krebs-Mehrschritt-Therapie: Hyperthermie und Hyperglykämie als Therapiebasis. Stuttgart: Hippokrates Verlag, 1997:110 ff

51 WBH TEC LLC High Level Whole Body Hyperthermia, P.O. Box 32267, Washington, D.C., 20007, USA

52 Robins HI, Cohen JD, Schmitt CL, Tutsch KD, Feyerabend C, Arzoomanian RZ, Alberti D, Oleire F, Longo W, Heiss C, Rushing D, Love R, Spriggs D. Phase-I Clinical trial of carboplatin and 41.8 °C whole-body hyperthermia in cancer patients. *J Clin Oncol* 1993;11:1787-94

53 Kerner T, Deja M, Ahlers O, Löffel J, Hildebrandt B, Wust P, Gerlach H, Riess H. Whole-body hyperthermia: a secure procedure for patients with various malignancies. *Intensive Care Med* 1999; 25:959-65.

54 Wust P, Riess H, Hildebrandt B, Löffel J, Deja M, Ahlers O, Kerner T, von Ardenne A, Felix R. Feasibility and analysis of thermal parameters for

- the whole-body-hyperthermia system IRATHERM2000. *Int J Hyperthermia* 2000; 4:325-39
- 55 Hegewisch-Becker S, Gruber Y, Corovic A, Pichlmeier U, Atanackovic D, Nierhaus A, Hossfeld DK. Whole-body hyperthermia (41.8 degrees C) combined with bimonthly oxaliplatin, high-dose leucovorin and 5-fluorouracil 48-hour continuous infusion in pretreated metastatic colorectal cancer: a phase II study. *Ann Oncol* 2002; 8:1197-1204
- 56 Hildebrandt B, Dräger J, Kerner T, Deja M, Löffel J, Strozczynski C, Ahlers O, Felix R, Riess H, Wust P. Whole-body hyperthermia in the scope of von Ardenne's systemic cancer multistep therapy (sCMT) combined with chemotherapy in patients with metastatic colorectal cancer: a phase I/II study. *Int. J. Hyperthermia* 2004; 3:317-33
- 57 Bakhshandeh-Bath A, Stoltz AS, Homann N, Wagner T, Stöltzing S, Peters SO. Preclinical and clinical aspects of carboplatin and gemcitabine combined with whole-body hyperthermia for pancreatic adenocarcinoma. *Anticancer Res* 2009 A; 8:3069-77
- 58 Atmaca A, Al-Batran SE, Neumann A, Kolassa Y, Jäger D, Knuth A, Jäger E. Whole-body hyperthermia (WBH) in combination with carboplatin in patients with recurrent ovarian cancer – a phase II study. *Gynecol Oncol* 2009; 2:384-8
- 59 Deja M, Ahlers O, Macguill M, Wust P, Hildebrandt B, Riess H, Kerner T. Changes in hepatic blood flow during whole body hyperthermia. *Int J Hyperthermia* 2010; 2:95-100
- 60 Ismail-Zade RS, Zhavrid EA, Alei`nikova OV, Potapnev MP, Belevtsev MV, Isai`kina IaI, Vashkevich EP, Savitski` VP. Use of LAK-cells and systemic chemotherapy with hyperthermia in the management of chemo-resistant tumors. *Vopr Onkol* 2010; 6:681-6
- 61 Zhao C, Dai C, Chen X. Whole-body hyperthermia combined with hyperthermic intraperitoneal chemotherapy for the treatment of stage IV advanced gastric cancer. *Int J Hyperthermia* 2012; 8:735-41
- 62 Herzog A. Extreme Ganzkörperhyperthermie bei Patientinnen mit metastasiertem Mammakarzinom, Abstract VII. Hyperthermie-Symposium der DGHT Berlin Sept 2016:14
- 63 Herzog A. Prolonged survival times in patients with advanced or metastatic pancreatic cancer after chemotherapy in combination with hyperthermia, Abstract ICHO, 11.-15.04.2016
- 64 Hildebrandt B, Hegewisch-Becker, Kerner T, Nierhaus A, Bakhshandeh-Bath A, Janny W, Zumschlinge R, Sommer H, Riess H, Wust P. Current status of radiant whole-body hyperthermia at temperatures > 41.5 °C and practical guidelines for the treatment of adults. The German 'Interdisciplinary Working Group on Hyperthermia'. *Int J Hyperthermia* 2005; 2:169-183
- 65 Steinhausen D, Meyer WK, Ardenne Mvon. Evaluation of systemic tolerance of 42.0 degrees C infrared-A whole-body hyperthermia in combination with hyperglycemia and hyperoxemia – A Phase-I study. *Strahlenther Onkol* 1994; 6:322-34
- 66 Krasny SA, Mavriches AV, Zhavrid EA, Sukonko OG, Polyakov SL. Combined treatment of renal cancer invading renal vein or vena cava interior. *Experimental Oncology* 1995; 17:318-322
- 67 Takeuchi T, Takeuchi A, Yokoyama M. Clinical experiences of far-Infrared WBH by the use of RHD 2002, In: Proc. of the 7th Int. Congr on Hyperth Onc, Roma, April 9-13 1996, Volume II:272-74.
- 68 Ardenne Mvon. Systemische Krebs-Mehrschritt-Therapie: Hyperthermie und Hyperglykämie als Therapiebasis. Stuttgart: Hippokrates Verlag 1997
- 69 Bremer K, Meyer A, Lohmann R. Pilot study of whole-body hyperthermia combined with chemotherapy in patients with metastasized pretreated progressiv breast, ovarian and colorectal carcinomes. *Tumordiagn u Ther* 2001; 22: 115-20
- 70 Wehner H, Ardenne Avon, Kaltofen S. Whole-body hyperthermia with water-filtered infrared radiation: technical-physical aspects and clinical experiences. *Int J Hyperthermia* 2001; 17:19-30
- 71 Ardenne Avon, Wehner H. Extreme whole-body hyperthermia with water-filtered infrared radiation. In: Baronzio GF, Hager ED, eds. Locoregional radiofrequency-perfusional and whole-body hyperthermia in cancer treatment: New clinical aspects. Georgetown: Landes Bioscience; 2005
- 72 Suvernev AV, Ivanov GV, Novozhilov SYu, Yefremov AV. Intensive hyperthermia therapy. Novosibirsk: Siberian Research Institute of Hyperthermia – Academic Publishing House GEO; 2011
- 73 Ardenne Mvon. Systemische Krebs-Mehrschritt-Therapie: Hyperthermie und Hyperglykämie als Therapiebasis. Stuttgart: Hippokrates Verlag, 1997:186
- 74 Gaworek J, Mayer CT. Tödliche Hitze für Tumorzellen. *Pflegezeitschrift* 2003;1:15-18
- 75 Reichel M, Scheeren T, Douwes O, Konrad RM. Tief intravenöse Analgosedierung zur extremen Ganzkörperhyperthermie in Kombination mit Chemotherapie. *Forum Komplementäre Onkologie*, In: Die Naturheilkunde 2004;3:4-8
- 76 Gaworek J, Douwes F. Tödliche Hitze für Tumorzellen – extreme Ganzkörperhyperthermie in der Onkologie (Teil 1). *Forum Komplementäre Onkologie* In: Die Naturheilkunde 2004;5:5-7. (Teil 2). *Forum Hyperthermie*, In: Die Naturheilkunde 2005;1:5-9
- 77 Ardenne Mvon. Systemische Krebs-Mehrschritt-Therapie: Hyperthermie und Hyperglykämie als Therapiebasis. Stuttgart: Hippokrates Verlag, 1997:182
- 78 Hand JW, Lagendijk JJW, Bach AJ, Bolomey JC. Quality assurance guidelines for ESHO protocols. *Int J Hyperthermia* 1989; 5:421-28
- 79 Heckel-Reusser S. Increasing the level of evidence – achievements and failures. Abstract VIII. Hyperthermie-Kongress der Deutschen Gesellschaft für Hyperthermie, Berlin Sept 2017
- 80 Wehner H. Nachsorge- und Überwachungsprotokoll gem. WHO Einteilung. gisunt® Klinik, Mühlenweg 144; 26384 Wilhelmshaven 2017. URL: <http://www.gisunt-klinik.de>